The effectiveness of the eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers

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Abstract

**Background:** People living with chronic leg ulcers frequently experience moderate to severe wound-related pain with the highest level of pain occurring at dressing change. Wound-related pain is not always able to be alleviated by oral analgesics alone. Persistent poorly-controlled leg ulcer pain physiologically impacts wound healing and prevents timely, effective wound management strategies being implemented which can negatively impact wound healing and health-related quality of life (HRQoL). Topical agents such as morphine gel and ibuprofen foam are used as primary dressings as a strategy for managing chronic leg ulcer pain. Studies investigating ibuprofen foam have shown significant improvement in chronic leg ulcer pain compared to standard care. There is insufficient evidence to suggest morphine gel is effective for chronic leg ulcer pain. Topical local anaesthetics, in particular the eutectic mixture of local anaesthetics (EMLA®), have been used for decades to relieve pain associated with debridement of chronic leg ulcers. However, their effectiveness as a primary dressing for managing chronic wound-related pain is yet to be evaluated.

Since there was no known evidence regarding the effectiveness of EMLA® as a primary dressing for painful chronic leg ulcers to relieve wound-related pain and its associated impact on wound healing and HRQoL this feasibility study was conducted.

**Study aims:** The primary aim of this study was to assess the processes, resources, management and scientific aspects of the study to ensure implementation of a larger study is feasible and to generate data that could be used for future sample size calculations. Study feasibility was assessed using the following criteria for determining success: recruitment of at least 80% of eligible patients within 12 months; retention of 80% of participants during the study period and achieving at least 80% adherence to the intervention protocol.
Secondary aims were to investigate the effectiveness of the daily topical application of EMLA® as a primary dressing to painful chronic leg ulcers as a pain-relieving strategy and the associated impact on wound healing and HRQoL; and whether improvement in pain levels is associated with reduced need for oral analgesia, particularly opiates.

**Design:** A pilot, parallel group, non-blinded, superior, randomised, controlled trial. There was a 4-week intervention period and a 12-week study period.

**Setting:** Six procedure clinics located in a public community nursing service Central Coast, New South Wales, Australia.

**Participants:** Participants (n = 60) were adult patients with painful chronic leg ulcers of varied aetiology. The preliminary screening criteria included a chronic leg ulcer of more than six weeks duration; pain relieving medications required to manage wound-related pain; and, the participant was able to be treated in a community nursing clinic.

**Intervention:** EMLA® was applied to the chronic leg ulcers daily for four weeks as a primary dressing followed by standard care.

**Data collection:** Feasibility data were collected on human resource requirements, number of home visits, use of consumables and study management including ease of administering data collection instruments. Wound-related pain was measured at baseline and each dressing change; chronic leg ulcer surface areas and HRQoL were measured at baseline, weeks 4 and 12.

**Outcomes:**

**Feasibility:** Although all proposed participants were recruited (n=60) the recruitment rate was lower than expected and it is possible some eligible patients were missed during the screening
process. Fifty-four participants remained in the study until completion for a 90% retention rate. Intervention fidelity was influenced by resource availability and participant factors such as increased wound-related pain. Data generated from the primary clinical outcome wound-related pain, was used to calculate the sample size for a larger study. Given two-sided significance of 0.05, a power of 0.8%, effect size 0.45 +/- 0.3 and variability/standard deviation of 2.2 +/- 0.2, 274 to 306 participants will be required for a larger randomised controlled trial. The sizes have been adjusted upwards based on an estimated dropout rate of 10%. However, an effect size of 0.45 is not clinically meaningful so a difference of at least two pain scores on the 11-point pain intensity Numerical Rating Scale used in this study is suggested as a clinically important difference. Recalculation using an effect size of two estimated that 52 participants would be needed to detect a clinically meaningful difference between the treatment and control groups based on pain as the primary outcome. Assuming a dropout of 10%, this figure was adjusted upwards to 58.

**Wound-related pain:** Mean pain scores were similar between the two groups at baseline ($p = 0.84$). During dressing change, mean pain scores across the 4-week intervention period were significantly lower in the intervention compared to the control group (intervention group: Mean (SD) 3.39 (2.16); control group: Mean (SD) 4.82 (2.27), $p = 0.02$). Mean pain scores after dressing change were also significantly lower for the intervention group over the 4-week intervention period (intervention group: Mean (SD) 2.71 (1.94); control group: Mean (SD) 3.92 (2.03), ($p = 0.03$).

**Wound healing and HRQoL:** During the intervention period there was no significant difference in wound sizes between groups (intervention group - Median (cm$^2$): 2.4, IQR: 1.3 – 12.7 v control group- Median (cm$^2$): 5.0, IQR: 2.5-9.9; $p = 0.05$). Mean HRQoL scores for all subscales at baseline, weeks 4 and 12 were similar between groups except for Wellbeing,
which was significantly higher in the intervention group at the end of the 4-week intervention period (intervention group - Mean 52.41, SD 24.50 vs. control group - Mean: 38.15, SD 21.25; \( p = 0.03, d = .62 \)).

**Conclusion:** It is feasible to conduct a larger multisite RCT following modifications to the study protocol. The study findings suggest that daily applications of EMLA® as a primary dressing reduces wound-related pain during and after dressing change, do not inhibit wound healing and may improve a person’s well-being.
Dedication

This thesis is dedicated to

all individuals who suffer wound-related pain

and

Pamela Joyce Woolfe

(1944 - 2015)

Mentor and Friend

Former Director of Nursing

Central Coast Local Health District Community Nursing Service
Acknowledgements

My supervisors are the best of the best. Thank you to Professor Andrea Marshall, my primary supervisor, Associate Professor Tom Buckley, Dr. Jennie King and Professor Wendy Moyle, for your expertise, guidance, support, encouragement, patience and friendship. What an amazing ride. You have taught me so much and I am forever grateful.

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Thank you to my family, my husband Brian, who patiently supported and encouraged me through this endeavour from the beginning and sacrificed himself many times by playing as much golf as he could to allow me writing time. Thank you to my children David and Louise for your constant support. Thank you, David, for your artistic contribution in Chapter 1. My grandchildren Wallace and Sullivan, born during this Ph.D. journey, for bringing such joy to my world and keeping me balanced.

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

___________________ 12th December 2018

Anne Purcell
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<td>ABPI</td>
<td>Ankle brachial pressure index</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>Ag</td>
<td>Silver</td>
</tr>
<tr>
<td>ANZCTR</td>
<td>Australian New Zealand Clinical Trials Register</td>
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<tr>
<td>AU</td>
<td>Australian currency</td>
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<tr>
<td>C</td>
<td>Control group</td>
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<tr>
<td>CINAHL</td>
<td>Cumulative Index of Nursing and Allied Health Literature</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetres</td>
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<tr>
<td>cm²</td>
<td>Centimetres squared</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CLU</td>
<td>Chronic leg ulcer</td>
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<tr>
<td>CTX</td>
<td>Clinical Trial Exemption</td>
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<tr>
<td>CWIS</td>
<td>Cardiff Wound Impact Schedule</td>
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<tr>
<td>$d$</td>
<td>Cohen’s $d$ - effect size</td>
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<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>EMBASE</td>
<td>Excerpta Medica database</td>
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<tr>
<td>EMLA</td>
<td>Eutectic Mixture of Local Anaesthetics</td>
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<tr>
<td>EMM</td>
<td>Estimated Marginal Means</td>
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<td>eTG</td>
<td>Therapeutic Guidelines Australia</td>
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<td>F</td>
<td>F-test</td>
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<td>g</td>
<td>Grams</td>
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<tr>
<td>HRQoL</td>
<td>Health-related Quality of Life</td>
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<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<td>Abbreviation</td>
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<tr>
<td>HSV</td>
<td>Herpes simplex</td>
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<td>I</td>
<td>Intervention group</td>
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<td>ICC</td>
<td>Intraclass correlation coefficient</td>
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<td>ICIS</td>
<td>Integrated Community Information System</td>
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<td>Inc</td>
<td>Incorporated</td>
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<td>IQR</td>
<td>Interquartile Range</td>
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<td>Intention-to-treat</td>
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<tr>
<td>LMM</td>
<td>Linear mixed model</td>
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<tr>
<td>LMX-4</td>
<td>Liposomal lidocaine cream 4%</td>
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<tr>
<td>LUMT</td>
<td>Leg Ulcer Management Tool</td>
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<tr>
<td>MEDLINE</td>
<td>Medical Literature Analysis and Retrieval System Online</td>
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<tr>
<td>MCAR</td>
<td>Missing Completely at Random</td>
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<td>ME</td>
<td>Maximum likelihood</td>
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<tr>
<td>mg</td>
<td>Milligrams</td>
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<td>MHz</td>
<td>Megahertz</td>
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<td>ml</td>
<td>Millilitres</td>
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<tr>
<td>MIMS</td>
<td>Monthly Index of Medical Specialties</td>
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<tr>
<td>mmHg</td>
<td>Millimetres of mercury</td>
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<td>MMPs</td>
<td>Matrix metalloproteinases</td>
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<tr>
<td>MMS</td>
<td>Mini-mental score</td>
</tr>
<tr>
<td>n</td>
<td>Number of patients</td>
</tr>
<tr>
<td>NBS</td>
<td>Numerical Box Scale</td>
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<tr>
<td>ng</td>
<td>Nanograms</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NR</td>
<td>Not reported</td>
</tr>
<tr>
<td>N₂O/O₂</td>
<td>Nitrous oxide/oxygen mixture</td>
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NRS  Numerical Rating Scale
NSAIDs  Non-steroidal anti-inflammatory drugs
NSW  New South Wales
p  p-value
p  Page
PASS  Power Analysis and Sample Size software
pH  Acidity or alkalinity of a solution
PNS  Peripheral sensory neuropathy
QLD  Queensland
r  Correlation coefficient
®  Registered trademark
Rx  Treatment
RA  Research assistant
RCT  Randomised controlled trial
REML  Restricted maximum likelihood
SA  Staphylococcus aureus
SD  Standard deviation
SNOSE  Sequentially numbered, opaque sealed envelopes
SP  Streptococcus pyogenes
SPSS  Statistical Package for Social Sciences
TGA  Therapeutic Goods Administration
TM  Trademark
VRS  Verbal rating scale
WUWHS  World Union of Wound Healing Societies
WRP  Wound-related pain
UK United Kingdom
VLU Venous leg ulcer
vs Versus
α Alpha
χ² Chi-square
% Percent
≤ Equal to or less than
≥ Equal to or greater than
@ At
φ Phi coefficient
**Glossary**

**Allodynia** - a painful response to a normally innocuous stimulus.

**Arterial ulcer** - lower leg ulcers commonly caused by peripheral arterial disease (also known as ischaemic ulcers).

**Biofilm** - a grouping of microbial cells that is irreversibly associated with a surface and enclosed in a matrix of primarily polysaccharide material.

**Compounding** - compounded medications are made based on a practitioner’s prescription in which individual ingredients are mixed together in the exact strength and dosage form required by the patient.

**Compression therapy** - a means of increasing blood flow activity in the lower limbs through strengthening vein support by applying pressure to the ankles and legs by wearing specifically designed stockings and bandaging systems.

**Cytokine** - small secreted proteins released by cells which have a specific effect on the interactions and communications between cells.

**Debridement** - the removal of non-viable tissue to promote wound healing.

**Dermis** - the thick layer of tissue below the epidermis containing blood capillaries, nerve endings, sweat glands, hair follicles, and other structures.

**Diabetic ulcers** - are mostly on the foot and occur because of various factors, such as mechanical changes in conformation of the bony architecture of the foot, peripheral neuropathy and atherosclerotic peripheral arterial disease, all of which occur with higher frequency and intensity in the diabetic population.

**Epithelialisation** - the formation of granulation tissue into an open wound allows the re-epithelialisation phase to take place as epithelial cells migrate across the new tissue to form a barrier between the wound and the environment.
**Eutectic mixture** - a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallisation process of one another resulting in a system having a lower melting point than either of the components.

**Hyperalgesia** - an increased response to a painful stimulus.

**Hyperpathia** - an exaggerated response to painful stimuli, especially repeated painful stimuli.

**Lipodermatosclerosis** - skin change of the lower legs often occurring in individuals who have venous insufficiency. It is a type of panniculitis (inflammation of subcutaneous fat).

**Methemoglobinemia** - a blood disorder in which too little oxygen is delivered to cells.

**Mixed ulcer** - lower leg ulcers caused by a combination of arterial disease and venous insufficiency.

**Neuronal sensitisation** - the process by which the response of a neuron to a given stimulus is increased.

**Neuropathic pain** - chronic pain often the result of nerve damage or a malfunctioning nervous system. The impact of nerve damage is a change in nerve function both at the site of the injury and areas around it.

**Nociceptive pain** - the most common type of pain people experience. It develops when the nociceptive nerve fibres are triggered by inflammation, chemicals, or physical events.

**Pain intensity** - the quality of the pain on a scale of 0 to 10.

**Pain severity** - state of the pain described as mild, medium, severe.

**Planimetry** - the measurement of plane surfaces. In this thesis it means measurement of chronic leg ulcer surface areas to track changes in their size.

**Primary dressing** - a dressing that is directly in contact with the wound bed.
**Pyoderma Gangrenosum** - an uncommon, ulcerative cutaneous condition of uncertain etiology often associated with systemic diseases.

**Secondary dressing** - a dressing that covers a primary dressing when the primary dressing does not protect the wound from contamination.

**Substance P** - compound thought to be involved in the synaptic transmission of pain and other nerve impulses. It is a polypeptide with eleven amino-acid residues.

**Venous ulcer** - a lower leg ulcer between the knee and the ankle caused by chronic venous insufficiency.
Acknowledgement of papers included in this thesis

Included in this thesis are three publications in Chapter 4 and one publication in the Appendices (Appendix 1), which are co-authored with my supervisors and another researcher. My contribution to each co-authored paper is outlined at the front of the relevant chapter. Appropriate acknowledgements of those who contributed to the research but did not qualify as authors are included in each paper.

The bibliographic details for these papers including all authors are:


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Student: Anne Purcell

Co-author of the papers and principal supervisor: Professor Andrea P. Marshall

Co-author of the papers and external supervisor: Associate Professor Tom Buckley

Co-author of the papers and external supervisor: Dr Jennie King

Co-author of the papers and associate supervisor: Professor Wendy Moyle
Dissemination of study results

Conference Presentations


Purcell, A., Buckley, T., King, J., Moyle, W., Marshall A.P. Central Coast Local Health District Nursing and Midwifery Research and Innovative Practice Conference. (2015) - The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers - a pilot randomised controlled trial. Gosford, NSW, 14th May.


Purcell, A., Buckley, T., King, J., Marshall, A.P. (2011). Northern Sydney Central Coast Health Service 2nd Nursing and Midwifery Research & Innovative Practice Conference. A randomised controlled trial to test the effectiveness, efficacy and tolerability of a eutectic mixture of local anaesthetic (EMLA®) 5% Cream as a primary dressing on painful lower leg ulcers – a pilot study - the journey continues - the practicality of clinical research. Gosford, NSW, 14th May.

Chapter 1 – Introduction

1.1 Introduction
Wounds that fail to heal are defined as chronic wounds and are an underlying epidemic affecting approximately 400,000 Australians (Queensland Government, AusHsi, Wound Innovations, & PHN Brisbane North, 2017). Chronic leg ulcers account for 16% of chronic wounds at the cost of over $AU1.5 billion annually. For adults with chronic leg ulcers, wound-related pain is reported to be the most prominent symptom. The impact of wound-related pain on an individual’s wound healing potential and physiological and psychosocial health-related quality of life (HRQoL) is considerable (Heinen, Van Achterberg, Scholte op Reimer, Van de Kerkhof, & de Laat, 2004; Herber, Schnepp, & Rieger, 2007; Hopman, Buchanan, VanDenKerkhof, & Harrison, 2013; Persoon et al., 2004; Price et al., 2008). Oral pharmacological analgesic agents including opioids are commonly prescribed to manage chronic leg ulcer pain. However, they are not always effective and have many side effects (Martel et al., 2015; Noble et al., 2010; Price et al., 2008). Topical application of analgesics or anaesthetics is a potential option when oral pharmacological agents are ineffective.

In this thesis, the daily topical application of the eutectic mixture of local anaesthetics 5% cream (EMLA®) as a primary dressing to painful chronic leg ulcers is examined as a potential pain-relieving strategy. In Chapter 1 an introduction to the study is provided which includes background information such as the definition, epidemiology and aetiology of chronic leg ulcers. A published clinical case study describing the use of EMLA® as a primary dressing on a painful chronic leg ulcer is provided as the impetus for this study. Further background information on the relationship between chronic leg ulcers, wound-related pain, wound healing and HRQoL is detailed. The research problem is identified and the significance of this study outlined. The chapter concludes with an overview of the structure of the thesis.
1.2 Background

1.2.1 Definition of a chronic leg ulcer

A chronic leg ulcer is defined as a lesion of the dermis, usually below the knee, which persists for six weeks or longer (Agale, 2013). The aetiology of chronic leg ulcers is varied. Most chronic leg ulcers are due to venous insufficiency (47.6%) with fewer being of mixed (venous and arterial) (17.6%) or arterial aetiology (14.5%). Other causes are responsible for 20.3% such as vasculitis, infection, neoplasia, calciphylaxis, pyoderma grangrenosum and drug-induced ulcers (Korber et al., 2011). With chronic leg ulcers there can be a complete loss of the epidermis, loss of some parts of the dermis, loss of subcutaneous fat and penetration into underlying anatomical structures (Frykberg & Banks, 2015). Chronic leg ulcers, as an example of a chronic wound, take longer to heal and are slower to respond to treatment compared to acute wounds (Frykberg & Banks, 2015).

1.2.2 Chronic leg ulcer epidemiology

The global prevalence and incidence of lower leg wounds, including chronic leg ulcers, varies between settings. In 2014, a comprehensive review of the prevalence and incidence of chronic wounds was reported with data from 69 studies used to estimate venous ulcer prevalence and incidence. Of these, eight reported a venous leg ulcer prevalence of 0.05-1.0% in the community and 2.5% in residential aged care (Graves & Zheng, 2014). While data on the prevalence of arterial ulcers was limited due to the scarcity of published studies (n = 3), two studies reported an overall prevalence of arterial ulcers in both hospital and community settings at 0.01%. One study reported an incidence of 0.02%-0.35% in the general population over one year (Graves & Zheng, 2014). The prevalence of chronic leg ulcers is higher in individuals with diabetes with estimates from 12 studies reporting prevalence of 0.02%-10% in the community setting and 1.2%-20.4% in the hospital setting (Graves & Zheng, 2014).

The rate of new venous or arterial ulcers in the general population over one year is the same (range: 0.02% to 0.35%) (Graves & Zheng, 2014). In the hospital setting the incidence of leg ulcers is twice as high (1.2% to 20%) as that reported for the community setting (0.02% to 10%) (Graves & Zheng,
2014). The incidence of diabetes-related ulcers is between 31.7% to 41% over a 1-year period in the community setting, which is much higher than for venous or arterial ulcers (Graves & Zheng, 2014). The incidence of venous leg ulcers is also higher in the older population (1.2 per 100) compared to the general population (18 per 100,000) (Graves & Zheng, 2014). The impact of case-mix, care quality, setting type or wound risk profile on reported variations in incidence and prevalence was not investigated, however, the range of the epidemiological estimates is likely wide enough to indicate the scale of the problem (Graves & Zheng, 2014).

1.2.3 A clinical experience with EMLA® as a strategy for managing chronic leg ulcer pain

The impetus for this study was a particular clinical case in 2008 that led to the use of EMLA® cream as a primary dressing, a dressing that is directly in contact with the wound bed (Purcell, Marshall, King, & Buckley, 2012). See Appendix 1 for the published case report which is the first to report the use of EMLA® for the ongoing management of chronic wound-related pain.

A 49-year-old woman with a 9-month history of an extremely painful right medial chronic venous leg ulcer presented to the Nurse Practitioner Wound Clinic for assessment and implementation of a wound management plan. She was debilitated, exhausted and emotional on arrival to the clinic as she continued to experience excruciating, unresolved wound-related pain from her leg ulcer. During clinical assessment, she described increasing difficulty with daily activities such as mobilisation, shopping, socialising, working and household tasks due to wound-related pain. She described her pain as sharp, shooting and burning with a Numerical Rating Scale (NRS) pain score of 9/10. For nine months her ability to sleep was considerably reduced because of wound-related pain.

Various analgesic agents including oral ibuprofen, paracetamol/codeine and oxycodone hydrochloride had been prescribed and were required daily but had little effect. Ineffective pain relief resulted in a painful wound and the inability to tolerate optimum wound management strategies such as compression therapy and a wound that failed to heal. Wound-related pain coupled with prescribed opiate analgesic medication dulled her cognitive and physical functioning. With most treatment
options exhausted, the topical application of EMLA® as a primary dressing was considered as an alternative treatment.

Topical application of EMLA® to the wound bed 30 to 60 minutes before debridement is usual practice (Aspen Pharmacare Canada Inc., 2017). Because conventional pain management strategies had been ineffective for this woman, EMLA® as a primary dressing was tested as a means to provide her with adequate pain relief. A measured dose of 1gm of EMLA® per 10cm² of wound surface area (the dose recommended for debridement (Aspen Pharmacare Canada Inc., 2017), was applied to the wound bed of the leg ulcer; a silicon foam was used as the secondary dressing. The dressing was left intact for 24 hours.

Within the first 24 hours, the women experienced a marked reduction in wound-related pain (from NRS 9/10 to 5/10), and she reported having her first full night sleep in nine months. The applications of EMLA® as a primary dressing continued daily. Within the first week, the opioid medication oxycodone hydrochloride was required only once a day and occasionally before the dressing change.

After two weeks, regular doses of slow-release oxycodone hydrochloride were no longer required and by week three her wound-related pain level was further reduced (NRS 3/10). She reported a significant improvement in her quality of life which she attributed to a reduction in wound-related pain and the need for opioid analgesia. She was able to walk normally, shop and socialise more frequently compared to the weeks before the EMLA® dressing was trialled. After four weeks compression therapy was able to be tolerated, the recommended first-line treatment for venous leg ulcers (Australian Wound Management Association Inc and New Zealand Wound Care Society, 2011).

Daily applications of EMLA® continued for 13 weeks and during this time there were no reports or clinical evidence of adverse events. Furthermore, there was no increase in exudate level, bacterial load or non-viable tissue on the wound bed. These results, together with compression therapy, resulted in significant improvement in wound healing time compared to the previous nine months. Wound healing
progressed over 13 weeks with the wound size reduced from 18.54 cm$^2$ to nearly complete healing (0.97 cm$^2$), as illustrated in Figures 1.1a, 1.1b, and 1.1c.

a) Pre-EMLA (18.54 cm$^2$)  
b) 1 week (11.44 cm$^2$)  
c) 12 weeks (0.97 cm$^2$)

![Wound Healing Progression]

Note: For privacy, the brown box beside the wound is covering a tattoo

**Figure 1.1** Wound healing progression over 13 weeks

Oral pain-relieving strategies for the patient’s severe chronic leg ulcer pain were ineffective and caused adverse side effects impacting her HRQoL. EMLA® used as a primary dressing brought relief which enabled optimal wound management strategies to be implemented thus positively impacting healing potential. However, this pain-relieving strategy requires further research evidence before it can be recommended with confidence.

The following sections in this chapter present evidence related to patient outcomes highlighted in the case report such as the relationship of chronic leg ulcers to wound-related pain, wound healing and HRQoL. The effectiveness of non-pharmacological and pharmacological pain-relieving strategies for chronic leg ulcer pain is also presented followed by the justification for investigating topical analgesic and anaesthetic agents for the management for chronic leg ulcer pain.

**1.3 The impact of chronic leg ulcers on patient-important outcomes**

Individuals with chronic leg ulcers can experience pain, delayed wound healing and poorer health-related quality of life (HRQoL). Pain is the most common symptom associated with a chronic leg ulcer with the prevalence of wound-related pain ranging from 69% (Domingues et al., 2016) to 87%
(Vandenkerkhof, Hopman, Carley, Kuhnke, & Harrison, 2013). The mean NRS pain score is reported to be 4.6 (NRS; range 0–10) (Heinen, Persoon, Van de Kerkhof, Otero, & Van Achterberg, 2007) where a score of equal to or greater than four is considered significant pain. Scores that are persistently four or greater can indicate uncontrolled wound-related pain (World Union of Wound Healing Societies, 2004).

People living with chronic leg ulceration may frequently experience moderate to severe wound-related pain which has been described as overwhelming, incessant and unrelenting particularly at rest, at night and at dressing change (Green, Jester, McKinley, & Pooler, 2014; Price et al., 2008; Upton, Solowiej, Hender, & Woodyatt, 2012). Strategies to manage wound-related pain can be ineffective. For example, data from an international, multisite survey of 1141 participants who took pain relief, suggested that approximately a fifth of participants found their pain management strategy ineffective. Over half (58%) expressed concern about long-term side-effects of pain medication (Price et al., 2008).

Poorly-controlled wound-related pain may contribute to the development of chronic stress. Higher pain intensity has been shown to be associated with higher levels of anxiety and stress (Upton et al., 2012; Woo, 2012). Stress can result in a range of physiological responses which can impact wound healing. These physiological changes include raised cortisol levels, increased blood pressure and cardiac output, reduced muscle mass, increased inflammatory function and decrease immune function (Upton & Solowiej, 2010). Furthermore, poorly controlled leg ulcer pain can prevent timely and effective wound management strategies being implemented thus promoting a suboptimal wound environment which may directly delay wound healing (Solowiej & Upton, 2010; Upton & Solowiej, 2010; Woo, 2008).

Chronic leg ulcers are debilitating and overwhelming. It is clear from the evidence that wound-related pain is the primary symptom perceived by individuals that suffer chronic leg ulcers. Pain and poor wound healing can negatively impact health-related quality of life (HRQoL) for individuals with chronic leg ulcers and living with a leg ulcer has been described as “a life of hell” (Lernevall, Fogh,
In a study reporting how a chronic leg ulcer affects an individual’s life, four themes emerged: 1) constant pain without the possibility of relief; 2) the eternal battle against the ulcer to survive; 3) the leg ulcer controls everyday life; and 4) a state between despair and hope, (Lernevall et al., 2017). Three systematic reviews including quantitative and qualitative studies explored the impact of leg ulceration on HRQoL and the authors categorised their findings into core domains: physical; occupational, social, psychological and the impact of leg ulcer treatment (Green et al., 2014; Herber et al., 2007; Persoon et al., 2004); the factors within each domain are detailed in Table 1.1. In Persoon et al’s., (2004) review, only half of the studies focused on venous leg ulcers whereas leg ulcer aetiology was not reported in the remaining studies. The majority of studies in Herber et al’s (2006) review focused on all ulcer types although numerous studies did not differentiate participants by leg ulcer aetiology. Green et al’s (2014) review built on the previous reviews and focused solely on venous leg ulcers. It is the first meta-analysis that clearly quantifies the considerable impact chronic leg ulcers have on individuals. Additionally, to determine the association between clinical and social variables, a large cross-sectional study of 758 participants showed that wound-related pain, social isolation and negative emotion were associated with leg ulcers greater than 10 cm² whereas sleep quality, energy, and mobility were not (Franks & Moffatt, 2006). Interaction of cognitive, emotional, personal, sensory and social responses may also influence pain perception, treatment adherence, wound healing and quality of life (Upton & Solowiej, 2010; Woo, 2012).
### Table 1.1 Chronic lower leg health-related quality of life domains and their content

(Green et al., 2014; Herber et al., 2007; Persoon et al., 2004)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physical</td>
<td>Pain, pruritis, exudate, malodour, mobility</td>
</tr>
<tr>
<td>2. Occupational</td>
<td>Job security, transportation, activities of daily living, personal hygiene</td>
</tr>
<tr>
<td>3. Socialisation</td>
<td>Isolation, disconnection</td>
</tr>
<tr>
<td>4. Psychological</td>
<td>Controlled by chronic leg ulcer, pessimism, depression, frustration, reduced confidence, loss of identity, uncleanliness, hopelessness, guilt, disappointment, anger, sadness</td>
</tr>
<tr>
<td>5. Impact of leg ulcer treatment</td>
<td>Wound-related pain caused by dressing type, removal or cleansing, compression therapy, dissatisfaction with treatment and progress, poor health resources, adherence, uninformed patients, expensive, time-consuming and exhausting</td>
</tr>
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</table>

Sub-optimum wound management including poor pain management can result in a continuous cycle of wound-related pain, wound chronicity and reduced HRQoL (illustrated in Figure 1.2). Innovative research to alleviate clinical factors such as pain could positively impact the negative consequences of lower leg ulcers.

**Figure 1.2** Relationship between chronic leg ulcers, wound-related pain, wound healing and HRQoL (Gouin & Kiecolt-Glaser, 2011; Walburn, Vedhara, Hankins, Rixon, & Weinman, 2009; Woo, 2012; Woo & Sibbald, 2008)
1.4 Wound-related pain

Wound-related pain has been identified as an important factor influencing both wound healing and HRQoL for individuals with chronic leg ulcers. Chronic leg ulcer pain is the response to noxious stimuli and tissue damage resulting in the direct excitation of the nociceptors in cutaneous free nerve terminals. This becomes the origin of pain perception making individuals with chronic leg ulcers susceptible to developing neuropathic pain (Woo & Sibbald, 2008). Within damaged peripheral tissue, noxious stimuli travel from peripheral nociceptors via primary afferent nerve fibres to the spinal cord where they terminate in the dorsal horn and synapse with second-order neurons which project to the higher centres of the brain (Bourne, Machado, & Nagel, 2014). Local injury produces an inflammatory cascade releasing pain-producing substances such as prostaglandins, bradykinin, substance P, potassium causing local vasodilation, oedema and release of other mediators resulting in a sensitising ‘soup’ that leads to peripheral sensitisation (Bourne et al., 2014). The physiological pathways of pain are presented in Figure 1.3.

![Figure 1.3 Physiological pathways of pain](image)
1.4.1 Causes of chronic leg ulcer wound-related pain

Understanding the underlying physiological or external cause of chronic leg ulcer pain can improve the design and targeting of effective wound-related pain-relieving strategies (van Hecke, Torrance, & Smith, 2013). There are four descriptors which illustrate the causes of wound-related pain that directly apply to chronic leg ulcers (Bechert & Abraham, 2009, p. 67; Swanson, 2014, p. 77):

- **Operative pain** results from the cutting or prolonged manipulation of tissue such as conservative sharp wound debridement the consequence which is a spontaneous, non-cyclic, inflammatory or neuropathic pain;

- **Incidental pain** caused by movement-related activities such as friction and shearing can create induced inflammatory or nociceptive incidental pain;

- **Background pain** caused by physiological events such as infection, ischaemia and acidosis can also lead to chronic inflammation and chronic pain with mixed characteristics;

- **Procedural pain** from routine interventions such as changing a dressing (including removal, cleaning and application) leads to induced cyclic inflammatory pain.

There are key factors associated with wound-related pain such as dressing change and wound type, size, and duration. For many individuals, the dressing change is considered “the worst part of living with a wound” with the wound itself the most common location for wound-related pain (Price et al., 2008). Procedural pain associated with dressing change is considered a primary cause of chronic leg ulcer pain. In a large, international, cross-sectional study of 2018 participants it was reported that over 14% experienced dressing-related pain most of the time and 17% experienced it all of the time.

Dressing-related pain could take 1-2 hours to subside for some participants (22%) but was longer for others with 10% of participants experiencing pain for 3-5 hours and 7.6% experiencing pain for more than five hours (Price et al., 2008). Another large international survey of 3918 nurses reported that
dressing removal generated the most wound-related pain and this was particularly the case for dried out, adherent dressings (Moffatt, Franks, & Hollinworth, 2002). While these two large studies highlight that dressing change is associated with significant pain for many patients, limitations for these surveys included: unvalidated questionnaires, the varied levels of expertise for data collectors and the meaning of the survey questions may have been open to interpretation during translation. Additionally, across nations and different cultures, survey design is affected due to limited access to quality sampling frames, the necessity to accommodate different languages, the availability of telecommunications and research infrastructure (Survey Research Center Institute for Social Research National Institute for Health, 2016).

The severity of the wound-related pain can have a major effect on wound care interventions such as choice of analgesia, the frequency of dressing changes and treatment setting. In a Delphi study of 21 expert clinicians to ascertain the effect of pain at dressing change, several other contributing factors that increased the pain experienced at dressing change were identified. These include infection, inappropriate dressing choice, peri-wound maceration, peri-wound contact dermatitis and a general deterioration in health status (Butcher & White, 2014). The findings of this study were based on expert opinion of clinicians which may not necessarily accurately reflect the experience of the person whose dressing was being changed. Since dressing removal and desiccated, adhered dressings cause the most severe wound-related pain (C. Bell & McCarthy, 2010; Moffatt et al., 2002) it is unsurprising that anticipatory pain before dressing removal and wound cleansing is significantly associated with increased anxiety levels (Woo, 2015).

Other contributing factors such as wound type, size and duration may also be associated with increased wound-related pain levels. Findings from a longitudinal study (n = 96) exploring the relationship between pain and venous, arterial and mixed chronic leg ulcers suggests that the size, location and leg ulcer aetiology have no effect on pain intensity although leg ulcers with a neuropathic component have higher daily pain scores compared to leg ulcers with no neuropathic signs and symptoms (Briggs,
Bennett, Closs, & Cocks, 2007). However, in this study, pain scores were only assessed over one day and leg ulcer type groups were not comparable in size at baseline. In an analytical cross-sectional study of 200 participants with either venous, arterial, pressure and diabetic ulcers, it was shown that 50% of individuals with arterial ulcers report higher pain scores compared to other leg ulcer types and also report their wound-related pain as the worst imaginable; 37.5% report moderate pain.

Furthermore, for individuals with venous ulcers, 17.9% report severe wound-related pain and 28.2% mild to moderate wound-related pain whereas 75% - 86% of participants with diabetic ulcers also experience wound-related pain despite having peripheral neuropathy. Limitations of this study were that formal diagnostic testing for accurate leg ulcer aetiology was lacking therefore accuracy of above data is questionable and secondary data was used thus data quality is uncertain.

The literature is inconclusive about the extent to which wound size influences wound-related pain. In a cross-sectional study of 758 individuals it was reported that wounds greater than 10cm² and of longer duration were associated with increased pain levels (Franks & Moffatt, 2006). However, in this study participants were examined at only one-time point irrespective of the stage of healing. Furthermore, the study may have reduced power due to the high floor effect in that the questionnaire used in the study to measure subjective health status, the Nottingham Health Profile, produces a high proportion of patients in perfect health despite having a chronic leg ulcer. In contrast, cross-sectional baseline assessment data from two randomized controlled trials with a combined sample size of 564 participants (Harrison et al., 2008; Harrison et al., 2011) was analysed and showed that neither size nor duration of the chronic leg ulcers were significantly associated with pain levels although there were trends for higher pain levels in smaller leg ulcers of shorter duration (Hopman et al., 2013).

There are other factors which can impact on wound-related pain. Findings from a systematic review showed that males complain more than women regarding pain associated with chronic leg ulcers, the highest pain intensity levels are reported by individuals with lower incomes and pain is influenced by time and season (Herber et al., 2007). Findings from a more recent study showed that being younger,
having arthritis and living with others are also associated with wound-related pain (Hopman et al., 2013). It has also been reported that chronic leg ulcer pain is statistically more likely to be associated with having a foot ulcer and shorter time with a wound care service (Nemeth, Harrison, Graham, & Burke, 2003). Psychosocial factors (culture, education, mental state) and environmental factors (timing of the procedure, setting, positioning of the individual, resources) can also influence the wound-related pain experience (Domingues et al., 2016).

1.4.2 Characteristics and types of wound-related pain

The characteristics of wound-related pain associated with venous leg ulcers are described as throbbing, burning, itchy, stinging, tender, aching, stabbing and sharp (Closs, Nelson, & Briggs, 2008). Descriptors for arterial leg ulcer pain can be sharp, stinging, burning and tender. For mixed leg ulcers throbbing, itchy, sore and tender are usually used (Closs et al., 2008).

The chronically inflamed state of a leg ulcer results in cellular and molecular dysfunction which may lead to several secondary mechanisms of wound-related pain (Cowin & Waters, 2014). The pain experience is affected by multiple and parallel interactive inhibitory and excitatory neural pathways including interactions with the immune, hormonal and body systems (Zouikr & Karshikoff, 2017). Secondary mechanisms of wound-related pain can be activated at the periphery and within the central nervous system causing allodynia, primary and secondary hyperalgesia and hyperpathia, all contributing to persistent, intense pain (Bourne et al., 2014; Voscopoulos & Lema, 2010). Pain perception and sensitisation leading to chronic pain are presented in Figure 1.4.
**Figure 1.4** Pain perception and sensitisation leading to chronic pain (Voscopoulos & Lema, 2010)

The path to chronic pain for individuals with chronic leg ulcers consists of three phases during which the properties of the pain type may change: phase 1 - chronic leg ulcer pain is predominantly nociceptive and if not managed effectively leads to phase 2 - persistent pain with nociceptive and neuropathic properties; if phase 2 is not managed effectively then pain leads to phase 3 - long-term refractory pain (Taverner, Closs, & Briggs, 2014). The journey from leg ulceration to the development of a chronic pain condition in older adults is presented in Figure 1.5.
### Painful Leg ulcer develops

**Phase 1**
- Acute pain
- Associated with stimuli from intervention and/or persistent pain;
- Pain reduced with appropriate acute pain management;
- Pain decreases with healing

**Phase 2**
- Recurring or non-healing leg ulcer leads to chronic pain;
- Pain predominantly nociceptive and may have neuropathic pain elements;
- Pain does not respond to acute pain management;
- Leg ulcer - healing stalled;
- Chronic pain develops - neuropathic and/or nociceptive

**Phase 3**
- Chronic state begins;
- Pain does not respond to acute pain management;
- Pain poorly managed which can lead to:
  - Insomnia;
  - Depression;
  - Suicidal ideation;
  - Pain at night;
  - Poor mobility;
  - Desire for leg amputation

### Factors exacerbating wound-related pain:
- Wound treatments;
- Inadequate pain management;
- Neuropathic pain not diagnosed;
- Insomnia;
- Hyperalgesia and allodynia;
- The older person is at greater risk of poor healing and recurrence, extended hyperalgesia and developing neuropathic pain, less likely to receive adequate analgesia and/or pain assessment and less likely to report pain.

**Figure 1.5** The journey from leg ulceration to the development of a chronic pain condition in older adults (Taverner et al., 2014)

Knowing the characteristics of wound-related pain associated with chronic leg ulcers coupled with an accurate diagnosis of pain type and secondary pain mechanisms will help with the selection of the most appropriate pain-relieving agents.

### 1.5 Management of wound-related pain

There are non-pharmacological and pharmacological approaches for reducing wound-related pain which are selected based on many patient and wound-related factors. These include the underlying cause of the pain; patient concerns; local factors such as ischaemia, infection, inflammation, moisture balance, exudate level, oedema, maceration of the surrounding skin and healing potential; wound-bed
preparation, wound-related pain at dressing change; dressing type and frequency of dressing change (Woo, Abbott, & Librach, 2013; Woo et al., 2008; World Union of Wound Healing Societies, 2007).

1.5.1 Non-pharmacological and pharmacological strategies to manage wound-related pain

Optimum wound management includes the use of non-pharmacological and pharmacological strategies to relieve wound-related pain associated with chronic leg ulcers (Butcher & White, 2014; Leppert, Malec-Milewska, Zajaczkowska, & Wordliczek, 2018; National Pain Summit Initiative, 2010; Woo et al., 2013; Woo et al., 2008; World Union of Wound Healing Societies, 2007). There are many non-pharmacological strategies used for the management of wound-related pain. These include communication, massage, hyperbaric oxygen, relaxation, hypnosis, acupuncture, laser therapy, electrical stimulation, and cognitive therapies. Drawing conclusions regarding the effectiveness and comparisons of these strategies on chronic non-cancer pain from meta-analyses and systematic reviews is difficult due to the wide variability of diagnostic criteria for different conditions, outcome measures, inclusion criteria, inconsistency of treatment methods and inclusion of participants from different countries and economic systems (Turk, Wilson, & Cahana, 2011). However, in general, the evidence suggests that non-pharmacological strategies to treat non-cancer chronic pain results in only a modest benefit at best and the evidence for long-term benefits is scarce (Dowell, Haegerich, & Chou, 2016; Turk et al., 2011). For wound-related pain specifically, the evidence is limited where there are only a few small studies with the evidence mostly based on expert opinion (Bechert & Abraham, 2009; Frenay, Faymonville, Devlieger, Albert, & Vanderkelen, 2001; Price et al., 2007; Tse, NG, & Chung, 2003; Woo et al., 2013; World Union of Wound Healing Societies, 2007). Even so, non-pharmacological strategies are still recommended when there is limited access to specialist pain management (Dowell et al., 2016).

Overall, effectiveness of non-pharmacological and pharmacological strategies to treat chronic pain are inconsistent and rather poor (Turk et al., 2011). Oral pharmacological treatments have been the mainstay for the treatment of chronic pain for centuries (Turk et al., 2011) and today are often
considered the preferred route of administration (Woo et al., 2013). The pharmacological strategies for the management of nociceptive and neuropathic wound-related pain include non-opiate, opiate, anxiotic and adjuvant therapies. Details are presented in Table 1.2.

Table 1.2 Pharmacological management of nociceptive and neuropathic wound-related pain

(Dworkin et al., 2010; Turk et al., 2011; Woo et al., 2013; World Union of Wound Healing Societies, 2007)

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Wound-related pain intensity</th>
<th>Pharmacological treatment</th>
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<tbody>
<tr>
<td>Nociceptive WRP</td>
<td>Mild WRP</td>
<td>Non-opiate</td>
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<tr>
<td></td>
<td></td>
<td>- acetylsalicylic acid</td>
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<td></td>
<td></td>
<td>- acetaminophen</td>
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<td></td>
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<td>- NSAIDs</td>
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<tr>
<td></td>
<td>Moderate WRP</td>
<td>Weak Opiate</td>
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<td></td>
<td></td>
<td>- Codeine</td>
</tr>
<tr>
<td></td>
<td>Severe WRP</td>
<td>Strong Opiate</td>
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<td>- Morphine</td>
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<td></td>
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<td>- Oxycodine</td>
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<td>- Hydromorphone</td>
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<td>Neuropathic WRP</td>
<td>Adjuvant therapies may be</td>
<td>indicated for neuropathic pain.</td>
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<tr>
<td></td>
<td>indicated for neuropathic</td>
<td>- Anti-depressants</td>
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<td></td>
<td>pain.</td>
<td>- Anti-convulsants</td>
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<td></td>
<td></td>
<td>- Topical anti-inflammatory</td>
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<td>- Topical local anaesthetic</td>
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<td>- Topical capsaicin</td>
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<td></td>
<td></td>
<td>Anxiotic agents</td>
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<td></td>
<td></td>
<td>Referral to a pain specialist</td>
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</tbody>
</table>

Abbreviations: WRP, wound-related pain; NSAID, non-steroidal anti-inflammatory drugs

Non-opioid pharmacological pain-relieving agents are effective and the preferred first-line treatment for chronic non-cancer pain, including chronic leg ulcer pain. An updated review of 18 systematic reviews and one meta-analysis by the Centre for Disease Control and Prevention, United States of America, found that non-opioid pharmacological treatments reduce potential harm and minimise the side effects when compared to opioid treatments (Dowell et al., 2016). Drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, anti-convulsive and anti-depressant drugs are
used successfully for chronic wound-related pain with or without opiates (Woo et al., 2013). However, non-opioid pharmacological pain-relieving strategies are not without significant side effects which include cardiovascular and gastrointestinal effects, toxicity, fatigue, dizziness, weakness and weight gain (Martel et al., 2015).

The severity and specific type of pain govern which agent to use for painful wounds (Woo et al., 2013). Non-opioid therapies with or without the addition of opioid agents are recommended for mild (NRS1-3/10) to moderate (NRS 4-6/10) wound-related pain. Strong oral opioid therapies such as morphine, hydromorphone and oxycodone are frequently prescribed for severe chronic nociceptive and neuropathic chronic leg ulcer pain (NRS > 6/10) that can be administered via different routes, with or without adjunct therapies (Woo et al., 2013). However, there is considerable debate globally about the benefits of opiates for chronic pain with the per capita consumption increasing and linked to increased morbidity and mortality (National Pain Summit Initiative, 2010; Von Korff, 2013). The prevalence of chronic non-cancer pain in individuals using opioids without a medical prescription was estimated in a meta-analysis of 18 systematic reviews to be approximately 48% to 60% which is higher than in general population samples (11% to 19%) (Voon, Karamouzi, & Kerr, 2017). Five of the included studies showed a wide variation of prescription opioids or other opioid use (0.05% - 81%) probably due to varying definitions of addiction. Publication bias was a limitation in this meta-analysis as was the varying eligibility criteria and outcome measures across reviews, the conclusion being that there is a serious deficit in high-quality evidence regarding prevalence, risk factors, assessment and treatment strategies regarding chronic pain and substance abuse (Voon et al., 2017).

Prescribing of opioids for painful chronic leg ulcers can be problematic. A systematic review which included data from 26 studies and 4893 participants who had been taking opioids via oral, transdermal or intrathecal administration for at least six months, reported that 10.3% of individuals treated with oral opioids long-term for chronic non-cancer pain were disappointed with the insufficient pain relief and subsequent adverse events (Noble et al., 2010). This study also showed that opioids could lead to
many adverse effects affecting gastrointestinal, respiratory, cardiovascular, central nervous system, musculoskeletal, endocrine, urological and immune systems (Noble et al., 2010). A review of 43 qualitative studies identified that long-term use of opioid therapy could lead to the development of similar adverse effects, addiction and misuse plus reduced quality of life and increased health care costs (Baldini, Von Korff, & Lin, 2012). Use of opioids for wound-related pain is also associated with a decrease in wound healing. In a longitudinal observational study of 450 participants with chronic wounds, those who received a mean opioid dose equal to or greater than 10mg were less likely to heal compared with patients who did not receive an opioid (Shanmugam, Couch, McNish, & Amdur, 2017). This study did not show causation, only that there was an association between opioid use and wound healing.

For many individuals, wound-related pain persists despite the use of conventional oral pharmacologic strategies including drugs listed in Table 1.2 (Price et al., 2008; Woo et al., 2013). It is apparent from the evidence above that there is a need to identify safe and effective wound-related pain management strategies and topical formulations may have a potential role in managing wound-related pain.

1.5.2 Topical drug delivery - advantages and mechanism of drug permeation through skin

Topical formulations are successful for the relief of moderate to severe chronic pain associated with arthritis, neuropathic and musculoskeletal conditions in addition to the successful reduction in concurrent pharmacological medication including opioids (Gudin et al., 2017; Gudin et al., 2018). Topical formulations can also play an important role in reducing wound-related pain (Briggs, Nelson, & Martyn-St James, 2012; Woo et al., 2013). The advantages associated with topical delivery of analgesic/anaesthetic drugs are that they are non-invasive; have greater acceptability; avoid gastrointestinal irritation; have targeted and sustained delivery; can be used regularly and consistently over time with no systemic accumulation; have fewer side effects; and, are convenient and affordable (Leppert et al., 2018; Pickering, Martin, Tiberghien, Delorme, & Mick, 2017; Singh, Mital, & Kaur, 2016).
Topical drugs applied to the skin or mucous membrane rely on passive diffusion leading to a moderately high concentration of the drug in the dermis and subcutaneous tissue creating a fast local effect while delivering only small amounts systemically (Singh et al., 2016). Delivery requires the drug to cross the stratum corneum (outer layer of the epidermis) to produce analgesia known as ‘targeted peripheral analgesia’ or ‘dampening’ of the pain mechanisms within the peripheral nervous system (Argoff, 2003) (Figure 1.6). The active ingredients in topical analgesic/anaesthetic applications separate, followed by diffusion through the external strata to the dermis which is highly dependent on the relative solubility of the active ingredients in the components of the delivery system and the stratum corneum (Azeem et al., 2009; Yaksh, Woller, Ramachandran, & Sorkin, 2015). In the clinical setting, topical local anaesthetic and analgesic agents are applied to intact skin, mucosa and also chronic leg ulcers to manage pain associated with wound debridement.

**Figure 1.6** Mechanism of drug permeation through the skin (Bhowmick & Sengodan, 2013).
1.5.3 Topical analgesia and painful chronic leg ulcers

Topical analgesic agents such as morphine, non-steroidal anti-inflammatory drugs, capsaicin, ketamine as well as tricyclic antidepressants have been used to treat chronic wound-related pain producing therapeutically effective drug concentrations for pain at a peripheral site of injury or inflammation without systemic adverse events (Argoff, 2013; Woo et al., 2013).

The discovery of opiate receptors on peripheral nerve terminals provided the theoretical base for the use of topically applied opioids such as morphine mixed with hydrogel as the carrier (Bastami, Frodin, Ahlner, & Uppugunduri, 2012; Briggs et al., 2012; Heilmann et al., 2013). Morphine produces analgesia both centrally and peripherally by working via local action on opioid receptors while keeping systemic concentrations low (Argoff, 2013; Peppin et al., 2015). Because morphine does not penetrate intact human skin well (Farley, 2011), the recommendation is that morphine only be applied to an open chronic wound. Morphine gel must be prescribed and is not commercially prepared which necessitates compounding of the product which reduces its accessibility. Following compounding, it is recommended that morphine gel is used immediately and not stored to avoid the risk of contamination. (Northamptonshire Heathcare, 2012). The often extended management of chronic leg ulcers and the logistics and storage issues of morphine gel especially in the community setting, may make use of this treatment impractical. Additionally, there is limited high quality research available to demonstrate the effectiveness of morphine gel in the management of pain associated with chronic leg ulcers.

The non-steroidal anti-inflammatory (NSAID) agent ibuprofen foam is another topical analgesic agent which has been used for the management of wound-related pain. To date there have been six RCTs conducted which demonstrate that ibuprofen foam is effective in treating nociceptive and chronic pain associated with chronic leg ulcers compared to placebo or standard care (Arapoglou et al., 2011; Domenech et al., 2008; Fogh et al., 2012; Gottrup et al., 2008; Romanelli, Dini, Polignano, Bonadeo, & Maggio, 2009; Sibbald, Coutts, Fierheller, & Woo, 2007). Its mechanism of action is related to anti-
inflammatory inhibition through prostaglandin synthesis although other mechanisms of action may be involved (Peppin et al., 2015).

There are other potential alternatives for the local management of wound-related pain such as topical amitriptyline, ketamine and capsaicin. However, there is little data to demonstrate efficacy particularly on chronic leg ulcers.

1.5.4 Topical local anaesthetics

In wound management, a number of different topical local anaesthetics (Table 1.3) have been used in the context of debridement of chronic leg ulcers (Aspen Pharmacare Canada Inc., 2017; Briggs et al., 2012).

Table 1.3 Topical local anaesthetics for wound-related pain (Australian Therapeutic Goods Administration, 2018)

<table>
<thead>
<tr>
<th>Anaesthetic Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eutectic mixture of local anaesthetics (EMLA® 5%) - Aspen Pharmacare, Australia Pty Ltd</td>
</tr>
<tr>
<td>Liposomal lidocaine cream 4% (LMX-4) - Orion Laboratories Pty Ltd, Perrigo, Australia</td>
</tr>
<tr>
<td>Lignocaine 2% gel - Pfizer (Perth) Pty Ltd</td>
</tr>
<tr>
<td>Lignocaine 5% dermal patch - Seqirus Pty Ltd Victoria, Australia</td>
</tr>
<tr>
<td>Lignocaine 10% spray - Aspen Pharmacare, Australia Pty Ltd</td>
</tr>
</tbody>
</table>

Local anaesthetics applied to the damaged skin can provide rapid pain-relief (Malamed, 2014) however, inflamed tissue such as in chronic leg ulcers may be more difficult to anaesthetise due to an acidic shift in pH, increased excitability of the nerves and increased vascularity (Lirk, Picardi, & Hollmann, 2014). At the site of administration topical anaesthetics reversibly block nerve conduction in a limited area by decreasing nerve cell membrane permeability to sodium ions in the dermis or mucosa creating a temporary loss of sensation (Figure 1.7) (Kumar, Chawla, & Goyal, 2015).

Local anaesthetics are divided into two groups: amides and esters. Amides have a prolonged action due to slow metabolism and are more stable than esters (Sobanko, Miller, & Alster, 2012) which have a
shorter action and fast metabolism (Malamed, 2014). In general, topical local anaesthetics have vasodilator properties and some formulations absorb rapidly, quickly reaching similar levels achieved by intravenous administration (Malamed, 2014). The onset of action is dependent on the site of application with mucosa and sites with stratum corneum having a faster onset of action (Kumar et al., 2015). The onset of action is also influenced by tissue vascularity, surface area and duration of application (Kumar et al., 2015), factors which should be considered when using local anaesthetics on chronic leg ulcers.

Figure 1.7 Mechanism of action of local anaesthetics (Edgcombe & Hocking, 2005).

In addition to relieving pain, local anaesthetics also have an anti-inflammatory effect. Although the inflammatory response to injury is fundamental for repair, excessive inflammation that occurs in chronic leg ulcers leads to the unwarranted generation of proinflammatory cytokine producing signals
which exacerbate tissue damage due to products derived from inflammatory cells (Zhao, Liang, Clarke, Jackson, & Xue, 2017). Application of local anaesthetics can modulate the inflammatory response and may prevent tissue damage (Cruz, Rocco, & Pelosi, 2017; Weinberg, Peake, Tan, & Nikfarjam, 2015).

Local anaesthetics can also suppress most bacteria if the concentration of the local anaesthetic is high enough. The precise antibacterial mechanism although unclear could be related to the interaction of the local anaesthetic with the cell wall (Cassuto, Sinclair, & Bonderovic, 2006). Local anaesthetics can inhibit the growth of numerous bacteria commonly associated with chronic leg ulcers such as \textit{Pseudomonas}, \textit{Staphylococcus}, \textit{Escherichia coli} and \textit{Streptococcus} (Cruz et al., 2017; Dowd et al., 2008; Johnson, Saint John, & Dine, 2008; Weinberg et al., 2015). Additionally, local anaesthetics also have antiviral and antifungal effects, for example, \textit{Herpes simplex} (HSV-1 and HSV-2) and \textit{Candida albicans} (Johnson et al., 2008; Weinberg et al., 2015).

Although topically applied, local anaesthetics can have some unwanted side effects. Local effects can include erythema, blanching oedema, stinging, rash, temperature alteration, skin sloughing, eschar formation, pruritus, petechiae and or purpuric reactions. However, these effects are generally temporary and mild (Shainhouse & Cunningham, 2004). Their effect on body systems is diverse including anti-nociceptive, anti-arrhythmic, antithrombotic effects as well as effects on the central nervous system although the danger is proportional to the concentration of the local anaesthetic in the circulation (Catteral & Mackie, 2011; Shainhouse & Cunningham, 2004).

The following section details evidence related to EMLA® and not the other topical local anaesthetic agents listed in Table 1.3. EMLA® is the agent used in the case report, is the most examined topical local anaesthetic agent used on chronic leg ulcers and the intervention for the present study.
1.5.5 Eutectic Mixture of Local Anaesthetics cream 5% (EMLA®)

EMLA®, an amide topical local anaesthetic cream released in Australia in 1991 and the United States of America in 1993, has been examined more than any other topical local anaesthetic or analgesic agent, is recommended for use on chronic leg ulcers and has a good safety profile. EMLA® is readily available over the counter and its primary use is on intact skin for procedures such as needle insertion or superficial surgical procedures.

For nearly three decades, EMLA® has been used on chronic leg ulcers to alleviate acute, operative pain associated with sharp debridement (Aspen Pharmacare Canada Inc., 2017). When used for debridement, the dose of EMLA® is 1 to 2g /10cm² up to a total of 10g then covered with an occlusive dressing to enhanced permeation into the tissues (Kumar et al., 2015; Sobanko et al., 2012). The recommended application time is 30 to 60 minutes to achieve sufficient anaesthesia before debridement (Aspen Pharmacare Canada Inc., 2017). In a systematic review of six RCTs (n = 343) examining topical agents for venous leg ulcers, a significant reduction in wound-related pain was reported when EMLA® was applied before wound debridement (Briggs et al., 2012).

The EMLA® formulation has a droplet anaesthetic concentration of lignocaine and prilocaine (80%) compared to lignocaine alone (20%). This clinically increases the active anaesthetic available to the sensory nerve (80%) while keeping the concentration low (5%) to reduce the chance of systemic toxicity (Juhlin, Hagglund, & Evers, 1989; Nykanen, Kissoon, Rieder, & Armstrong, 1991; Taverner et al., 2014).

EMLA® increases tissue perfusion (Arildsson, Nilsson, & Stromberg, 2000; Ashley, Quick, El-Behesey, & Bromley, 1999; Bjerring, Andersen, & Arendt-Nielsen, 1989; Hafner, Thomma, Eichner, Steins, & Junger, 2003; Hsieh et al., 2007; Wiles, Dobson, & Moppett, 2010). The highest rates of absorption are found in inflamed tissue (Tadicheria & Berman, 2006), an important consideration when applying EMLA® to a chronic leg ulcer which is in a constant state of non-resolving.
inflammation. The longer EMLA® is applied, the deeper the analgesia effect. For a 60-minute application time on the intact skin, the depth of the anaesthetic effect is 3mm; for 120 minutes the depth increases to 5mm (Bjerring & Arendt-Nielsen, 1990). Although systemic uptake is an important consideration with repeated and extended application in older adults, (Aspen Pharmacare Canada Inc., 2017), the evidence suggests that EMLA® is safe after repeated applications (2 to 10 g) to chronic leg ulcers (Effendy, Gelber, Lehmann, Huledal, & Lillieborg, 2015; Enander, Nilsen, & Lillieborg, 1990). In this context, accumulation of lignocaine or prilocaine or their metabolites in plasma levels was not demonstrated when applied for 30 to 45 minutes before debridement up to 15 repeated applications treatment (Lok et al., 1999). Furthermore, when applied for 24 hours (5 - 10 g) plasma levels of lignocaine and prilocaine were only one-fifth of those associated with toxicity (Stymne & Lillieborg, 2001).

1.6 Justification for investigating topical pain management strategies for chronic leg ulcer pain

There has been an ever-increasing consumption of oral and systemic opiates used to manage moderate to severe wound-related pain as well as prolonged consumption of NSAIDs and acetaminophen frequently used to treat mild pain (Arnstein, 2013). All of these treatments have systemic adverse side effects. Topical approaches may be a solution to reduce these challenges. Topical analgesic/anaesthetic treatments may also help reduce the risk of addiction, adverse events and drug interaction by avoiding the need for oral, parenteral or transdermal pain-relieving agents (Arnstein, 2013). The improved use of currently available topical anaesthetics and analgesics together with continued rigorous research will help to ensure that this method of medication delivery will reduce pain intensity and assist wound healing for individuals with significant chronic leg ulcer pain.

1.7 Research Problem

There is evidence that topical analgesic formulations are effective in reducing chronic leg ulcer pain particularly in the context of debridement (Briggs et al., 2012; Gethin, Cowman, & Kolbach, 2015).
However, there is limited evidence regarding the use of topical analgesics as a primary dressing and no evidence for the use of topical anaesthetics such as EMLA® as a primary dressing on chronic leg ulcers over an extended period. This highlights an important gap in our knowledge of pain management strategies for individuals with painful chronic leg ulcers.

1.8 Significance of the study
Current pain-relieving strategies for painful chronic leg ulcers are not always successful hence the need for new ways to manage wound-related pain either in combination with current strategies or separately. This study contributes to new evidence-based knowledge that can be used to inform further research and clinical practice. No prior study has explored the use of EMLA® as a primary dressing on painful chronic leg ulcers and this pilot study lays an essential foundation for future evaluation of the effectiveness of this novel therapy. EMLA® is accessible without prescription in Australia and is easily applied to a wound. If shown to have a positive impact on pain, EMLA® may be a promising strategy for managing painful chronic leg ulcers potentially empowering individuals to manage their own pain and be more independent of health services. The process and participant outcomes in this study can be used to inform a larger, multisite RCT ensuring a robust and feasible study that can inform clinical practice.

1.9 Structure of the thesis
Following the presentation of chapter 1 this thesis is divided into a further four chapters as follows:

In chapter 2 a systematic, comprehensive, critical appraisal and synthesis of the literature on the effectiveness of topical pharmacological treatments for painful chronic leg ulcers is provided including the methods used to conduct the review, presentation of the findings, discussion, identification of gaps in the literature and conclusion.

In Chapter 3 methodological details are provided including the specific research question and study aims. The methodological approach used was a pragmatic, pilot, parallel group, non-blinded, superior,
randomised, controlled trial conducted to primarily assess the feasibility of the study protocol to inform a larger multi-centre RCT.

In Chapter 4 the key findings, strengths, and limitations from this pilot RCT study are presented. Through the inclusion of three published peer-reviewed papers the results initially report feasibility outcomes relating to undertaking an RCT in a public community health service; secondly, the effect of the intervention on chronic leg ulcer pain intensity at dressing change and lastly, the effect of the intervention on chronic leg ulcer healing and participants’ HRQoL. Additional unpublished data is included after the published feasibility and pain manuscripts. Due to the inclusion of published papers, this chapter also includes the discussion for this thesis followed by the chapter conclusion.

In Chapter 5 an overview of the study methods and findings, recommendations for clinical practice and future research, in addition to conclusions of the study are presented.
Chapter 2 - Literature Review

2.1 Introduction

Pain associated with chronic leg ulcers is significant and can impact wound healing and health-related quality of life. Although current oral pain-relieving strategies are available, these are sometimes ineffective and consequently, chronic pain develops. Chronic pain may result in the high consumption of oral and systemic opiates and other pain-relieving strategies which can lead to misuse and the development of side effects, highlighting the need for alternative pain management strategies. Topical pain-relieving strategies may be a promising option for the management of chronic painful leg ulcers.

For this thesis, a review of the literature on the use of topical analgesics and local anaesthetics in the management of pain associated with chronic leg ulcers is reported and highlights the state of the science in this area. A systematic approach to identifying relevant literature was used and the literature critically appraised and synthesised.

2.1.2 Previous reviews

There have been two previous reviews (Briggs et al., 2012; Vanscheidt, Sadjadi, & Lillieborg, 2001) conducted on the use of topical agents and dressings for the management of pain associated with debridement of chronic leg ulcers. The first review by Vanscheidt et al., (2001) reported on data from 12 studies which evaluated the efficacy and tolerability of EMLA® for the management of wound-related pain before debridement. Four double-blind RCTs and one open RCT were included and suggested that a 30 to 45-minute application of EMLA® to the wound bed was effective pain management for sharp debridement. Post debridement analgesia lasted four hours and the timeframe for debridement was reduced if EMLA® was applied beforehand. Data from the studies included in this review also suggest that repeated application of EMLA® did not change the bacterial flora of the leg ulcer, rarely caused sensitisation and plasma levels remained within acceptable limits (Vanscheidt et al., 2001). Vanscheidt et al., (2001) included studies with methodologies other than RCTs such as
open, uncontrolled studies thus the methodological quality of included studies was less rigorous than the more recent updated systematic review by Briggs et al., (2012).

The study by Briggs et al., (Briggs et al., 2012) included eight studies where topical agents or dressings were used to manage wound-related pain associated with venous leg ulcers. Six studies were included in the earlier review by Vanscheidt et al. (2001). One unpublished study (Johnson & Repper, 1992) was also included. EMLA® was the intervention under investigation in six studies and slow-release topical ibuprofen foam was the intervention in two studies. All studies included in this review were RCTs although overall, methodology was poorly reported and sample sizes were small ranging from 43 - 110.

A meta-analysis by Briggs et al., (2012) demonstrated that there was a statistically significant reduction in operative pain when EMLA® was applied before debridement. Only one study investigating EMLA® reported healing outcomes showing no difference between study groups and three studies reported adverse events (burning and itching) with no significant difference between EMLA® or placebo creams. For the two studies investigating an ibuprofen foam dressing, their time frames and pain measures were too heterogeneous for data to be pooled. Results of the studies were conflicting with only one study showing a statistically significant reduction in pain for this patient group. One ibuprofen dressing study reported leg ulcer healing with no significant difference between groups and one study reported local adverse events such as infection, eczema, urticaria and blisters with no statistical difference between a dressing containing ibuprofen and a dressing without ibuprofen (Briggs et al., 2012). The release of ibuprofen was dependent on the presence of exudate therefore, its use for pain management where chronic leg ulcers have no or low exudate may not be appropriate (Briggs et al., 2012).

Even though the search strategy for this systematic review was comprehensive, publication bias may still be apparent. Additionally, five of the of the studies that reported leg ulcer size (all RCTs investigating EMLA®) excluded individuals with chronic leg ulcers greater than 50 cm² therefore, the
analgesic efficacy and effectiveness of EMLA® in larger chronic leg ulcers is unknown and requires further research.

The findings from these two reviews (Briggs et al., 2012; Vanscheidt et al., 2001) suggest that topical EMLA® may be useful for reducing acute pain in the context of leg ulcer debridement and ibuprofen is effective in reducing chronic leg ulcer pain. As suggested by Briggs et al. (2012), there is a considerable lack of data regarding the effect of topical pain-relieving agents on leg ulcer healing and long-term use causing them to recommend further research in this area.

Since the review by Briggs et al. (2012), the body of evidence for the use of topical analgesia and anaesthetics for the management of wound-related pain associated with chronic leg ulcers has continued to grow. The purpose of the review reported in this chapter is to assess whether topical anaesthetic or analgesics confer any benefit regarding wound-related pain for individuals with chronic leg ulcers.

2.2 Methods
The rigor of a review is dependent on the reliability and validity of the review process. A systematic approach, informed by the methods described by Pare and Kitsiou (Pare & Kitsiou, 2016), was used when undertaking this review to ensure relevant literature was identified. The rigor of this review is reflected in the transparency of the methodology and reliability of the approach used. The problem has been identified, the literature research process documented, data extracted and the literature critically appraised and synthesised (Pare & Kitsiou, 2016).

2.2.1 Problem identification
The clinical problems that guided the literature review are: (1) chronic leg ulcers are painful; (2) oral pharmacological strategies for the treatment of wound-related pain associated with chronic leg ulcers are not always effective; and, (3) topical agents and dressings may be useful in managing pain associated with chronic leg ulcers. These problems led to the following research question:
Are topical local anaesthetic and topical analgesic agents effective in reducing pain associated with chronic leg ulcers?

2.2.2 Literature search

An extensive search of the literature was conducted using the following electronic databases: Medical Literature Analysis and Retrieval System Online (Medline (Ovid), Excerpta Medica database (Embase, (Ovid), Cumulative Index of Nursing and Allied Health Literature (CINAHL, EBSCO), Joanna Briggs Institute (Ovid) and the Cochrane Library (Wiley). MeSH headings using four key concepts including chronic leg ulcers, topical anaesthetics, topical analgesics and pain was used to create a framework for identifying relevant search terms (Greenlee & Rice, 2013). MeSH terms and keywords are presented in Table 2.1.

Table 2.1 MeSH headings and keywords used for search strategy

<table>
<thead>
<tr>
<th>Chronic leg ulcers</th>
<th>Topical anaesthetics</th>
<th>Topical analgesics</th>
<th>Pain</th>
</tr>
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<tbody>
<tr>
<td>MeSH</td>
<td>MeSH</td>
<td>MeSH</td>
<td>MeSH</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>Anesthetics, Local</td>
<td>Analgesics, opioid Administration, Topical Analgesics</td>
<td></td>
</tr>
<tr>
<td>Varicose ulcer</td>
<td>Lidocaine</td>
<td>Anti-Inflammatory Agents, Non-Steroidal</td>
<td></td>
</tr>
<tr>
<td>Foot ulcer</td>
<td>Prilocaine Administration, Topical Analgesics</td>
<td></td>
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<tr>
<td></td>
<td>Administration, Topical Analgesics</td>
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<tr>
<td>Keywords</td>
<td>Keywords</td>
<td>Keywords</td>
<td>Keywords</td>
</tr>
<tr>
<td>Varicose ulcer$</td>
<td>Topical local an'esthetics</td>
<td>Morphine</td>
<td>Pain$</td>
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<td>Venous ulcer$</td>
<td>Lidocaine</td>
<td>Amitriptyline</td>
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<td>Leg ulcer$</td>
<td>Prilocaine</td>
<td>Capsaicin</td>
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<td>Foot ulcer$</td>
<td>EMLA</td>
<td>Ketamine</td>
<td></td>
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<tr>
<td>Stasis ulcer$</td>
<td>“Eutectic mixture local an'?esthetics”</td>
<td>NSAIDs</td>
<td></td>
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<tr>
<td>Arterial ulcer$</td>
<td></td>
<td>Non-steroidal anti-inflammatory$</td>
<td></td>
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<tr>
<td>Mixed ulcer$ Isch?emic Feet adj ulcer$</td>
<td>Topical anti-inflammatory$</td>
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</table>
The date of the search ranged from January 1990 to April 2018. This date range was chosen as EMLA® was first included in the Australian Register of Therapeutic Goods in August 1991 (Australian Government Department of Health Therapeutic Goods Administration, 2018) and topical opioids were first used in the early 1990s (Weinberg et al., 2015). To ensure that relevant literature had not been missed in the electronic search, hand-searching of international consensus documents and position statements relating to wound management and their reference lists was conducted.

Inclusion criteria

The inclusion criteria for the review were:

- Studies investigating commonly used topical local anaesthetics lignocaine or prilocaine and topical analgesic agents such as ketamine, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, tricyclic antidepressants (amitriptyline) or capsaicin on participants with chronic leg ulcers;
- Wound-related pain associated with chronic leg ulcers as a primary or secondary outcome;
- Studies where the topical local anaesthetic or topical analgesic agent was the intervention or the control;
- Studies where at least one third of participants had chronic leg ulcers;
- Studies published in the English language;
- Peer-reviewed published studies;
- Human, adult studies.

Exclusion criteria

- Case series and case reports were excluded;
- Tetracaine 0.5%, adrenaline 0.05%, cocaine 11.8% (TEC) and lignocaine, epinephrine 0.1%, tetracaine 0.1% (LET) also provide anaesthesia to non-intact skin. However, they
are not eutectic mixtures and are not approved for use in Australia by TGA (Australian Therapeutic Goods Administration, 2018; Kumar et al., 2015) therefore, studies reporting evaluation of these products were not included.

2.2.3 Search outcomes

Fifty-three additional articles on the use of topical analgesic and local anaesthetic agents to manage pain associated with chronic leg ulcers were identified within the published literature that were not included in Briggs et al.’s (2012) systematic review. The literature search identified a total of 331 articles from data-bases and other sources including hand searching. The number of articles identified in each data base was: Medline 66, Embase 40, CINAHL 31, Joanna Briggs Institute 3, Cochrane 4, PubMed 171. Hand searching of international consensus documents and position statements identified an additional 16 articles. After removing duplicates (n = 123), articles were screened by title and abstract; 148 articles were excluded. The full texts of five studies (Johns, 1999; Johnson & Repper, 1992; Larsson-Stymne, Rostein, & Widman, 1990; Slawson, 1999; Wanger, Eriksson, & Karlsson, 1990) were not able to be obtained despite repeated attempts and were therefore not included. A total of 55 articles were assessed against the inclusion and exclusion criteria, 22 articles were included in the full-text review. A flow diagram of this process is presented in Figure 2.1.
Records identified through individual database searching; (n = 315)  
Additional records identified through other sources including hand searching; (n = 16)  
Records screened after duplicates removed for relevance by title and/or abstract; (n = 208)  
Records excluded by title and abstract (not relevant); (n = 148)  
Full-text papers; (n =60)  
Unable to obtain full text of article; (n = 5)  
Full-text articles assessed for eligibility; (n = 55)  
Full-text articles excluded (n = 33)  
Reasons:  
- Not chronic leg ulcers (n = 5);  
- Not topical analgesics or anaesthetics (n = 2);  
- Reviews (n = 11);  
- Pain not reported (n =6);  
- Case reports (n = 8);  
- Other (n=1)  
Studies included in review (n =22)  

Figure 2.1 Prisma flow diagram of search outcomes

2.2.4 Data extraction and quality appraisal

Studies that met the inclusion criteria were classified into two major categories: (1) topical analgesics (Table 2.2) and (2) topical local anaesthetics (Table 2.3). Data from relevant papers were extracted by one researcher using data extraction sheets which contained the following items: date, authors, study aim, design, setting, sample size, intervention, and main findings. Data extraction and quality appraisal of the selected studies that met the inclusion criteria was undertaken by the candidate with the results reviewed and discussed with the thesis supervisors.
Assessment of the quality of the included articles was guided by the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist for the included RCTs (Schulz, Altman, Moher, & Group, 2010), Critical Appraisal Skills Programme (CASP) checklists (Critical Appraisal Skills Programme UK, 2018) and the wound component of the Cochrane Risk of Bias Tool (Cochrane Wounds, 2011). These tools were developed after some of the papers included in this review had been published, however, the same criteria were used in assessment regardless of year of publication.

2.3 Results

Twenty-two articles were identified which met the inclusion criteria (Table 2.2 and 2.3). Of the 22 included articles, there were 18 RCTs, one quasi-experimental study, two cross-over studies and one retrospective, observational medical record review. One article (Romanelli et al., 2009) reported a sub-analysis from a previous study. Topical analgesics were evaluated and reported in 10 articles; ibuprofen foam was the intervention in seven articles and morphine gel was evaluated and reported in three articles.

Local anaesthetics were the interventions used in 12 studies. Two RCTs (Enander et al., 1990; Holm, Andren, & Gafford, 1990) included data from small observational studies. One investigated plasma concentrations over four hours following EMLA® application (Enander et al., 1990) and the other investigated pain reduction over the 30 minutes following EMLA® application (Holm et al., 1990). The majority of studies (n = 20) were conducted in Europe, most commonly in Sweden (n = 5). Since the systematic review by Briggs et al. in 2012 only three additional studies investigating local anaesthetics were identified (Cuomo et al., 2014; Effendy et al., 2015; Traber et al., 2016) that met the inclusion criteria. Only one was an RCT (Cuomo et al., 2014). Outcome measurement time-points ranged from 10 minutes to 3 weeks. Current research relating to topical local anaesthetic or analgesic agents for painful chronic leg ulcers was limited with the majority of the included literature more than five years old (86%).
2.3.1 Category 1 - Topical analgesic agents

Of the 10 studies evaluating topical analgesia only two topical analgesic agents were used as primary dressings to manage chronic leg ulcer pain; seven studies used ibuprofen foam and three used morphine gel as the interventional agent (Table 2.2).

For all studies investigating topical analgesic agents, pain was the primary outcome measure and a variety of pain assessment tools were used to assess pain including the numerical rating scale, visual analogue scale, visual rating scale and numerical box scale. Venous leg ulcers were the predominant ulcer type and the surface areas of leg ulcers were less than 54 cm$^2$. Wound size was reflected in the inclusion criteria in all studies except for one (Jorgensen, Friis, & Gottrup, 2006).

In six of the studies investigating ibuprofen foam there was a statistically significant reduction in wound-related pain when compared to a placebo or standard care; the remaining study showed a reduction in wound-related pain compared to standard care. Ibuprofen foam as a primary dressing can remain in place for up to a week depending on the level of exudate. It is designed for acute and chronic wounds and slowly releases ibuprofen when it comes in contact with exudate (Jorgensen et al., 2006). The dose of ibuprofen was the same for all studies (0.5mg/cm$^2$ =112.5mg) although one study did not report the dose (Romanelli et al., 2009). Half of the studies compared ibuprofen foam with a placebo and the other half with standard care. Although half of the studies in this review had large sample sizes (120-835) some had fewer than 25 participants (Jorgensen et al., 2006; Sibbald et al., 2007). These small studies were not powered to show a difference likely contributing to Type II error. Only four of the studies investigating ibuprofen reported an a priori sample size calculation (Domenech et al., 2008; Fogh et al., 2012; Gottrup et al., 2008; Romanelli et al., 2009). In general, the reporting of methodology was poor in that some or all-important methodological elements such as method of randomisation, allocation concealment, loss-to-follow-up, intention to treat analysis, blinding and baseline comparability were not included (Table 2.4). The study by Gottrup et al. (2008) was the only study that reported methodology appropriately.
Over 70% of studies in the ibuprofen group reported adverse events (Domenech et al., 2008; Fogh et al., 2012; Gottrup et al., 2008; Jorgensen et al., 2006; Romanelli et al., 2009) which related specifically to ibuprofen foam as the interventional agent. These adverse events included local reactions such as infection, eczema, blisters, increased pain and wound size, erythema, bleeding and peri-ulcer deterioration. In one study, no adverse events relating to ibuprofen foam were reported during the study period (Sibbald et al., 2007).

It is unclear whether morphine gel is effective in reducing pain associated with venous, arterial or mixed leg ulcers when applied topically due to the small sample sizes in all studies therefore a Type II error may exist. Morphine gel (morphine sulphate injection mixed with a hydrogel) is usually applied daily to painful chronic or palliative wounds for the relief of pain (Northamptonshire Heathcare, 2012; Shanmugam et al., 2017) although twice daily is often required (Jansen et al., 2009). All studies investigating morphine gel used a placebo gel as the comparator (Bastami et al., 2012; Jansen et al., 2009; Vernassiere et al., 2005). A range of doses were reported including 0.5mg/cm², 10mg and 0.5%/gm. All studies had fewer than 25 participants (Table 2.2) where Type II error was likely. None reported undertaking a sample size calculation a priori. The reporting of methodology was poor for all morphine gel studies in that some or all-important methodological elements were not included (Table 2.4).

All three studies in the morphine gel group reported adverse events associated with application of the morphine gel (Bastami et al., 2012; Jansen et al., 2009; Vernassiere et al., 2005). Local adverse reactions included itching, burning pain, stinging, eczema, ineffective pain relief and infection. Systemic adverse reactions were dizziness, nausea, vomiting and drowsiness.
### Table 2.2 Topical analgesic agents for painful chronic leg ulcers - characteristics of included articles

<table>
<thead>
<tr>
<th>Article</th>
<th>Study aim</th>
<th>Design</th>
<th>Sample, Setting and Ulcer type</th>
<th>Primary and Secondary outcomes</th>
<th>Intervention, Dose and Follow-up</th>
<th>Main findings (Pain only)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ibuprofen foam</strong></td>
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<tr>
<td>Fogh et al., 2012; Denmark, France, Germany and Spain</td>
<td>To investigate the pain-relieving effectiveness of an ibuprofen foam dressing on painful CLUs</td>
<td>A multi-centre, double-blind RCT</td>
<td>n = 120; Hospitals, wound clinics and community setting; CLU type: venous</td>
<td>Primary outcome: pain as measured with the NRS; Secondary outcomes: healing rates, peri-ulcer condition, local and adverse reactions</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) Dose: 0.5 mg/cm² of ibuprofen (112.5 mg); versus (C) Placebo foam without ibuprofen; Follow-up: 5 days</td>
<td>Pain relief was significantly greater in the intervention group ($p = 0.04$)</td>
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<tr>
<td><em>Arapoglou et al., 2011; Europe</em></td>
<td>To examine if wound aetiology affects the pain-relieving properties of an ibuprofen-releasing foam</td>
<td>A secondary analysis of data from a multicentre, parallel group RCT</td>
<td>n = 688; 12 countries, 184 centres in inpatient and outpatient departments; CLU type: venous</td>
<td>Primary outcome: pain as measured with the NRS and 5-point scale (relief); Secondary outcome: None</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) Dose: 0.5 mg/cm² of ibuprofen (112.5 mg); versus</td>
<td>Statistically significant improvement in pain relief in all wound aetiology subgroups</td>
</tr>
<tr>
<td>Study Authors, Year, Country</td>
<td>Objective</td>
<td>Design</td>
<td>Sample Size</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Dose</td>
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<tr>
<td>Romanelli et al., 2009, Italy</td>
<td>To compare the effect of an ibuprofen foam dressing with local best practice on painful CLUs</td>
<td>A sub-analysis of a multicentre, open, comparative, parallel-group RCT</td>
<td>n = 185; 34 outpatient clinics; CLU type: Venous, arterial, mixed, vasculitis</td>
<td>Primary outcome: pain as measured with the NRS and VAS; Secondary outcomes: QOL, safety</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) vs. (C) standard care; Dose: NR</td>
<td>Follow-up: 1 to 7 days; 2nd daily dressings</td>
</tr>
<tr>
<td>Domenech et al., 2008, Europe</td>
<td>To compare an ibuprofen-releasing foam dressing with local best practice for painful exuding wounds</td>
<td>Multicentre, comparative, parallel group RCT</td>
<td>n = 853; 12 countries, 184 centres in inpatient and outpatient departments; CLU type: venous, arterial, mixed and diabetic</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: QOL, local and adverse reactions, oral medications, exudate, healing rates, peri-wound condition</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) Dose: 0.5 mg/cm^2 of ibuprofen (112.5 mg); versus (C) standard care; Follow-up: 7 ± 2 treatment days</td>
<td>Total pain relief scores were significantly in favour of the treatment group (p &lt; 0.0001); Mean pain intensity decreased over time in both groups; the reduction was significantly greater in the treatment group</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>N</td>
<td>Outcome</td>
<td>Comparator</td>
<td>Findings</td>
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<tr>
<td>Gottrup et al., 2008; 13 EU countries</td>
<td>To compare the performance and safety of an ibuprofen foam with foam without ibuprofen on painful CLUs</td>
<td>Multi-centre, double-blind, parallel-group RCT</td>
<td>122</td>
<td>Primary outcome: pain as measured with the VRS and NBS; Secondary outcomes: QOL, local and adverse reactions</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) Dose: 0.5 mg/cm² of ibuprofen (112.5 vs. (C) Placebo foam without ibuprofen; Follow-up: 1-5 days</td>
<td>A statistically significant and sustained improvement in pain relief ($p &lt; 0.05$) and pain intensity ($p &lt; 0.001$) in the ibuprofen foam group across the five-day period with a quick onset of action</td>
</tr>
<tr>
<td>Sibbald et al., 2007; Canada</td>
<td>To evaluate a continuous low-level release of ibuprofen foam dressing on painful exuding CLUs</td>
<td>An open comparative and prospective, block-randomised study</td>
<td>24</td>
<td>Primary outcome: pain as measured with the VAS and NBS; Secondary outcomes: healing rates, peri-wound condition; Non-viable tissue</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) Dose: 0.5 mg/cm² of ibuprofen (112.5 vs. (C) standard care; Follow-up: 1 week</td>
<td>Ibuprofen-foam dressing decreased acute and chronic wound pain significantly compared to standard care: Acute pain: $p = 0.0405$; Chronic pain: $p = 0.0217$</td>
</tr>
<tr>
<td>Study Authors &amp; Year</td>
<td>Description</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Follow-up</td>
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<tr>
<td>Jorgensen et al., 2006; Denmark</td>
<td>To test pain reduction, safety and efficacy of Biatain® Ibu non-adhesive on painful CLUs</td>
<td>A single-blinded crossover study</td>
<td>n = 10 + 2; A wound-healing outpatient centre; CLU type: venous</td>
<td>Primary outcome: pain as measured with the VRS and NBS; Secondary outcomes: Safety, local and adverse reactions</td>
<td>(I) A foam dressing 15 x 15 (ibuprofen foam) vs. (C) A foam without ibuprofen; Dose: 0.5 mg/cm² of ibuprofen (112.5 mg) 2nd to 3rd daily; Follow-up: 3 weeks</td>
<td>Pain levels were significantly better during the Biatain® Ibu treatment phase than treatment with Biatain® before and after Biatain treatment phase ($p \leq 0.0001; p = \leq 0.005$)</td>
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<tr>
<td>Bastami et al., 2012; Sweden</td>
<td>To evaluate the analgesic effect of topically applied morphine on painful CLUs</td>
<td>Single centre, double-blind, placebo-controlled, crossover, pilot RCT</td>
<td>n = 21; A dermatology department and primary care centres; CLU type: venous; 2 CLUs not defined</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: local and adverse reactions</td>
<td>(I) Morphine gel Dose: Morphine 0.5mg/cm², for CLUs less than 1 cm² – 1-3mg/ml; vs. (C) Placebo gel – same ingredients without morphine; Follow-up: Participants treated</td>
<td>No difference in pain between groups ($p=0.172$)</td>
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<tr>
<td>Study Source</td>
<td>Objective</td>
<td>Designation</td>
<td>Participants</td>
<td>Outcomes</td>
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<tr>
<td>Jansen et al., 2009;</td>
<td>To assess whether topical morphine is effective in relieving pain from</td>
<td>Double-blind, placebo-controlled</td>
<td>n = 10;</td>
<td>Primary outcome: pain as measured with the NRS; Secondary outcomes: local and adverse reactions</td>
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<tr>
<td>Netherlands</td>
<td>arterial CLUs due to arterial insufficiency and whether this effect is</td>
<td>three-way crossover, pilot RCT</td>
<td>Two dermatology outpatient departments; CLU type: arterial</td>
<td>Three double-blind treatments: Morphine gel vs. morphine s/c infusion and placebo gel</td>
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<td>is centrally or peripherally mediated</td>
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<td>(I) Morphine Dose: 0.5% 1g in hydrogel, 1g equals 1 ml; placebo gel (hydrogel without morphine) plus morphine 5mg subcutaneous infusion;</td>
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<td>2) (C) Placebo gel plus a subcutaneous infusion of</td>
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<td>No pain relief for participants with arterial CLUs</td>
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<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Sample Size</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Findings</td>
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<tr>
<td>Vernassiere et al., 2005; France</td>
<td>To assess the efficacy of the topical application of morphine on painful CLUs</td>
<td>Prospective bi-centre, controlled, double-blind RCT</td>
<td>n = 24; Two dermatology outpatient departments; CLU type: venous, arterial and mixed</td>
<td>(I) Morphine gel Dose: 10mg Morphine/gel; vs. (C) Placebo (Intrasite gel); Follow-up: daily for five days before, immediately after, 1 h and 12 h after application</td>
<td>(C) Placebo gel plus an s/c placebo infusion; Follow-up: Each treatment for one day over three days</td>
<td>No statistical significance regarding the efficacy of topical morphine relating to pain (no statistical analysis provided)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLUs, chronic leg ulcers; RCT, randomised controlled trial; VAS, visual analogue scale; VRS, verbal rating scale; NRS, numerical rating scale; NBS, Numerical box scale; NR, not reported; QOL, quality of life; mg, milligrams; g, grams; h, hours; min, minutes; s/c, subcutaneous; ml, millilitres.

**Note:** *Arapoglou et al., (2011) is a secondary analysis of a previous study by Domenech et al., (2008).*
2.3.2 Category 2 - Topical local anaesthetic agents

All 12 studies in this category investigated lignocaine/prilocaine (EMLA® 5%) cream in the context of debridement of chronic leg ulcers (Table 2.3). Pain was the primary outcome in all but two studies (Effendy et al., 2015; Lok et al., 1999) and the visual analogue scale was the predominant pain assessment tool used. The findings in this group suggest that EMLA® was effective in reducing wound-related pain associated with debridement of chronic leg ulcers in all but two studies (Cuomo et al., 2014; Enander et al., 1990) although the methodological reporting of all studies was poor.

Venous leg ulcers were again the predominant leg ulcer type included in this group. The surface areas of each chronic leg ulcer in the majority of these studies were less than 50 cm² (83%).

Nine studies compared EMLA® 5% with either a topical placebo (Agrifoglio et al., 2000; Holm et al., 1990; Lok et al., 1999; Rosenthal et al., 2001), lignocaine 10% spray (Cuomo et al., 2014), EMLA® 2% (Enander et al., 1990) or nitrous oxide-oxygen mixture inhalation (Claeys et al., 2011; Traber et al., 2016); the comparator in one study was unknown (Hansson, Holm, Lillieborg, & Syren, 1993). One retrospective, observational study (Blanke & Hallern, 2003) evaluated the effectiveness of EMLA® 5% in a sample of 1084 participants with a variety of wound types including chronic leg ulcers. The number of applications of EMLA® ranged from 1 to 15. Most studies applied EMLA® 30 minutes prior to debridement. Two studies extended the application time of EMLA® to 45 minutes (Agrifoglio et al., 2000; Lok et al., 1999) and two studies to 60 minutes (Blanke & Hallern, 2003; Holst & Kristofferson, 1998). One study only applied EMLA® for 10 minutes (Cuomo et al., 2014). The maximum dose of EMLA® was 10g in 67% of studies (Agrifoglio et al., 2000; Claeys et al., 2011; Effendy et al., 2015; Enander et al., 1990; Holm et al., 1990; Holst & Kristofferson, 1998; Lok et al., 1999; Rosenthal et al., 2001). In the medical record review conducted by Blanke and Hallern (2003), some participants received up to 150g of EMLA® topically. Findings from three studies measuring plasma concentrations of lignocaine and prilocaine in EMLA® 5% and EMLA® 2% following application to chronic leg ulcers indicate that toxic levels are not reached after repeated
applications for debridement (Effendy et al., 2015; Enander et al., 1990; Holm et al., 1990). In the study by Enander et al., (1990), plasma concentrations were higher for individuals with arterial leg ulcers compared to venous leg ulcers, however, this finding is not supported by the more recent study by Effendy et al., (2015) where it was indicated that ulcer type does not have any impact on plasma concentrations although leg ulcer size does have a significant impact.

There were no major adverse reactions to EMLA® reported. More than half the studies reported adverse reactions which were largely local skin reactions such as burning, pallor, erythema, itching, stinging and oedema (Blanke & Hallern, 2003; Claeys et al., 2011; Enander et al., 1990; Hansson et al., 1993; Holm et al., 1990; Lok et al., 1999; Rosenthal et al., 2001).

In the majority of studies, the sample sizes were small (range: 10 to 110) and there were fewer than 70 participants in eight out of 12 studies in this group. A statistically significant reduction in pain during debridement was observed in all but two studies (Cuomo et al., 2014; Enander et al., 1990) possibly because of the small sample sizes contributing to Type II error. Only two studies reported undertaking a sample size calculation a priori (Agrifoglio et al., 2000; Claeys et al., 2011).
### Table 2.3 Topical local anaesthetic agents for painful chronic leg ulcers - characteristics of included articles

<table>
<thead>
<tr>
<th>Article</th>
<th>Study aim</th>
<th>Design</th>
<th>Sample, Setting and Ulcer type</th>
<th>Primary and Secondary outcomes</th>
<th>Intervention, Dose and Follow-up</th>
<th>Main findings (Pain only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traber et al., 2016; Switzerland</td>
<td>To compare the analgesic efficacy of 50% N₂O/O₂ with lidocaine/prilocaine (EMLA®) in CLU debridement</td>
<td>A prospective, controlled, single-center, crossover design study</td>
<td>n = 21; A specialist vein clinic outpatient unit; CLU type: venous, foot ulcers</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: pain after debridement, Duration of treatment sessions</td>
<td>EMLA®&lt;sup&gt;®&lt;/sup&gt; Dose: NR dose for 30 min vs. 50% N₂O/O₂ Dose: on demand; For both groups, debridement after 3 min and sustained until final dressing; Follow-up: Four debridement sessions per participant</td>
<td>EMLA® was more effective for reducing pain during sharp debridement of CLUs compared to inhaled 50% N₂O/O₂ gas premix in chronic leg ulcer debridement (p = 0.001)</td>
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<tr>
<td>Effendy et al., 2015; Europe</td>
<td>To determine plasma concentrations and analgesia efficacy for EMLA® on CLUs following repeated application for debridement</td>
<td>Quasi-experimental study</td>
<td>n = 25 (2 participants not debrided; Five outpatient departments; CLU type - venous, mixed, vasculitic</td>
<td>Primary outcome: plasma concentrations; Secondary outcome: pain as measured with the VAS</td>
<td>Leg ulcer size at least 50 cm²; EMLA® cream Dose: 10g daily; Plasma concentrations: blood samples were drawn 30, 60, 80, 100, 120, 140, 160, 180 and 240 min after first and last application and immediately</td>
<td>Plasma concentrations: were similar on days 1 and 10 for lidocaine, prilocaine and for the sum of both local anaesthetics; The size of the ulcer had a significant effect on peak values (p = &lt;0.01);</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
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<td>Cuomo et al., 2014; Italy</td>
<td>RCT</td>
<td>n = 50;</td>
<td>Pain: was significantly lower before the start of the application on days 2, 4, 6 and 8; Pain: NR</td>
<td>Follow-up: 10 days</td>
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<td>Setting NR;</td>
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<td>venous</td>
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<td>Claesys et al., 2011; France</td>
<td>A multicentre, prospective open-label pilot RCT</td>
<td>n = 41;</td>
<td>Pain: NR dose applied for 10 min vs. Topical lignocaine 10% spray</td>
<td>Lignocaine 10% spray has a more immediate anaesthetic although the effect is superficial;</td>
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<td>Setting NR;</td>
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<td></td>
<td>venous, arterial, mixed</td>
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<tr>
<td>Blanke et al.,</td>
<td>Retrospective</td>
<td>n =1084 -</td>
<td>Chronic leg ulcers size ranged</td>
<td>For all participants except</td>
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<tr>
<td>Year</td>
<td>Country</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Participants</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
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<tr>
<td>2003; Germany</td>
<td>Analgesic effectiveness, safety, tolerability of EMLA® on a variety of wound types including CLUs when used for sharp debridement</td>
<td>Observational study</td>
<td>(including CLUs and diabetic ulcers n =360); CLUs, diabetic ulcers, decubitus ulcers, abscess revisions, anal and coccyx fistulae, postoperative wounds, burns</td>
<td>Pain. Type of pain measure -NR. Secondary outcomes: adverse effects, dose, duration of application</td>
<td>Between 5 - 360 cm²; Dose: 3 - 150g per application; Duration of application: 45 - 60 min; Follow-up: a median of 3 repeated debridement for each participant</td>
<td>Three (arterial CLUs), analgesia was adequate for debridement; Premature removal of EMLA® was not required on any patient</td>
</tr>
<tr>
<td>Rosenthal et al., 2001; Canada</td>
<td>To assess and compare pain intensity during debridement after different application times with EMLA® before debridement of CLUs</td>
<td>Multi-centred, double-blind, placebo-controlled, parallel RCT</td>
<td>n = 101; Four outpatient dermatology centres; CLU type: venous, arterial, mixed</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: local and adverse reactions</td>
<td>(I) EMLA® cream vs. (C) Placebo cream</td>
<td>Dose for (I) and (C): approximately 2g/10cm², maximum of 10g for 30 minutes (Range: 25–37); Follow-up: One application only</td>
</tr>
<tr>
<td>Agrifoglio et al., 2000; Italy</td>
<td>To confirm the anaesthetic effect of EMLA® cream compared to a placebo cream when used for sharp debridement</td>
<td>A double-masked, placebo-controlled RCT</td>
<td>n = 110; Seven angiology and vascular surgery outpatient</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcome: Clinician judgment</td>
<td>(I) EMLA® cream vs. (C) Placebo cream</td>
<td>Dose for (I) and (C): approximately 2.5g/10cm², A statistically significant improvement in pain scores were observed in the EMLA® group (p &lt;0.0001); Clinicians found debridement</td>
</tr>
<tr>
<td>Study</td>
<td>Objective</td>
<td>Design</td>
<td>Subjects</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Findings</td>
</tr>
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<tr>
<td>Lok et al., 1999; France</td>
<td>To assess the effect of EMLA® on the number of debridements to clean a CLU pain during debridement and safety after repeated doses</td>
<td>Multicentre, double-blind, placebo RCT</td>
<td>n = 69; Outpatient Departments of Dermatology or Phlebology; CLU type: venous</td>
<td>Primary outcome: number of debridement’s required to obtain a clean CLU; Secondary outcomes: pain as measured with the VAS and duration of debridement; local and adverse reactions, plasma concentrations</td>
<td>(I) EMLA® cream versus (C) Placebo cream Dose for (I) and (C): 1-2 g/10 cm², max 10 g applied to CLU for 30 to 45 min before debridement; Follow-up: until ulcer was clean in up to 15 debridements</td>
<td>EMLA® significantly decreased pain scores for debridement by 50% compared to placebo group (p &lt;0.01)</td>
</tr>
<tr>
<td>Holst et al., 1998; Sweden</td>
<td>To assess and compare pain intensity during debridement after different application times with lidocaine/prilocaine cream (EMLA®) before debridement of</td>
<td>Single-blind, three-armed, parallel group RCT</td>
<td>n = 59; Inpatients; CLU type: venous, arterial, diabetic</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: duration of the cleansing procedure</td>
<td>EMLA® application times compared at different time-points - 10, 20 or 60 minutes of treatment; Dose: 2gm/10 cm², maximum 10g; Follow-up: 10, 20 or 60 min</td>
<td>Pain intensity decreased significantly with increased EMLA® application time (p = 0.001)</td>
</tr>
<tr>
<td>Authors</td>
<td>Study Goal</td>
<td>Design</td>
<td>Sample Size</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Experimental Details</td>
</tr>
<tr>
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</tr>
<tr>
<td>Hansson et al., 1993; Sweden</td>
<td>To assess repeated topical analgesia with EMLA® 5% cream for cleansing CLUs</td>
<td>Open, repeat dose, parallel-group RCT</td>
<td>n = 43; Outpatient, multicentre, Departments of Dermatology and Surgery; CLU type: venous</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: bacterial load, debridement efficacy, healing rates, local and adverse reactions</td>
<td>(I) EMLA® 5% cream Dose: Thick layer, maximum 5 gm for 30 min vs. (C) Unknown; Follow-up eight consecutive treatments separated by an interval of 2 – 9 days</td>
<td>EMLA® significantly reduced pain scores from debridement ($p = 0.0008$); and post-debridement pain vs. control group ($p = 0.021$)</td>
</tr>
<tr>
<td>Enander et al., 1990; Sweden</td>
<td>To assess plasma concentrations and the analgesic effect of EMLA® cream for the surgical cleansing of CLUs</td>
<td>Part 1 – Plasma concentrations - Observational study; Part 2 – Analgesic effect: Double-blind, four-period, cross-over study randomly allocated to 2% and 5% EMLA® cream</td>
<td>Part 1 – Plasma concentrations: n = 8; Part 2 – Analgesic effect: n = 10 Single site - Setting NR; CLU type: venous, immunological origin</td>
<td>Two primary outcomes: plasma concentrations and pain as measured with the VAS; Secondary outcomes: adverse reactions</td>
<td>Part 1 – Plasma concentrations: 8-10g of EMLA 2% applied for 60 min. Follow-up - Blood samples were taken before application and at 60, 90, 120, 150, 180, 240 min; Part 2 – Analgesic effect: EMLA® 2% versus EMLA® 5% - each participant received both concentrations once during 1st and 2nd treatment and once during 3rd and 4th</td>
<td>Part 1 – Plasma concentrations: Maximum individual plasma concentrations - Lidocaine: 205ng/ml Prilocaine: 79 ng/ml, 20 times lower than those associated with toxicity; Part 2 – Analgesic effect: No difference between the analgesic effect of 2% and 5% EMLA®, Pain intensity was lower</td>
</tr>
<tr>
<td>Holm et al., 1990; Sweden</td>
<td>To assess the analgesic effects of lidocaine/prilocaine cream (EMLA®) to control pain during debridement of CLUs</td>
<td>Two consecutive parts: (1) Open, non-randomised study (2) A double-blind, placebo-controlled RCT</td>
<td>(1) n = 50 (2) n = 30; Outpatient department; CLU type: venous, arterial</td>
<td>Primary outcome: pain as measured with the VAS; Secondary outcomes: plasma concentrations, local and adverse reactions</td>
<td>(1) EMLA® on all participants; Dose: Application times: 10, 20 and 30 min; (2) (I) EMLA® Dose: 5g cream on all but three participants where 10g used vs. (C) Placebo cream. Both groups had 30-minute application time; Follow-up: None</td>
<td>(1) Of the 50 participants, 41 reported no or slight pain; (2) EMLA® significantly reduced pain scores vs placebo group ($p &lt; 0.01$)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLUs, Chronic leg ulcers; RCT, randomised controlled trial; EMLA®, eutectic mixture of local anaesthetics; VRS, verbal rating scale; VAS, visual analogue scale; NRS numerical rating scale; N\textsubscript{2}O/O\textsubscript{2}, Nitrous oxide/oxygen mixture; NR, not reported; QOL, quality of life; mg, milligrams; g, grams; ng, nanograms; LMX-4, liposomal lidocaine cream; h, hours; min, minutes.
2.4. Assessment of methodological quality

2.4.1 Randomised controlled trials

Nine of the 22 studies included in this review were RCTs. Methodological quality was evaluated using the following determinants: allocation concealment, lost to follow-up, baseline comparability, intention-to-treat (ITT) analysis and blinding of assessors or participants. Most of the RCTs included in this review were at risk of selection, detection, performance and attrition biases (Mansournia, Higgins, Sterne, & Hernan, 2017). The level of risk was often unable to be determined due to poor reporting. Details of the methodological assessment are presented in Tables 2.4 and Tables 2.5.

Although randomisation is crucial to the internal validity of an RCT, it is how a study is randomised through appropriate random allocation and allocation concealment methods that will prevent selection bias, which may produce an overestimation of the treatment effect (Suresh, Yasaswini, & Reshma, 2016). The method of randomisation was reported in less than a quarter of the RCTs (22%) (Claeys et al., 2011; Gottrup et al., 2008; Romanelli et al., 2009; Sibbald et al., 2007) and only one RCT reported how the allocation sequence was generated (Sibbald et al., 2007). Even though the CONSORT checklist was introduced in 2010, methods of randomisation and allocation sequence were only reported in one study published after 2010 (Claeys et al., 2011).

Allocation concealment is the mechanism used to implement the random allocation sequence and the method of allocation should be clearly described when reporting the outcomes of an RCT (Schulz et al., 2010). Separating the act of randomisation from the investigator who is recruiting participants by using allocation concealment prevents investigators from unconsciously or otherwise influencing which participants are assigned to a given study group resulting in a more robust RCT (Clark, Fairhurst, & Torgerson, 2016; CONSORT, 2017). Allocation concealment was reported in six of the RCTs included in this review (Claeys et al., 2011; Domenech et al., 2008; Fogh et al.,
Sealed envelopes were the most commonly used method, however, whether the envelopes were sequentially numbered opaque envelopes (SNOSE) (Clark et al., 2016) was not reported. One study reported using a centralised randomisation process (Claeys et al., 2011) and another a telephone system provided by an external company, set up and based on the randomisation list (Fogh et al., 2012).

Baseline equivalence was only reported in three RCTs (Claeys et al., 2011; Fogh et al., 2012; Vernassiere et al., 2005). Loss-to-follow-up was reported in 10 studies: eight studies in the topical analgesic group (Range: 3 to 12 participants; Dropout rate: 1% to 41%) and two studies in the topical local anaesthetic group (Range: 1 to 87 participants; Dropout rate: 7% to 20%).

Intention-to-treat analysis was defined in this review as including all randomised participants in the group to which they were randomised regardless of noncompliance, withdrawal, protocol deviation, or anything that happened after randomisation (Gupta, 2011). The quantity of the ITT effect is determined by the quantity and type of adherence to the assigned treatment (Mansournia et al., 2017). Five studies reported ITT (Claeys et al., 2011; Domenech et al., 2008; Gottrup et al., 2008; Romanelli et al., 2009; Vernassiere et al., 2005). ITT was unclear in one study as they reported that no data were excluded; more detail was not available (Rosenthal et al., 2001). It is unknown whether the remaining trials employed ITT.

Blinding of both the assessor and the participant was reported for over half of the RCTs included in this review (Agrifoglio et al., 2000; Bastami et al., 2012; Enander et al., 1990; Fogh et al., 2012; Gottrup et al., 2008; Holm et al., 1990; Jansen et al., 2009; Lok et al., 1999; Rosenthal et al., 2001; Vernassiere et al., 2005). In one study, only the
investigator was blinded to the treatment allocation (Holst & Kristofferson, 1998). For all other RCTs neither the investigators nor participants were blinded.
Table 2.4 Assessment of methodological quality of randomised controlled trials - topical analgesic agents

<table>
<thead>
<tr>
<th>RCT</th>
<th>Randomised (Method)</th>
<th>Allocation concealed</th>
<th>Loss to follow-up</th>
<th>Intention-to-treat analysis</th>
<th>Assessor blinding</th>
<th>Participant blinding</th>
<th>Baseline comparability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical analgesic agents for painful chronic leg ulcers</strong></td>
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<td></td>
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<tr>
<td><strong>Ibuprofen foam</strong></td>
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<td></td>
</tr>
<tr>
<td>Fogh et al., 2012</td>
<td>No</td>
<td>Yes (Telephone system)</td>
<td>27</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – age, sex, height, weight, CLU size, duration and compression type; CLU size statistically different at baseline – ((p = 0.0009))</td>
</tr>
<tr>
<td>Arapoglou et al., 2011</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes – CLU type</td>
</tr>
<tr>
<td>Romanelli et al., 2009</td>
<td>Yes (Block randomisation)</td>
<td>NR</td>
<td>22</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes – age, sex, CLU size, duration and type</td>
</tr>
<tr>
<td>Domenech et al., 2008</td>
<td>No</td>
<td>Yes (Sealed Envelopes)</td>
<td>87</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes – age, sex, CLU duration and size</td>
</tr>
<tr>
<td>Gottrup et al., 2008</td>
<td>Yes (Block randomisation)</td>
<td>Yes (Sealed Envelopes)</td>
<td>29</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – age, sex, height, weight, medical history</td>
</tr>
<tr>
<td>Sibbald et al., 2007</td>
<td>Yes (Block randomisation)</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes – age, CLU duration, size, type. Pain medications and intensity, wound bed, peri-wound skin,</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
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<tr>
<td>Bastami et al., 2012</td>
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<td></td>
</tr>
<tr>
<td>Jansen et al., 2009</td>
<td>No</td>
<td>NR</td>
<td>1; 17 before baseline assessment</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Vernassiere et al., 2005</td>
<td>No</td>
<td>NR</td>
<td>10</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – sex, age, CLU type and duration, pain intensity</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLU, chronic leg ulcer; RCT, randomised controlled trial; NR, not reported; NHMRC, National Health and Medical Research Council; Rx, treatment
Table 2.5: Assessment of methodological quality of randomised controlled trials - topical local anaesthetic agents

<table>
<thead>
<tr>
<th>RCT</th>
<th>Randomised (Method)</th>
<th>Allocation concealed</th>
<th>Loss to follow-up</th>
<th>Intention-to-treat analysis</th>
<th>Assessor blinding</th>
<th>Participant blinding</th>
<th>Baseline comparability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuomo et al., 2014</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Claeys et al., 2011</td>
<td>Yes (Block randomisation)</td>
<td>Yes (Centralised randomised process)</td>
<td>12</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes – age, sex, MMS, CLU type, non-viable tissue type, CLU size and duration, VAS, VRS</td>
</tr>
<tr>
<td>Rosenthal et al., 2001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Unclear “no data excluded.”</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – sex, age, weight, Rx duration, CLU size and duration, diabetes, analgesics and antibiotics</td>
</tr>
<tr>
<td>Agrifoglio et al., 2000</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes - age, sex, weight</td>
</tr>
<tr>
<td>Lok et al., 1999</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes – age, sex, CLU type and size</td>
</tr>
<tr>
<td>Holst et al., 1998</td>
<td>NR</td>
<td>Yes (Sealed Envelopes)</td>
<td>NR</td>
<td>NR</td>
<td>Yes (Application time)</td>
<td>No</td>
<td>Yes – CLU size and duration</td>
</tr>
<tr>
<td>Hansson et al., 1993</td>
<td>NR</td>
<td>Yes (Sealed Envelopes)</td>
<td>3</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Yes – age, sex, CLU size and location, diabetes, antibiotics</td>
</tr>
<tr>
<td>Holm et al., 1990</td>
<td>No (Part 2 ulcer)</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>Yes (Part 2)</td>
<td>Yes (Part 2)</td>
<td>Yes – CLU duration, location and size</td>
</tr>
<tr>
<td>Enander et al., 1990</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes - analgesic effect only</td>
<td>Yes - analgesic effect only</td>
<td>Yes - age, CLU size, type and duration</td>
</tr>
</tbody>
</table>

**Abbreviations:** CLU, chronic leg ulcer; RCT, randomised controlled trial; NR, not reported; NHMRC, National Health and Medical Research Council; MMS, Mini-mental score; Rx, treatment
2.4.2 Quasi-experimental, cross-over and observational studies

Two studies, one in the topical analgesic group (Jorgensen et al., 2006) and one in the topical local anaesthetic group (Traber et al., 2016) were cross-over studies; and one study in the topical local anaesthetic group (Effendy et al., 2015) was a quasi-experimental study. Only one study reported baseline comparability (Effendy et al., 2015). One study used a cross-over design to investigate ibuprofen foam compared to placebo foam as a primary dressing for painful chronic leg ulcers (Jorgensen et al., 2006); another investigated EMLA® compared with N₂O/O₂ (Traber et al., 2016) as treatments for chronic leg ulcers before debridement. Two RCTs (Enander et al., 1990; Holm et al., 1990) included data from small preliminary observational studies. One investigated the application times of EMLA® (Holm et al., 1990) and the other plasma concentrations (Enander et al., 1990).

A large retrospective, observational medical record review of data over a 6-year period from one clinic was conducted to confirm the analgesic effectiveness, safety and tolerability of EMLA® on a variety of wound types including CLUs when used for sharp debridement. Data from this study included ulcer size, EMLA® dose, pain assessment and complications (Blanke & Hallern, 2003). However, there are considerable limitations regarding this study. A convenience sample was used which has limitations with respect to generalisability of the results. Additionally, the author failed to report whether data abstractors were trained or monitored or whether standardised abstract forms were used or any exclusion criteria and did not address inter-rater or intra-rater reliability or ethical considerations (Vassar & Holzmann, 2013).

2.5 Discussion

In this review, a summary of the evidence of topical analgesic and local anaesthetic agents has been provided. Two previous reviews suggest that topical analgesic and topical local anaesthetic agents may be useful in reducing wound-related pain associated with chronic leg ulcers (Briggs et al., 2012; Vanscheidt et al., 2001). Their findings indicated that topical ibuprofen permeated foam was successful in reducing chronic pain associated with chronic leg ulcers and morphine gel was not
affective for the same wound type. In both reviews, all studies investigating EMLA® found it to be successful in reducing acute operative pain associated with the debridement of chronic leg ulcers.

This review reported in this thesis on past evidence relating to topical analgesic and local anaesthetic agents as pain management strategies for chronic leg ulcers. Using a systematic approach this present review identified a further six studies that met the inclusion criteria related to EMLA® that were not included in the formative systematic review by Briggs et al. (2012). Only one study was published after 2012. Additionally, a further five studies relating to topical ibuprofen foam and three studies relating to topical morphine gel were also identified; none were published after 2012. No other studies relating to other topical analgesic or topical local anaesthetic agents that met our inclusion criteria were found. Findings in this review are similar to previous reviews in that ibuprofen foam and morphine gel were applied as primary dressings to treat chronic wound-related pain. The findings also suggest that ibuprofen foam may be successful in reducing chronic leg ulcer pain, however, there was insufficient data to suggest similar effectiveness for the application of morphine gel. EMLA® was the local anaesthetic agent used in all studies in the topical anaesthetic group and was applied to chronic leg ulcers to prevent acute pain associated with debridement. The findings from all studies suggested that EMLA® was effective when used for this purpose.
It is important to consider where research on this subject has come from, whether it is robust then build on this previous research (Shorten, 2013). In this review 18 out of 22 studies were RCTs. The purpose of randomisation is to achieve baseline equivalence between study groups so that any change in outcomes can be attributed to the intervention rather than the difference being potentially explained by differences in group characteristics (Elkins, 2015). The majority of studies in this review did not conform to reporting requirements (Schulz et al., 2010) therefore, the risk of selection, detection and performance biases was often unable to be determined. However, the insufficient information provided in the articles leads to the assumption of poor trial quality but this cannot truly be assessed (Soares et al., 2004). Nevertheless, only 20% of RCTs blinded the participants and investigators, 8% reported how their allocation sequence was generated and only a quarter reported allocation concealment. The risk of attrition bias was also high with less than 20% of RCTs reporting whether participants were accommodated in an ITT analysis and less than 10% reported participant withdrawals. One study in this group had a dropout rate of 29%. Furthermore, most studies included in this review were older than 5 years, although it is recognised that only valuing recent evidence over robust evidence may misinform practice (Shorten, 2013).

To improve the validity of a clinical trial an appropriate sample size is important to be able to detect a difference between two or more groups as near to reality as possible. A small sample size increases the potential for Type II error resulting in the applicability and utility in the clinical setting unlikely (G. S. Kumar, 2014). Conversely, clinical trials with larger sample sizes can result in a waste of resources decreasing the validity or accuracy of the trial due to a low response-rate and difficulty maintaining data quality (Kumar, 2014). In this review, 13 of the 22 studies had a sample size of less than 100; all studies investigating morphine gel group had sample sizes less than 25 as did two out of seven studies investigating ibuprofen foam and eight out of the 12 investigating EMLA®. Even though the retrospective, observational medical record review had a
very large sample size, the study design has other inherent methodological limitations that sample size alone could not overcome.

In this review, the findings from the evidence relating to topical analgesic and topical local anaesthetic agents for the relief of chronic leg ulcer pain indicates that topical agents are effective in reducing pain associated with chronic leg ulcers except for morphine gel. What this review has added to the body of knowledge is that, to date, the only topical formulations used as primary dressings for chronic leg ulcer pain have been ibuprofen foam and morphine gel. EMLA® has never been used in this novel way even though it is the predominant and most long-standing topical pain-relieving agent used for relief of operative pain associated with the debridement of chronic leg ulcers.

The evidence presented in this review regarding EMLA® supports why it was chosen as the intervention for the study conducted and presented in this thesis. The evidence suggests that EMLA® is a superior topical agent for reducing operative pain associated with the debridement of chronic leg ulcers, is fast acting, has low systemic uptake and only results in minor local adverse effects. Furthermore, even though the evidence indicated that ibuprofen foam may significantly reduce chronic leg ulcer pain, it was not considered for this study as it was not on the NSW state contract when the study commenced, therefore, was not on the Central Coast Local Health District formulary which restricted availability. There were no such restrictions for EMLA® and a published case report (Purcell et al., 2012) indicated the potential usefulness of EMLA® as a primary dressing for chronic pain associated with chronic leg ulcers.

The limitations of this review are that publication bias is unclear. Even though a comprehensive search strategy was attended and evaluation of research protocols and interviews with trial investigators may have assisted in assessing study quality more accurately (Soares et al., 2004); this was not carried out. Additionally, it is recommended that at least two researchers screen and appraise the literature to increase the probability of extracting the most relevant articles and
appraising the literature accurately (Bigby & Williams, 2003; Edwards et al., 2002); only one researcher screened and appraised the literature included in this review.

2.6 Gap in the literature

Topical analgesics and anaesthetics provide an important pain relief alternative when oral analgesia is ineffective or results in significant side effects. There are a limited number of studies which examine the use of topical analgesics or local anaesthetics to manage chronic leg ulcer pain. What studies are available are limited mostly by small sample sizes and poor methodological quality. Accurate assessment of methodological quality was disadvantaged by the poor reporting outlined in the available papers.

The strongest evidence available is for the use of intermittent short applications of EMLA® prior to debridement for operative pain relief, which has been shown to be systemically safe without negatively impacting wound healing. The evidence for the effectiveness of EMLA® for debridement together with a positive clinical experience using EMLA® as a primary dressing suggested that EMLA® may be effective in managing chronic pain for individuals with chronic leg ulcers. To date, this approach has not been evaluated in the literature, so it was unclear whether using EMLA® as a primary dressing would lead to reduced wound-related pain for longer periods which, in turn, may have a positive impact on wound healing and HRQoL.

This gap in the evidence requires further exploration and needs to include the effects EMLA® may have on wound-related pain, the healing potential of chronic leg ulcers and HRQoL. This pilot study will inform a future multisite, randomised, controlled trial.

2.7 Conclusion

This review has identified limited, inconsistent evidence for the use of topical analgesics and topical local anaesthetic agents to treat painful chronic leg ulcers. EMLA® and ibuprofen foam
have been shown to be effective agents for reducing wound-related pain associated with chronic leg ulcers.

Through the literature review reported in this chapter, there is the need for further research regarding the use of EMLA® to relieve chronic wound-related pain for chronic leg ulcers. EMLA® remains the most widely used topical agent for chronic leg ulcer pain relief albeit mostly in the context of wound debridement. The next chapter outlines the methodological framework for this study which has been designed to evaluate study feasibility of an RCT to examine EMLA® as a primary dressing for the management of painful chronic leg ulcers.
3.1 Introduction

The effect of wound-related pain associated with chronic leg ulcers and the impact on wound healing and health-related quality of life is presented in Chapter 1. A literature review identified a gap in knowledge and the formulation of the following research question: *Is the eutectic mixture of local anaesthetics (EMLA®) effective for reducing wound-related pain when used as a primary dressing on painful chronic leg ulcers, and what impact does this pain-relieving strategy have on wound healing and health-related quality of life?*

A pilot study was undertaken to evaluate important study parameters that would inform a larger study to ensure the implementation of a larger study is feasible and to generate data that will indicate the variability needed to do a properly powered future study. The framework that guided assessment of the study feasibility is presented in this chapter together with a detailed description of the study protocol and implementation processes. The study design and methodological processes including ethical considerations, study interventions, data collection instruments and data analysis are presented.

3.2 Research design

3.2.1 Feasibility

Feasibility is an overarching concept within which three distinctly different types of studies can be differentiated. They are: 1) a pilot RCT in which the future RCT or parts of it are conducted on a smaller scale (piloted) to see if it can be done; 2) non-randomised pilot studies; and 3) non-piloted feasibility studies where attempts are made to determine whether a larger study can be done although the intervention is not implemented (Eldridge et al., 2016). There are two variations to the first type of study, external and internal pilot studies. An external pilot study is a stand-alone study planned and conducted independently to a
larger study where outcome data are not included in the data set of a larger study. An internal pilot study forms the first part of a larger study and data generated can be included in the final analysis (Avery et al., 2017).

For this study, an external, in preference to an internal pilot study was chosen. EMLA® as a primary dressing on painful chronic leg ulcers had never previously been investigated therefore, how to best operationalise the study protocol was identified as an area for learning. An external pilot study was preferable as it allows greater freedom to change study design in a larger study once the results of the external pilot study have been analysed compared to an internal pilot study (Eldridge & Kerry, 2012).

Pilot studies are an essential phase of the research process and key in the development, modification or different application of new interventions (Arain, Campbell, Cooper, & Lancaster, 2010; Leon, Davis, & Kraemer, 2011; Thabane et al., 2010). Trial methodologists and funding bodies recommend pilot studies particularly if the study is a novel application of an intervention such as in this study (Craig et al., 2008; Thabane et al., 2010).

3.2.2 Framework
Although there are other frameworks to measure feasibility outcomes (Bowen et al., 2009; Eldridge et al., 2016; Smith & Harrison, 2009), for this study Thabane et al.’s framework was used as it provided comprehensive recommendations and guidance for reporting the results of pilot studies adopted from the CONSORT Statement (Schulz et al., 2010; Thabane et al., 2010). Based on earlier work (van Teijlingen & Hundley, 2002; van Teijlingen, Rennie, Hundley, & Graham, 2001), Thabane et al., (2010) concluded that the rationale for conducting and successfully reporting feasibility outcomes in a pilot study could be grouped under four broad classifications: Processes, Resources, Management and Scientific (Thabane et al., 2010). Study processes included validation of the recruitment and
randomisation processes, study consents, retention rates, suitability of the eligibility criteria, data collection instruments and intervention fidelity. To prevent unnecessary spending or wasting of resources in a larger study, the feasibility of conducting this RCT in a public community health service was measured by assessing the availability and commitment of human resources, the time to perform study processes, availability and quality of study equipment and the cost estimates to conduct such a study. Human and data management outcomes were also assessed including personnel challenges, participant burden and data management challenges.

3.2.3 Study aims and hypotheses

In this pilot study the feasibility of the study processes, resources, management and scientific aspects of the study were assessed (Thabane et al., 2010). The generation of data related to wound-related pain was used for a sample size calculation for a larger study. However, there is potential for results from pilot studies to mislead sample size calculations for a larger RCT, so it is crucial to exercise caution (Arain et al., 2010; Kraemer, Mintz, Noda, Tinklenberg, & Yesavage, 2006; Thabane et al., 2010).

The secondary aims of this study were to investigate the:

- effectiveness of the daily topical application of EMLA\textsuperscript{©} as a primary dressing applied to painful chronic leg ulcers as a pain-relieving strategy. In an adequately powered RCT designed to assess intervention effectiveness, pain would be the primary outcome measure;

- impact of a daily application of EMLA\textsuperscript{©} on chronic leg ulcers on wound healing, and;
• impact of a daily application of EMLA® on chronic leg ulcers on health-related quality of life.

It was determined that the study would be feasible as defined by priori targets for recruitment and retention. Selection of pre-determined criteria was informed by previously published feasibility studies (Marshall et al., 2016; Moore, Carter, Nietert, & Stewart, 2011). Study feasibility was assessed using the following criteria for determining success:

- recruitment of at least 80% of eligible participants within 12 months;
- retention of 80% of participants during the study period;
- achieving at least 80% adherence to the intervention protocol.

3.2.4 Pilot study design

For this pilot study an RCT was selected because it is considered the gold standard in experimental research and when well-designed and executed, RCTs provide the most reliable information on intervention efficacy or effectiveness (Akobeng, 2005; Schulz et al., 2010). For this pilot study, a pragmatic, parallel group, non-blinded, superiority, RCT was conducted.

A pragmatic approach was selected to assess the effectiveness of the intervention in a routine real-life practice setting. Pragmatic studies allow for greater variation in study procedures to maximise applicability and generalisability while providing relevant evidence to clinical practice and policy (Avery et al., 2017; Patsopoulos, 2011). Pragmatic studies have higher external validity than efficacy studies even though some internal validity is sacrificed (Singal, Higgins, & Waljee, 2014). However, one of the strengths of an RCT is the diversity of the study participants between groups which helps maintain internal validity (Godwin et al., 2003). In pragmatic studies the intervention is more often compared with standard care as indicated in this study, allowing a more modified approach for each participant (Singal et al.,
Compliance can be influenced by the population, for example, in this case, the participants in this study were mostly older persons with multiple comorbidities and in significant pain. Non-compliance with the assigned treatment in an RCT can undermine randomisation and potentially weaken the estimate of treatment effect (Ye, Beyene, Browne, & Thabane, 2014) therefore, assessment of compliance to the study intervention is important before any investment in a larger study.

Regardless of the intervention, there are many potential biases that can be introduced into any study. An RCT was selected as the preferred study design because it is better able to eliminate sources of bias regarding allocation concealment and blinding. Additionally, an RCT will clearly show the probability that differences in the outcomes between the intervention and the control groups simply indicate chance, so any positive treatment effect provides confidence in the efficacy of the intervention (Akobeng, 2005; Eskes et al., 2012; Portela, Pronovost, Woodcock, Carter, & Dixon-Woods, 2015; Schulz & Grimes, 2002a). Results in an RCT are likely to be closer to a true effect than for other research methods as the processes used while conducting an RCT reduce the risk of confounding factors influencing outcomes (Akobeng, 2005). This is a particular advantage in wound care studies due to the different chronic leg ulcers aetiologies in the sample, the different treatment options in the control group and the multiple comorbidities of this patient group (Eskes et al., 2012).

3.2.5 Ethical considerations

To conduct medical research on human subjects, ethical principles must be adopted to protect the rights and interests of individual research participants and any individuals involved in the research to prevent harm (World Medical Association, 2013). To guide the conduct of ethical research the seven key principles are: social and clinical value, scientific validity, fair subject
selection, favourable risk-benefit ratio, independent review, informed consent, and respect for potential and enrolled subjects (Emanuel, Wendler, & Grady, 2000).

This study was conducted in accordance with the 1975 World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects (World Medical Association, 2013). The goals of the study never took precedence over the participant’s rights, health, wellbeing and interests. Measures to minimise risk were implemented and monitored, the study processes conformed to accepted scientific and evidenced-based principles, every precaution was taken to protect the participant’s privacy and confidentiality of their personal information and consent was voluntary. Additionally, prior to data collection, this study underwent ethical and scientific evaluation receiving ethics approval from the NSW Health accredited Human Research Ethics Committee (HREC): Harbour, Northern Sydney Central Coast Health (NSCCH) (HREC/09/HARBR/162) and was subsequently ratified by Griffith University HREC (NRS/16/12/HREC) (Appendices 2 and 3). As stipulated by the National Statement on Ethical Conduct in Human Research 2007, the World Medical Association Declaration of Helsinki and Australian Clinical Trial Handbook (National Health and Medical Research Council, Australian Research Council, & Australian Vice-Chancellors Committee, 2007; Therapeutic Goods Administration, 2006; World Medical Association, 2013), prior to beginning the clinical phase, this clinical trial was registered in the publicly accessible Australian New Zealand Clinical Trials Register (ANZCTR 12609001080213). In keeping with these guidelines, both positive as well as negative and inconclusive results must be published or made publicly available (World Medical Association, 2013).

The study intervention EMLA® is a pharmaceutical product approved for use on chronic leg ulcers although studies have not been undertaken with the aim of using EMLA® as a primary dressing. EMLA® has been evaluated by the TGA for quality, safety and efficacy on chronic
leg ulcers and entered into the Australia Register of Therapeutic Goods thus is not considered experimental and has general marketing approval. Clinical trials that are not using unapproved goods particularly prescription medicines (EMLA® is an over-the-counter medication in Australia), do not require Clinical Trials Notification (CTN) and Clinical Trial Exemption processing at the TGA thus the use of EMLA® on chronic leg ulcers in a clinic trial was lawful (Therapeutic Goods Administration, 2018). The HREC determined, with advice from the Director of Pharmacy, that TGA approval was not required as EMLA® is already approved by the TGA (ARTG ID 12886) for ‘topical anaesthesia of leg ulcers to facilitate mechanical cleansing and debridement.’ Additionally, the safety profile of EMLA® indicated a low risk to human subjects and the exclusion criteria for the study was guided by the contraindications, warnings and precautions listed by the manufacturer Aspen Pharmacare (St Leonards, Australia). Up to November 2017, EMLA® was manufactured by AstraZenaca.

3.2.5.1 Consent

Consent procedures were guided by the Australian Therapeutic Goods Administration (TGA) Guidance on Good Clinical Practice (CPMP/ICH/135/95) (Therapeutic Goods Administration, 2000) and the National Health and Medical Research Council National Statement of Ethical Conduct in Human Research (National Health and Medical Research Council et al., 2007). Before gaining informed written consent, the investigator discussed all relevant aspects of the study with the patient and they were provided with a plain-language Participant Information Statement (Appendix 4). The information statement informed the patient of all study protocols and procedures. Assistance was offered to participants who required it where each section of the document was read to the patient and their understanding confirmed.
Additionally, participants were informed of current evidence-based treatment options for chronic leg ulcers and wound-related pain and how the study intervention differed. Voluntary participation and the patient’s right to withdraw at any time while not affecting care by the community nursing service was explained and reinforced. Patients were given the opportunity to ask questions throughout the consent process which were addressed before they voluntarily signed the study consent. In addition to the study consent, the Central Coast Local Health District clinical photography consent was also required in line with health service policy. Before signing this consent, patients were informed that this allowed investigators to take photos of the chronic leg ulcers, to upload them onto the patient’s electronic medical record and to use the photos for education, conference presentations and publications as necessary.

3.2.5.2 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB), guided by the Data Monitoring Committees: Lessons, Ethics, Statistics Charter (Grant et al., 2005), provided ongoing independent review of the risks and benefits for study participants and addressed safety issues related to the drug or device being trialled to protect participant health and safety. It is possible that unknown risks may have occurred following the application of this pharmaceutical product. The participants were mostly older persons and therefore potentially more vulnerable to adverse outcomes due to impairments in multiple physiological systems (Holroyd-Leduc et al., 2016).

Participants recorded any problems or adverse reactions to the intervention in their Pain Diary which was reviewed at each clinic visit. The participant was assessed for any adverse reaction such as transient local reactions, skin sensations and allergic reactions (Aspen Pharmacare Canada Inc., 2017). Adverse events were documented by the nurse in the participant’s electronic medical record and a Notification of Adverse Event form was completed followed by immediate notification to and discussion with the chief investigator, the PhD candidate. In the event of any adverse reaction in the intervention group, treatment
was ceased immediately and the medical team notified. Notifications of adverse events were mandatory and reported promptly to the NSCCHS HREC and the DSMB.

In keeping with the Australian Therapeutic Goods Administration (TGA) Guidance on Good Clinical Practice (CPMP/ICH/135/95) (Therapeutic Goods Administration, 2000) the DMSB was established and chaired by a senior academic researcher with extensive experience in clinical research. Other members were a clinician with research and statistical analysis experience and an experienced research coordinator. This study was not commercially sponsored and the DSMB was independent of any funding.

3.2.6 Setting and sample
This pilot RCT was conducted in six procedure clinics located in a public community nursing service in New South Wales (NSW), Australia (Figure 3.1). Five clinics were open from 0830 hours to 1630 hours Monday to Friday and one clinic was open four days per week. All clinics were closed on the weekends and public holidays. Home visiting was available through the community nursing service.

Figure 3.1
Location of Central Coast Local Health District NSW Community Nursing Clinics (Central Coast Local Health District, 2018; Stralia Web's Regional Network, 2018)
All registered nurses employed in this setting were experienced in wound management. Approximately three-quarters of individuals who access the community service do so for wound management, of which 75% are chronic leg ulcers (Central Coast Health Community Nursing Service, 2017). In the 12-month period to August 2008, 1029 individuals presented with chronic leg ulcers.

3.2.6.1. Sample size

A sample size of 60 was selected for this study as it was considered a good representation of the target population, large enough to provide practical information about the feasibility aspects of the study (Thabane et al., 2010) and to accommodate possible attrition throughout the 12-week study period. Although reported sample sizes for pilot studies vary, the median sample size per arm is often 30 (Billingham, Whitehead, & Julious, 2011). Ideally, sample size should be based on the realities of recruitment and the requirements for examining feasibility (Arain et al., 2010; Leon et al., 2011). In an external pilot study such as this, there is a ‘trade-off’ between maximising the precision of estimates of important parameters and sample size which impacts resources, time and costs of a study (Teare et al., 2014). Additionally, participants in an external pilot study do not contribute to the estimation of the treatment effect in a larger definitive study (Teare et al., 2014). There is an inbuilt ambiguity in-between treatment group effect size estimates from small samples sizes (Arain et al., 2010; Leon et al., 2011). Attrition rates are often high in wound studies due to comorbidities associated with this patient group particularly when the study period is long, where wounds may deteriorate and the innate difficulty adhering to the protocol over many weeks (Gottrup, Apelqvist, & Price, 2010). Even so, for this study attrition rates were anticipated to be 10% since two-thirds of clinical trials are less than 10% (Zang et al., 2008). The participants had a vested interest to remain in the study as they wanted their chronic leg ulcers to improve.
Patients with painful chronic leg ulcers of varying aetiology, that is, venous, arterial, mixed or diabetic ulcers, were eligible for this study. A two-stage screening process where potentially eligible patients were initially identified by the community nurses followed by a more thorough screening by the thesis author or research assistant (RA). Patients were first screened by the community nurses using a screening tool which contained the preliminary study criteria: a chronic leg ulcer of more than six weeks’ duration; pain-relieving medications required to manage wound-related pain; and, the patient was able to be treated in a community nursing clinic. Nine months after the commencement of the study an RA was also employed for 17 months (total: 50 days) to search through the community nursing electronic medical record database using the same criteria to identify eligible participants for recruitment.

Following identification of potentially eligible patients, the patients were visited in their home or seen at their next scheduled clinic visit for wound care where they were assessed against the inclusion/exclusion criteria to determine eligibility (Table 3.1). Potential participants were required to meet all the following inclusion and exclusion criteria to be considered eligible for this study then they were invited to participate in the study. The theoretical basis for the inclusion and exclusion criteria is presented in Table 3.1.
Table 3.1 Participant Inclusion and Exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more chronic lower leg ulcer(s) of at least six weeks’ duration.</td>
<td>Lower leg ulcers are the most painful wound type (European Wound Management Association, 2002) and become chronic when they do not heal as expected. A wound is considered chronic when signs of healing do not occur within a six week period (MacLellan, 2007).</td>
</tr>
<tr>
<td>Wound up to 100cm² in size in total</td>
<td>The maximum recommended dose of EMLA is 10gms; the maximum dose/surface area ratio is 1-2gms EMLA® to 10cm² of wound surface area. Therefore, the maximum wound size of 100cm² was selected for this study. This dose/surface area ratio is recommended for the application of EMLA® when used for the debridement of non-viable tissue from a CLU (Aspen Pharmacare Canada Inc., 2017).</td>
</tr>
<tr>
<td>Patients with low to moderate wound exudate as assessed using the Leg Ulcer Measurement Tool (LUMT)</td>
<td>Low to moderate wound exudate will enable the EMLA® to remain on the wound bed over 24 hours and not run off the wound.</td>
</tr>
<tr>
<td>NRS pain score ≥ 4 at assessment and/or within the previous week</td>
<td>WRP ≥ 4 on the NRS indicates uncontrolled pain during or after dressing change which signifies pain management is required (van Dijk, Kappen, van Wijck, Kalkman, &amp; Schuurmans, 2012).</td>
</tr>
<tr>
<td>Patients currently requiring oral analgesics due to previously reported wound-related pain</td>
<td>The patients most likely to benefit from participation in the study would be those already requiring pain relief for WRP.</td>
</tr>
<tr>
<td>Patients ≥ 18 years of age.</td>
<td>Chronic leg ulcers are more prevalent in adults</td>
</tr>
<tr>
<td>Patients with the capacity (cognition and/or language) to consent to participation.</td>
<td>Adults must have the capacity to consent or refuse medical treatment (The Australian Law Reform Commission, 2014).</td>
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</table>
Patients have the capacity to attend community nursing procedure clinics on week days when the clinic is open. This was in accordance with the NSCCH Home Safety Procedures for Community Nursing, CCH (PR2007_016).

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients scheduled for lower limb amputation.</td>
<td>Amputation of the lower limb with a CLU would negate the need for wound management of the CLU.</td>
</tr>
<tr>
<td>History of peripheral sensory neuropathy of the feet.</td>
<td>Sensory loss is a common symptom of peripheral sensory neuropathy and patients may not experience WRP (Azhary, Farooq, Bhanushali, Majid, &amp; Kassab, 2010), therefore would not be able to physically respond to the effects of the study intervention.</td>
</tr>
<tr>
<td>Patients that have had or require the use of EMLA® for debridement of the wound bed within the previous four weeks before recruitment.</td>
<td>Four weeks was an arbitrary period to minimise any potential effect EMLA® may have on baseline WRP data. There is no data to support this statement.</td>
</tr>
<tr>
<td>Patients with suspected wound malignancy or pyoderma gangrenosum, confirmed by biopsy.</td>
<td>The management of leg ulceration caused by malignancy or pyoderma gangrenosum requires specific management (Rice, 2007). Treatment of these ulcer types in the same way as venous, arterial or diabetic foot ulcers could result in poor patient outcomes.</td>
</tr>
<tr>
<td>Patients with diagnosed localised or spreading clinical wound infection.</td>
<td>Wound-related pain is increased when a wound is infected and management of wound infection requires the introduction of strategies that may influence pain levels (International Wound Infection Institute (IWII), 2016).</td>
</tr>
<tr>
<td>End stage palliative care patients.</td>
<td>End stage palliative patients often require increased use of non-opioid and opioid pain-relieving medications for palliation (World Health Organisation, 2011) making it difficult to attribute any changes in reported pain to EMLA® as a treatment.</td>
</tr>
</tbody>
</table>
Patients where EMLA® is contraindicated or cautioned. Repeated doses of EMLA® may increase blood levels therefore, to minimize the chance of participant harm, as per manufacturers recommendations, any patients who reported sensitivity to lignocaine or prilocaine, had methemoglobinemia or severe hepatic disease, or were prescribed Class III anti-arrhythmic or sulphonamide drugs were excluded from the study (Aspen Pharmacare Canada Inc., 2017).

*Abbreviations:* EMLA®, Eutectic Mixture of Local Anaesthetic; WRP, wound-related pain; CLU, chronic leg ulcer; NRS, Numerical Rating Scale; HRQoL, health-related quality of life; NSCCH, Northern Sydney Central Coast Health; CCH, Central Coast Health.
3.2.7 Randomisation

Randomisation is the most accepted and reliable method for reducing bias in clinical trials (Doig & Simpson, 2005). Randomisation was undertaken to ensure similar levels of known and unknown risk factors and clinical characteristics were present in both groups (Beller, Gebski, & Keech, 2002) and also to ensure an objective assessment of the true advantages of the intervention on wound-related pain, wound healing and HRQoL. Although the determination of group equivalence at baseline is important in RCTs, this can be difficult to achieve in smaller sample sizes that might be used in pilot studies. With smaller sample sizes, confounding factors may not be distributed equally between groups despite the use of a randomisation process (Efird, 2011).

The randomisation procedure was conducted using Power Analysis and Sample Size software (National Council for the Social Studies, Kaysville, Utah). Prelisted numbers 1 to 60 were randomly assigned to the treatment or control group using a computer-generated set of random block numbers. The randomisation process was conducted by a researcher who was not involved in screening or consenting patients. Randomisation processes were explained and participants were made aware that there was no guarantee of group allocation.

3.2.8 Allocation concealment

Allocation concealment “prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group” (CONSORT, 2017). It is often considered the most important part of randomisation (Paludan-Muller, Teindl Laursen, & Hrobjartsson, 2016) and is achievable on all RCTs (Doig & Simpson, 2005). Evidence shows that inadequate allocation concealment can yield up to 40% larger estimates of effect and greater heterogeneity in results allowing allocation bias to leak into a trial (Schulz & Grimes, 2002b).

To reduce the potential for allocation bias in this study, allocation concealment before randomisation was achieved by placing randomly assigned group allocations into sequentially
numbered, opaque sealed envelopes (SNOSE) (Doig & Simpson, 2005) numbered 1 to 60 by an independent person who held the code key. Envelopes were stored in the office of the Clinical Nurse Consultant, Research at Gosford Hospital. Treatment allocation remained concealed until consent was obtained. The participant was then assigned the next consecutive study identification number and group allocation was known. This method was selected to preserve allocation concealment because of the minimal resources available during this pilot study. Even though there are many methods to effectively preserve allocation concealment such as pharmacy-controlled randomisation, 24-hour phone-in or web-based central randomisation and numbered or coded containers for a placebo-controlled trial, they are expensive and require considerable infrastructure support (Doig & Simpson, 2005). SNOSE is the most manageable and uncomplicated method of maintaining allocation concealment while not requiring specialised technology (Doig & Simpson, 2005). The method is considered as reliable as any other method if investigators thoroughly develop and monitor the allocation process (Schulz & Grimes, 2002b).

3.2.9 Blinding

Blinding is designed to prevent perceptions about the advantages of an intervention over another which would influence outcomes leading to biased results mainly when outcome measures being used are subjective such as wound-related pain and HRQoL (Akobeng, 2005; Eskes et al., 2012).

Ideally, blinding as many individuals as practically possible such as participants, clinicians, data collectors, outcome adjudicators and data analysts limits bias in clinical trials (Karanicolas, Farrokhyar, & Bhandari, 2010). A methodological challenge in wound dressing studies evaluating primary outcomes is the lack of blinding (Gottrup et al., 2010) however, blinding in all wound care studies is complicated and difficult to achieve due to distinct characteristics of the dressings (Gottrup et al., 2010; O'Donnell & Lau, 2006). Blinding participants is impossible when comparing an intervention to standard care and could introduce performance bias (Bolton, 2016; Venkatraman, Anand, Dean, & Nettleton, 2002). In wound care studies, blinding of
assessment outcomes at least is recommended although this can be difficult to do (Bolton, 2016; Eskes et al., 2012; Gottrup et al., 2010). It is important since most outcomes are subjective such as wound-related pain and are susceptible to overestimation in favour of the intervention (Eskes et al., 2012; Schulz & Grimes, 2002a).

Although blinding of participants is a strategy which can reduce bias, particularly in the reporting of psychological or physical responses to the treatment (Schulz & Grimes, 2002a), it was not possible to blind participants in this study because a suitable placebo was not able to be sourced. Creams without active ingredients of the same colour, texture and consistency as EMLA® were unavailable and the health service pharmacy was unable to compound a suitable product. Only one known study has used E45 cream (Crookes Healthcare Ltd, Nottingham, UK) as the placebo when comparing it to EMLA® (Fassoulaki, Sarantopoulos, Melemeni, & Hogan, 2000) however, its suitability as a placebo was questionable due to the thicker consistency and different texture when compared to EMLA® and it is not widely available in Australia. Furthermore, investigators considered the introduction of daily dressing changes to enable a placebo cream to be applied to the control group had the potential to negatively impact the level of wound-related pain and wound healing due to the absence of any active pharmaceutical ingredients, therefore, was difficult to justify ethically. However, the authors acknowledge that individualised care through specific interventions can improve patient satisfaction, HRQoL, functional ability, risk of depression and pain (Edwards, Finlayson, Courtney et al., 2013; Suhonen, Valimaki & Leina-Kilpi, 2005). In a future study, economic argument would need to distinguish the costs of human resources and the positive impact of nurse contact from the effect of the intervention.

The risk associated with conducting this unblinded RCT was the potential for false or biased participant reporting regarding serious reactions and participant dissatisfaction with the study intervention resulting in participant dropout (Venkatraman et al., 2002). Participants in the
intervention group were aware they were receiving the active intervention so may have perceived this to be an improved treatment and were hopeful about its effects thus resulting in a positive skew in the data. This may introduce response bias in that participants may have wanted to avoid disappointing the investigator leading to exaggerated benefits and reduced reporting of side effects; the control group may have felt either deprived or relieved receiving standard care (Schulz & Grimes, 2002a). There was also the potential for transfer of clinician bias onto participants. Clinician influence could be manifested in the differential administration of co-interventions and dose adjustment, encouragement or discouragement of participants to continue in the study particularly for those in the intervention group, and/or influence the recording of participant responses (Schulz & Grimes, 2002a), especially if the clinician believed that EMLA® is likely to reduce wound-related pain more effectively than standard care.

When participants, clinicians and investigators cannot be blinded to the intervention in a clinical trial, to minimise bias, study groups need to be treated as equally as possible including co-interventions, management of complications and frequency of follow up (Karanicolas et al., 2010). In line with this evidence, in this study, protocols were developed to ensure that study groups were treated as equally as possible apart from the intervention. Data analysis was undertaken with a supervisor who was blinded to treatment allocation until the study assignment was disclosed. The code was broken on completion of the study and following the completion of the data analysis.

3.2.10 Study Interventions

An intervention period of four weeks and a study duration of 12 weeks were chosen as evidence relating to wound healing shows that failure of a wound to progress at four weeks indicates a high probability that the wound will remain unhealed after eight additional weeks of treatment (Cardinal, Eisenbud, Phillips, & Harding, 2008; Frykberg & Banks, 2015). Where more than one leg ulcer was present, the largest ulcer was used as the reference ulcer and all ulcers were treated as per treatment allocation.
3.2.10.1 Intervention group

The intervention was the topical application of EMLA® to chronic leg ulcers. EMLA® is a non-sterile, preservative free, 1:1 oil emulsion eutectic mixture of two amide local anaesthetics. One gram of EMLA® contains lignocaine 25mg/ml and prilocaine 25mg/ml, polyoxyethylene fatty acid esters, carboxypolymethylene and distilled water. When mixed they form an oil at temperatures above 16º centigrade; pH is 8.7 to 9.7 providing better penetration than either drug by itself and permitting higher concentrations to be used safely (Kumar et al., 2015; Sobanko et al., 2012). Lignocaine and prilocaine are similar regarding their action on excitability threshold of the peripheral nerve, membrane potential and conduction velocity without residual effects (Truant, 1965). Prilocaine is approximately 60% more effective on an isolated nerve compared to lignocaine and does not have residual effects thus is less toxic (Astrom & Persson, 1961; Englesson, Eriksson, Ortengren, & Wahlqvist, 1965; Malamed, 2014).

Following wound cleansing with normal saline 0.9%, a measured dose of 1-2 g/ml of EMLA® per 10cm² was applied to a maximum dose of 10g/100cm² to the chronic leg ulcer then a secondary dressing applied. The intervention was applied daily for four weeks or until the chronic leg ulcer had healed. If after four weeks the chronic leg ulcer remained unhealed, the participant reverted to standard care for the remaining 8-week study period. The calculated dose of EMLA® was based upon manufacturer recommendations for the application of EMLA® when applied to chronic leg ulcers for debridement. A limit of 10g was employed as pharmacokinetic data for doses larger than 10gm were unavailable (Aspen Pharmacare Canada Inc., 2017). Each participant was provided with his/her own 30 gm tube/s of EMLA® to prevent cross-infection. A Gosford Hospital clinical drug trial pharmacist monitored EMLA® use through a site accountability log, a drug supply authority and a participant specific log (Appendices 5, 6 and 7). Operational dispensing protocols of EMLA® and other primary/secondary dressings are presented in Appendix 8.
3.2.10.2 Control group

Participants in the standard care group (control) had their wounds cleansed with normal saline 0.9% and then received primary dressings deemed appropriate by the treating clinician at the time of each visit for the entire 12-week study period. Consistent with the standard practice in the Central Coast Community Nursing Service, the number of primary dressings for the control group was not limited to one dressing type. Dressing type was influenced by the wound presentation and dressing frequency ranged from daily to weekly. The primary dressings available for this study are presented in Table 3.2. Standard care (standard practice) was guided by the Australian Standards for Wound Management and the Australian and New Zealand Clinical Practice Guideline for the Prevention and Management of Venous Leg Ulcers (Australian Wound Management Association Inc., 2010; The Australian Wound Management Association Inc. & The New Zealand Wound Care Society, 2011), the most current guidelines at the time the study was in progress. For participants in the control group standard care continued during the study period until the wound was healed.

Table 3.2 Primary dressings available to community nurses

<table>
<thead>
<tr>
<th>Category</th>
<th>Trade name</th>
</tr>
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<tbody>
<tr>
<td>Alginate</td>
<td>Kaltostat&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrocolloid</td>
<td>Duoderm&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrofibre&lt;sup&gt;TM&lt;/sup&gt;</td>
<td>Aquacel&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Solosite&lt;sup&gt;®&lt;/sup&gt; gel, Intrasite&lt;sup&gt;®&lt;/sup&gt; gel</td>
</tr>
<tr>
<td>Non-adherent contact layer</td>
<td>Atrauman&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rapid capillary</td>
<td>Vacutex&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Enzyme alginogel</td>
<td>Flaminal&lt;sup&gt;®&lt;/sup&gt; hydro, Flaminal&lt;sup&gt;®&lt;/sup&gt; forte</td>
</tr>
<tr>
<td>Povidine iodine mesh</td>
<td>Inadine&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cadexamer Iodine</td>
<td>Iodosorb&lt;sup&gt;®&lt;/sup&gt; powder/oointment</td>
</tr>
<tr>
<td>Silver impregnated</td>
<td>Aquacel Ag&lt;sup&gt;®&lt;/sup&gt;, Acticoat&lt;sup&gt;®&lt;/sup&gt;</td>
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</tbody>
</table>
3.2.10.3 Secondary dressing - intervention and control groups

To reduce bias, both groups received the same secondary dressing for the duration of the study - Zetuvit® (Paul Hartmann Pty Ltd, 2003). Zetuvit® was chosen over other secondary dressings for this study following a table-top comparison with a silicon foam dressing and Zetuvit Plus® when placed over EMLA® in a 24-hour period. It was visually observed that there was less uptake of the EMLA® by the Zetuvit®. However, this evidence is anecdotal, and no studies could be located that measured the uptake of EMLA® into any dressing with or without the addition of exudate.

Zetuvit® is a sterile individually sealed absorbent pad covered with non-adherent polyamide/viscose nonwoven cover with an absorbent core made from chlorine-free bleached smooth cellulose. It is multi-layered and protective and can absorb moderate to heavy exudate from wounds which can be contained in the central core of the dressing. The absorption capacity of Zetuvit® 10 x 10cm, 10 x 20cm and 13.5 x 25 cm is 47.5ml, 95ml and 152 ml respectively (Paul Hartmann Pty Ltd, 2003). The impact of the primary and secondary dressings on wound pain was product dependent (Meuleneire & Ruknagel, 2013; Thomas, 2003; White, 2005).

3.2.10.4 Specialised wound care

Compression therapy, the gold standard for the management of chronic leg ulcers with a venous or mixed aetiology and standard practice within the health service, was commenced or continued if clinically indicated on participants in both the intervention and control groups (Central Coast Local Health District, 2015; Partsch, Flour, & Smith, 2008; The Australian Wound Management Association Inc. & The New Zealand Wound Care Society, 2011). It would be unethical not to apply compression therapy to those participants for whom it was clinically indicated as healing potential would have been negatively impacted.

In both groups, conservative sharp wound debridement was implemented if clinically indicated
that is, if there was non-viable tissue evident on the wound bed (Gethin et al., 2015). To eliminate operative pain all participants received EMLA® before the procedure which was then removed before debridement (Briggs et al., 2012). EMLA® was reapplied after debridement for participants in the intervention group who required debridement during the intervention period.

3.2.11 Strategies to promote intervention fidelity

An in-depth scheduled educational session of approximately 90 minutes was given by the thesis author to community nurses who were directly involved in patient care, participant monitoring and data collection. Any new nursing staff who were to be involved in the study were given the same level of training prior to participation in data collection. Educational content of these sessions is presented in Appendices 9a, 9b, 9c and 9d.

3.2.12 Outcomes

The primary outcome of this pilot study was to assess feasibility as defined by recruitment, retention and intervention adherence. The aim was to resolve any methodological challenges and to ensure the best use of the results to inform the design and implementation of a larger sample, lengthier, effectiveness RCTs thus enhancing the probability of its success (Bowen et al., 2009; Hubbard et al., 2016; Leon et al., 2011; Thabane et al., 2010; van Teijlingen & Hundley, 2002; Van Teijlingen et al., 2001). To test whether the research protocol was feasible, the study processes and resources, any issues related to human and data management in addition to issues relating to the study intervention were assessed (Thabane et al., 2010). Secondary outcomes were patient-related and included the effect of the intervention on chronic leg ulcer pain, wound healing and HRQoL; important outcomes in a future effectiveness trial.

3.2.12.1 Feasibility outcomes

Assessment of study feasibly was the primary outcome and recruitment; retention and adherence were the key components of feasibility assessed. The predetermined criteria for feasibility included the ability to recruit 80% of participants in 12 months, appropriateness of the eligibility
criteria that may impact recruitment and the availability of dedicated research personnel. It was anticipated that 80% of the participants would be retained during the study period. Reasons for not retaining participants in the study were documented to understand factors influencing feasibility. It was also anticipated that at least 80% adherence to the intervention protocols would be maintained. Since adherence depends on the participant and the treating nurse following the intervention protocols (Dodd, White, & Williamson, 2012), protocol deviations or violations were identified and the reasons why these occurred were documented. The strategies for ensuring treatment fidelity were examined for sufficiency such as skill acquisition, standardisation of training strategies and intervention delivery protocols.

3.2.12.2 Patient-related outcomes

The patient-related outcomes for this study included wound-related pain, wound healing and HRQoL. Wound-related pain was assessed to determine the effect of the intervention, a topical anaesthetic, on painful chronic leg ulcers. Guidelines offering recommendations for comprehensive assessment and pain management including wound-related pain are available however, they are mostly not specific to the older person (Collett, O'Mahoney, Schofield, Closs, & Potter, 2007; Hadjistavropoulos et al., 2007; Herr et al., 2006; World Union of Wound Healing Societies, 2004). More recently a guideline specific to pain management for older persons has emerged (British Geriatrics Society, 2013) and this is particularly relevant considering most individuals with painful chronic leg ulcers are over the age of 65 years. Poor pain assessment coupled with the reluctance of older people to report pain, leads to poor management and increases the risk of adverse effects associated with pain (Department of Veterans Affairs, 2000; Eriksen, Jensen, Sjogren, Ekholm, & Rasmussen, 2003; Idvall, Bergqvist, Silverhjelm, & Unosson, 2008; Paice & Cohen, 1997; Wilson & McSherry, 2006).

In Australia, comprehensive assessment of wound-related pain using a validated pain scale such as the numerical rating scale or visual analogue scale is recommended (The Australian Wound
Management Association Inc. & The New Zealand Wound Care Society, 2011; Wounds Australia, 2016). Specific recommendations include investigation and documentation of pain location, severity, characteristics, triggers and relievers, the frequency of pain and the impact on health-related quality of life (The Australian Wound Management Association Inc. & The New Zealand Wound Care Society, 2011). Additionally, pain assessment needs to determine the aetiology and presentation of non-cyclic, cyclic and chronic wound pain (Wounds Australia, 2016). These recommendations are congruent with the current international guidelines on the assessment of wound-related pain of chronic leg ulcers (Bobham & Flemister, 2008; eTG. Therapeutic Guidelines Australia, 2013; Wound Ostomy Continence Nurses Society, 2012).

Wound healing is the main objective of any wound management strategy. As previously discussed in Chapter 1, wound-related pain directly impacts wound healing (Solowiej & Upton, 2010; Upton & Solowiej, 2010; Woo, 2008). Measurement of the rate of healing is important in this study as an assessment of wound-related pain is the primary clinical outcome. The effect of the study intervention on chronic leg ulcer pain may impact healing rates so wound measurement over time is crucial to monitoring the success of this wound management strategy by providing a baseline from where wound healing can be measured and by potentially predicting wound healing outcomes (Flanagan, 2003; Little, McDonald, Jenkins, & McCarron, 2009).

The literature supports the use of prognostic methods to predict the likelihood of complete wound closure. Initial chronic leg ulcer size coupled with ulcer duration can predict which wounds will heal by 24 weeks. Prediction models suggest that there is a 29% chance that a wound less than 10cm² and of less than 12 months’ duration at the first visit will not heal by 24 weeks. The chance of the wound not healing by 24 weeks is greatly increased (78%) if the wound size is greater than 10cm² and greater than 12 months duration (Margolis et al., 2004). Additionally, margin advancement, initial healing rate, the percentage of wound surface area reduction and wound healing trajectories are also strong indicators of complete healing at 12 weeks; the poor healing rate at 4 weeks suggests that a wound is unlikely to heal by 8 weeks.
HRQOL was assessed because the presence of a chronic leg ulcer, particularly a painful one, can impact an individual’s physiological, psychological, occupational and social quality of life considerably. The success or failure of the intervention on painful chronic leg ulcer would likely be evident by the impact on the participants HRQoL.

3.2.13 Data collection and study instruments

3.2.13.1 Feasibility data

Quantitative and qualitative data were collected and assessed to measure key study processes, resources, management and scientific feasibility which would inform a subsequent RCT in a public community health service. Feasibility data were collected throughout the study by the thesis author and recorded in field notes. The contents of the key feasibility measures are presented in Table 3.3.
### Table 3.3 Contents of feasibility measures (Thabane et al., 2010)

<table>
<thead>
<tr>
<th>Feasibility measure</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Processes</strong></td>
<td>Assessment of processes that are key to a subsequent study: recruitment, retention, refusal and adherence rates; eligibility criteria and whether they are sufficient or too restrictive; and participants understanding of data collection tools</td>
</tr>
<tr>
<td><strong>Resources</strong></td>
<td>Assessment of process time and budget issues: length of time to complete data collection tools; availability and quality of equipment; appropriateness of software; commitment of health service and data collectors; capacity of participating clinics; investigator burden; capacity for participants to attend clinics; continuity of nursing services; the number of home visits; use of dressing consumables</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Assessment of potential human and data problems: adequacy of human resources to conduct a study in the timeframe; challenges for participating centers, study personnel and investigators; data entry problems; variability of data; data duplication; forgotten data values; study supervision; clinician capabilities</td>
</tr>
<tr>
<td><strong>Scientific</strong></td>
<td>Assessment of intervention safety: evaluating the participant's physiological responses to the intervention such as transient local reactions at the wound site, skin irritation or sensations and purpuric or petechial lesions in addition to monitoring of adverse events such as allergic reaction (Aspen Pharmacare Canada Inc., 2017).</td>
</tr>
</tbody>
</table>

#### 3.2.13.2 Participant clinical data

Baseline data were collected from participants before initiating the intervention and are presented in Table 3.4. Socio-demographic data included participant’s age, sex, employment and nationality. Medical and surgical history included chronic leg ulcer type (venous, arterial, mixed, incompressible or diabetic), duration (weeks), surface area (cm$^2$) and ankle brachial pressure index (ABPI) in addition to screening for 23 comorbidities. Data on medications such as opiates,
non-steroidal anti-inflammatory drugs (NSAIDs), other pain medications, antihypertensive, anticoagulant, antibiotic medications and nicotine were also collected.

Participant clinical data relating to wound-related pain, wound healing and HRQoL were collected at baseline and throughout the study. Outcome assessment time points are presented in Table 3.5 and data collection instruments used, outcome measures, estimated time of completion, psychometric properties and rationale for their use are presented in Table 3.6.

**Table 3.4 Baseline measurements**

<table>
<thead>
<tr>
<th>Participant history</th>
<th>Wound-related pain</th>
<th>HRQoL relating to CLU</th>
<th>CLU Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Socio-demographic history;</td>
<td>- WRP at dressing change -</td>
<td>- Social life;</td>
<td>- Leg ulcer surface area;</td>
</tr>
<tr>
<td></td>
<td>- Before</td>
<td>- Wellbeing;</td>
<td>- Aetiology and duration of leg ulcer;</td>
</tr>
<tr>
<td>- Medical and surgical history</td>
<td>- During</td>
<td>- Physical symptoms;</td>
<td>- Ankle Brachial Pressure Index;</td>
</tr>
<tr>
<td></td>
<td>- After;</td>
<td>- Overall HRQoL</td>
<td>- Leg ulcer measurement:</td>
</tr>
<tr>
<td></td>
<td>- Pain type;</td>
<td></td>
<td>- Exudate type and amount</td>
</tr>
<tr>
<td></td>
<td>- Quality;</td>
<td></td>
<td>- Necrotic tissue type and amount</td>
</tr>
<tr>
<td></td>
<td>- Location;</td>
<td></td>
<td>- Granulation type and amount</td>
</tr>
<tr>
<td></td>
<td>- Pain medications;</td>
<td></td>
<td>- Condition of wound edges</td>
</tr>
<tr>
<td></td>
<td>- Effects on activities</td>
<td></td>
<td>- Peri ulcer viability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Oedema type and location</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Assessment of bioburden</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Wound-related pain intensity and frequency assessment over previous 24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- How HRQoL relates to the leg ulcer</td>
</tr>
</tbody>
</table>

*Abbreviations:* WRP, wound-related pain; CLU, chronic leg ulcer; HRQoL, health-related quality of life.
Ankle Brachial Pressure Index and Lower Limb Risk Assessment tool

An ABPI, in conjunction with clinical assessment data using a Lower Limb Risk Assessment Tool (Appendix 10 and 11), was collected on each participant. This information assists the clinician to classify the leg ulcer type before the implementation of any management options (Australian Wound Management Association Inc and New Zealand Wound Care Society, 2011; Templeton & Telford, 2010; Vowden & Vowden, 2001) and is standard practice in the Central Coast Community Nursing Service. An ABPI is a non-invasive measure to determine large vessel peripheral arterial disease in the lower limb before application of compression therapy. The accuracy of the leg ulcer diagnosis is enhanced by the combination of both the ABPI and clinical assessment (Australian Wound Management Association Inc and New Zealand Wound Care Society, 2011). A Dopplex MD2 bi-directional Doppler with high sensitivity wide beam EZ8 or 5MHz probe (ArgoHuntleigh, Macquarie Park, NSW, Australia) was used to assess ABPIs in this study.

Ankle Brachial Pressure Indexes were obtained following randomisation unless the participant had vascular studies performed within the previous 6 months which were reviewed by a vascular surgeon. In these instances, ABPI reports were requisitioned from the vascular surgeons for review and data collection.
Table 3.5 Outcome assessment time points

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRP intensity</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At every dressing change</td>
</tr>
<tr>
<td>WRP over past 24 hours</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At every dressing change</td>
</tr>
<tr>
<td>When pain felt at home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Whenever pain perceived at home</td>
</tr>
<tr>
<td>CLU size</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CLU appearance and progress</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HRQoL</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Abbreviations:* WRP, wound-related pain; CLU, Chronic leg ulcer; HRQoL, Health-related quality of life.
<table>
<thead>
<tr>
<th>Data collection instrument</th>
<th>Outcome measure</th>
<th>Estimated time of completion</th>
<th>Psychometric properties</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound-related pain at dressing change monitoring and evaluation tool (World Union of Wound Healing Societies, 2007) (Appendix 12)</td>
<td>Wound-related pain intensity: the higher the score, the higher the WRP.</td>
<td>1 minute</td>
<td>NRS - discriminative power relating to chronic pain. Test, re-test reliability high ($r = 0.96$); Construct validity - highly correlated with the VAS for chronic pain conditions (reported range: 0.86 to 0.95) (Hawker, Mian, Kendzerska, &amp; French, 2011)</td>
<td>To determine the effectiveness of the intervention on WRP intensity. A reliable and valid pain assessment tool that has high compliance rates and superior responsiveness (Ferreira-Valente, Pais-Ribeiro, &amp; Jensen, 2011; Hjermstad et al., 2011)</td>
</tr>
<tr>
<td>Wound-related pain at dressing change assessment tool (World Union of Wound Healing Societies, 2007) (Appendix 13) The tool was completed by participants unless physically impaired or burdened</td>
<td>Wound-related pain response to intervention over the previous 24 hours, included: WRP timing, location, quality, medications</td>
<td>5 minutes</td>
<td>- Data collection tool not validated however its development was informed with multidisciplinary input and incorporated recommendations from the WUWHS; it was</td>
<td>- To capture the multidimensional aspects of the participant’s overall WRP experience over the previous 24 hours after application of the intervention; - Enables early identification of the participant’s WRP at dressing change so effective strategies may be implemented if</td>
</tr>
</tbody>
</table>
and effects on sleep and activities of daily living subsequently endorsed by the WUWHS in 2008 (World Union of Wound Healing Societies, 2004) necessary. It is practical, quick and easy to use

| **American Geriatric Society Pain Diary** (American Geriatric Society Panel on Persistent Pain in Older Persons, 2002) (Appendix 14) | WRP intensity; - The frequency of the consumption of pain-relieving medications | Less than 5 minutes | Data collection tool not validated however pain diaries are considered ‘valid and reliable measures of pain severity and activity’ (p. S23) and based on real-time rather than recall particularly in clinical trials and community settings (Hadjistavropoulos et al., 2007(Dansie & Turk, 2013)) |-to identify factors that intensified or reduced pain and strategies used to alleviate pain; - The tool was developed specifically for older individuals with persistent pain and recommended by an international multidisciplinary expert panel for researchers and clinicians (Hadjistavropoulos et al., 2007); - Limitations - non-adherence, considerable participant burden, recall bias and issues with current pain as an anchor for retrospective reporting (Dansie & Turk, 2013; Hadjistavropoulos et al., 2007) |
|---|---|---|---|

| **Wound photography and 2-dimensional photo-digital planimetry** | Chronic leg ulcer measurement over time (cm²) | 15 minutes including download onto a computer for | Inter-rater reliability and intra-rater reliability are higher than traditional wound tracing methods (94% and 98.3% respectively) | - This technique avoids direct contact with the wound and is quick and user friendly; - An objective measurement of wound healing was obtained and a photographic record was able to be retained and use for |
photography specifications (Appendix 15);
- Wound measurements were performed by a health service aid and an enrolled nurse who were blinded to the participant’s group assignment; definitive measurement was by a Nurse Practitioner - wound management who was not blinded. An example of digital photography and planimetry in ICIS is presented in Figure 3.2

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>- Comprises 14 clinician and 3 patient-rated domains;</td>
<td>- Exudate type and amount; Up to 10 minutes Concurrent construct validity high ($r = 0.82$) with excellent intrarater/interrater reliability for the total LUMT scores (ICC $&gt;0.75$) and for many of the 14 domains. Some domains were less reproducible (Woodbury et al., 2004)</td>
</tr>
<tr>
<td>- Each domain has 5 ordered response categories coded 0 to 4;</td>
<td>- Wound surface area, depth and undermining;</td>
</tr>
<tr>
<td>the sum of the clinician-rated and</td>
<td>- Necrotic tissue type and amount;</td>
</tr>
<tr>
<td></td>
<td>- Granulation type and amount;</td>
</tr>
<tr>
<td></td>
<td>- Wound edge status.</td>
</tr>
<tr>
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</tbody>
</table>
patient-rated domains are totalled to ascertain overall leg ulcer assessment over time;  
- A reduction in scores over time indicates an improvement of the CLU

<table>
<thead>
<tr>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consists of 47 items across 4 subscales</strong> –</td>
<td><strong>HRQoL while experiencing WRP;</strong></td>
<td><strong>5 to 10 minutes</strong></td>
<td><strong>The CWIS has good internal consistency reliability (Cronbach’s $\alpha = 0.77 - 0.96$), and a high level of reproducibility ($p = &lt;0.001$)</strong></td>
</tr>
<tr>
<td>- 3 subscales use 5-point Likert scale: Social life, Well-being and Physical symptoms and Daily Living;</td>
<td><strong>- Participants ability to socialise;</strong></td>
<td></td>
<td>- The CWIS can discriminate between health states (healed vs non-healed wounds);</td>
</tr>
<tr>
<td>These subscales are changed onto a 0-100 scale using a formula provided by the developers of the tool;</td>
<td><strong>- Participants well-being regarding the wound and anxiety about the wound outcome;</strong></td>
<td></td>
<td>- Is sensitive enough to distinguish between experiences of a wound from other factors present in this patient population;</td>
</tr>
<tr>
<td></td>
<td><strong>- The impact of symptoms on comfort and daily functioning of the participant;</strong></td>
<td></td>
<td>- A validated condition-specific measure questionnaire to assess the HRQoL in participants with chronic wounds of the lower limb irrespective of the ulcer aetiology (Jaksa &amp; Mahoney, 2010; Price &amp; Harding, 2004);</td>
</tr>
</tbody>
</table>
Overall HRQoL consists of 2 questions using an 11-point Likert scale - How good is your quality of life? and How satisfied are you with your overall quality of life? - For all subscales, a high score signifies a positive rating

Has been validated linguistically for translation into French, German, US English and Swedish (Acquadro, Price, & Wollina, 2005; Fagerdahl, Bostrom, Ulfvarson, Bergstrom, & Ottosson, 2014), which would be a benefit for use in future international multisite trials;

Disease-specific HRQoL tools support the importance of pain for people with chronic leg ulcers and also highlight the impact of sleep disturbance, exudate, malodour, and social isolation on HRQoL however, as with generic tools, these tools also exhibit variations in the degree of sensitivity to changes in ulcer status (Green & Jester, 2010)

Abbreviations: WRP, wound-related pain; CLU, chronic leg ulcer; HRQoL, health-related quality of life; NRS, Numerical Rating Scale; WUWHS, World Union of Wound Healing Societies; ICIS, Integrated Community Information System; RA, research assistant; LUMT, Leg Ulcer Management Tool; ICC, intraclass correlation coefficient; r, correlation coefficient.
In this study, self-report questionnaires were used to capture data on wound-related pain and HRQoL. Self-report methods are robust regarding adaptability and directness and frequently yield information from participants that can be difficult to gather using other methods (Polit & Beck, 2017). Despite these advantages, self-reports have their weaknesses. The most serious weakness is the validity and accuracy of self-reports. Individuals can distort the data resulting in random measurement error and systematic bias particularly if respondents have an imperfect recall or deliberately give misleading answers (Polit & Beck, 2017; van de Mortel, 2008). The investigators were cognisant of the limitations of this method when interpreting the results.

3.2.14 Data storage, confidentially and management

As per the Australian Code for the Responsible Conduct of Research (National Health Medical Research Council, Australia Research Council, & Universities Australia, 2007) and in line with ethics requirements, all study data were safely and securely stored in a locked cabinet at each clinic until it was collected by the chief investigator where it was then securely stored at the Peninsula Sector of the Central Coast Local Health District Community Nursing Service. Participant confidentiality and anonymity were maintained in any publications or presentations.
Data were transcribed into a Microsoft Excel® database and checked for accuracy that is, whether it was clean, correct and useful. Data collection time points were coded then all data were imported into Statistical Analysis for Social Sciences (SPSS Version 22, Chicago, USA) for analysis. A random sample (17%) of the data was verified against original questionnaires. The error rate was 3.7%.

3.3 Data analysis

3.3.1 Intention-to-treat
This study adhered to the intention-to-treat (ITT) principle, which means that all participants who were enrolled and randomised to treatment were analysed in the groups to which they were allocated regardless of whether they received or adhered to the intervention (Armijo-Olivo, Warren, & Magee, 2009). This prevented the rationale for randomisation being defeated which could also lead to bias (Akobeng, 2005; Eskes et al., 2012). To limit bias, ITT analysis is considered the gold standard for the analysis of data in clinical trials (Armijo-Olivo et al., 2009). ITT can be achieved with or without missing data (Armijo-Olivo et al., 2009). There is some conflict in the literature regarding the use of ITT as it has been suggested that ITT is too cautious and susceptible to Type II error and reduces power as it eases the magnitude of the effect size (Sheiner & Rubin, 1995). However, other evidence suggests that ITT has the same power as other approaches as all participant data is considered in the analysis thus less susceptible to bias (Lachin, 2000).

3.3.2 Feasibility analysis
To examine the feasibility and acceptability of the study protocol, feasibility analysis using descriptive statistics was conducted based on screening rate, participant eligibility, reasons for exclusion, randomisation, consent rate, reasons for not participating, recruitment rate, retention rate and intervention adherence. Quantitative data from field notes were analysed using descriptive quantitative data.
### 3.3.3 Analysis of secondary outcomes

Between-group demographic and clinical data were analysed using independent t-tests for normally distributed data and Mann-Whitney U Test was used for data not normally distributed. Chi-square test was used for categorical data. Due to the exploratory nature of the study, there was no adjustment for multiple testing as methods to correct for this can be overly conservative and conceal potentially interesting findings (Gelman, Hill, & Yajima, 2012).

Mean pain scores before, during, and after dressing change were analysed from baseline to week 4 to determine the effect of the intervention compared to standard care, then from weeks 4 to 12 following the cessation of EMLA® and resumption of standard care in the intervention group. To accommodate dependency in the data due to repeated measurements from the same individual over a period, linear mixed model analysis was used to analyse the change over time in mean pain scores before, during and after dressing (Cnaan, Laird, & Slasor, 1997; Krueger & Tian, 2010). This method of analysis was used to accommodate missing data where cases with missing observations at random time points were not automatically excluded from all time points.

Assumptions for linear mixed models were also assessed. Little’s Missing Completely at Random (MCAR) test (Little, 1988) was used to test for missing cases missing completely at random. The two methods for estimating the parameters in a linear mixed model are maximum likelihood (ML) and restricted maximum likelihood (REML). In this study, where it was always the intention to explore the fixed factors of group membership, time, their interaction, and individual subject as the random factor, there would not be much difference between models estimated with ML or REML (Twisk, 2006). However, REML is more appropriate for smaller sample sizes, as is the case with this study (Kenward & Roger, 1997).

To determine the magnitude of the treatment effect between the intervention and the control groups for pain before, during and after dressing change, effect sizes between the Estimated Marginal Means (EMMs) were calculated; the phi coefficient was calculated for outcomes
analysed using chi-square (Cohen, 1988). A medium effect size was considered clinically relevant. All $p$ values were two-sided.

Health-related quality of life data were analysed from baseline to week 4 (conclusion of the intervention period), to determine the effect of the intervention on HRQoL compared to standard care. Data were analysed from week 4 to week 12 to determine any changes to HRQoL in the post-intervention period. Linear mixed model analysis was also used for HRQoL data analysis to accommodate dependency in the data due to repeated measurements from the same individual over a period (Krueger & Tian, 2010). All subscales for HRQoL were analysed separately and were normally distributed at each time point. For all HRQoL subscales, effect sizes between the Estimated Marginal Means (EMMs) were calculated to determine the magnitude of treatment effect between the intervention and the control groups. In our study, a medium effect size was considered clinically relevant as the evidence shows that a mean effect size of 0.495 has been calculated for generic and disease-specific HRQoL instruments (Norman, Sloan, & Wyrwich, 2003). All $p$ values were two-sided. The description of SPSS Mixed Syntax is presented in Appendix 18.

Wound surface areas measured by digital planimetry were analysed at baseline, weeks 4 and 12. To test for differences between the groups at each time point, the Mann-Whitney U Test was used.

3.4 Summary

This chapter describes the methods used in this pragmatic, parallel group, non-blinded, superiority, pilot, randomised, controlled trial. The results of this study are presented in the following chapter comprising of three publications. The first publication presents the primary findings that are, the feasibility of the study processes, resources, management and scientific aspects of the study and the second and third publications present the patient-centred clinical findings; wound-related pain, wound healing and HRQoL.
Chapter 4 – Results and Discussion

4.1 Introduction
The principal findings of this study are presented and discussed in the three co-authored publications that comprise this chapter. Findings from additional data not included in the three papers are also presented and discussed. The primary aim of this parallel group, non-blinded, superiority, pilot randomised, controlled trial (RCT) was to explore the feasibility of the intervention and research methods with the intent for this learning to inform a subsequent study. The feasibility assessment of this pilot study has been reported in the first publication in *Pilot and Feasibility Studies* (Purcell, Buckley, King, Moyle, & Marshall, 2018). The secondary aim of this study was to evaluate the clinical outcomes. Wound-related pain was identified as the primary clinical outcome of interest for a subsequent effectiveness trial. The effectiveness of EMLA® applied daily as a primary dressing in reducing wound-related pain in participants with painful chronic leg ulcers was investigated and reported in the second publication published in *Advances in Skin and Wound Care* (Purcell et al., 2017a). Health-related quality of life and wound healing were selected as secondary clinical outcomes with results reported in the third publication published by the *International Journal of Lower Extremity Wounds* (Purcell et al., 2017b).

4.2 Feasibility
The first publication presents the primary findings of this pilot study conducted as a pragmatic, parallel group, non-blinded, superiority RCT in a large community nursing service. Sixty patients were recruited into the study for 12 weeks and randomised to the intervention or control group to investigate the effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers. Since this is the first study to investigate EMLA® used in this way, it was important to evaluate and report on the feasibility of the study processes, resources, management and scientific aspects of the study. The findings demonstrate that a subsequent study of the
effectiveness of EMLA® applied as a primary dressing on painful chronic leg ulcers is feasible. By doing this study, the study processes can be enhanced and strengthened.

**Statement of contribution to co-authored publication**

The first co-authored publication in this chapter has been published in *Pilot and Feasibility Studies*. The details including all authors are:


*My contribution to the publication involved:*

- Critical review of the literature to inform the design of the study
- Study design
- Ethical and governance approvals
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the initial draft of the paper
- Revision of the paper for important intellectual content
- Approval of the final version
- Dissemination of results

I completed the research and writing of the publication with methodological and editorial advice from my PhD supervisors Professor Andrea Marshall, Associate Professor Tom Buckley, Professor Wendy Moyle and Dr Jennie King.

(Date) 10.12.18

Student: Anne Purcell

(Date) 9.12.2018

Co-author of publication and primary supervisor: Professor Andrea Marshall

(Date) 10.12.18

Co-author of publication and external supervisor: Associate Professor Tom Buckley
Co-author of publication and associate supervisor: Professor Wendy Moyle

Co-author of publication and external supervisor: Dr Jennie King

4.2.1 Publication 1: Eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers: a pilot randomised controlled trial

Publication status: Published: 7th July 2018.


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Griffith University, Gold Coast, QLD and Central Coast Local Health District Community Nursing Service, Wyong, NSW.
Eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers: a pilot randomised controlled trial

Anne Purcell1,2,3*, Thomas Buckley4, Jennie King3,4, Wendy Moyle1,2 and Andrea P. Marshall1,2,5,6

Abstract

Background: The physical, occupational, social and psychological impact of chronic leg ulcers (CLUs) on an individual is considerable. Wound-related pain (WRP), the most common symptom, is frequently reported as moderate to severe and mostly occurs at dressing change. WRP pain may not be alleviated by oral analgesics alone. Persistent poorly controlled leg ulcer pain can negatively impact wound healing and health-related quality of life (HRQoL).

Methods: A pilot, parallel group, non-blinded, randomised controlled trial was conducted in six procedure clinics located in a public community nursing service in New South Wales, Australia to evaluate eutectic mixture of local anaesthetics (EMLA®) on painful CLUs when used as a primary dressing. The primary objective was to assess feasibility by using pre-determined criteria: at least 80% recruitment rate, 80% retention rate and 80% adherence to the study protocol. Key eligibility criteria were that participants had a painful CLU no larger than 100 cm², a numerical rating scale (NRS) wound-related pain intensity score equal to or greater than 4, low to moderate exudate, no contraindications to EMLA® and capacity to consent. One hundred and seven patients with painful CLUs were screened for eligibility; 56% (n = 60) were eligible and consented to participate in the study. Participants were randomly assigned to the intervention (n = 30) or control (n = 30) groups. The intervention group received a measured dose of the topical anaesthetic EMLA® 5% cream daily as a primary dressing for 4 weeks followed by usual wound management for a further 8 weeks. The control group received usual wound management. Participants and investigators were not blinded to the treatment. WRP was measured at every dressing change. Wound healing and HRQoL were measured at baseline, 4 and 12 weeks.

Results: Recruitment rate was lower than expected which likely meant patients were missed. Study retention rate was 90% (n = 54). Intervention fidelity was impacted by availability of resources and patient factors such as increased WRP.

Conclusion: This study identified that a larger randomised controlled trial investigating EMLA® applied as a primary dressing on painful chronic leg ulcers is feasible with modifications to the study protocol.

Trial registration: Australian New Zealand Clinical Trials Register: Registered 16 December, 2009

Keywords: Chronic leg ulcers, Wound-related pain, EMLA®
Background

Wound-related pain (WRP) is the most common symptom of CLUs with reported prevalence as high as 85% [1, 2]. The most significant pain occurs at dressing change [3, 4]. For many individuals, WRP persists despite the use of conventional pharmacologic strategies such as oral analgesia [4]. Topical analgesia and anaesthetics applied directly to the wound bed is an option for relieving WRP [5]. The eutectic mixture of local anaesthetics cream (EMLA®) has been shown to be effective for relieving pain that occurs during debridement of CLUs [5]. Regulations for the use of EMLA® on open wounds such as CLUs and its drug schedule status may differ between countries. High quality evidence evaluating topical anaesthetics for managing WRP is still emerging [5–7].

In our published single-case report [8], we suggested that the topical application of EMLA® as a primary dressing may be a promising therapy for managing pain associated with CLUs but recognised that this treatment was yet to be empirically tested. Additionally, most individuals with painful CLUs are older with multiple co-morbidities so higher rates of non-compliance are more likely. Therefore, in line with current recommendations, we conducted a pragmatic, external pilot, parallel group, randomised controlled trial (RCT) to evaluate the protocol implementation which would inform a larger trial [9]. A pragmatic approach was selected to assess the potential effectiveness of the intervention, the secondary objective, in a routine real-life practice setting. To assess feasibility as the primary outcome of this study, we were guided by the feasibility framework developed by Thabane et al. [10] including the following:

1. Eligibility, recruitment and retention; 2. resource requirements; 3. human resources and data management; and 4. scientific assessment to identify potential effectiveness and any adverse events resulting from the intervention [10].

Study feasibility was assessed using the following predetermined criteria for determining success:

- Recruitment of at least 80% of eligible patients within 12 months;
- Retaining 80% of participants in the study;
- Achieving 80% adherence to the intervention protocol

This paper reports on the feasibility findings of this pilot study. Patient-related outcomes were evaluated in this pilot study as secondary outcomes with the findings reported elsewhere [11, 12].

Methods

Study design

This feasibility study was a pilot, parallel group, non-blinded, randomised, controlled trial (RCT). The study protocol was approved by the Northern Sydney Health (AU RED Ref. HREC/09/HARR/162) and the Griffith University Human Research (GU Ref No: NRS/16/12/HREC) Ethics Committees (HREC), registered with the Australian New Zealand Clinical Trials Register (ACTRN12609001080213) and conducted in accordance with the Declaration of Helsinki (revised 2013); written informed consent was obtained from all participants. The study is reported according to the CONSORT 2010 statement [13] (Fig. 1). In line with Good Clinical Practice (GCP) [14], complications such as adverse reactions to EMLA® or wound infection were reported to the Data Safety and Monitoring Board (DSMB) and HREC.

Setting and sample

Participants considered for inclusion in this study were individuals already referred to a large health district community nursing service in New South Wales, Australia. This study was conducted across six procedure clinics within the service where approximately three-quarters of patients required wound management; 76% had one or more CLUs [15].

Community nurses assisted with preliminary screening of patients and notified the study investigators of any patient with a lower leg ulcer greater than 6 weeks’ duration, who required analgesia for WRP and had the capacity to attend the community nursing clinics for wound management. Potential patients were assessed against the inclusion and exclusion criteria (Table 1) by a member of the research team. Eligible patients were informed of the study and consent obtained.

A sample size of 60 was selected for this study as it was thought to be a good representation of the target population, large enough to provide practical information about the feasibility aspects of the study [10]. Although reported sample sizes for pilot studies vary, the median sample size per arm is often 30 [16]. In an external pilot study such as this, there is a ‘trade-off’ between maximising the precision of estimates of important parameters and sample size which impacts resources, time and costs of a study [17]. To address feasibility, we enrolled 60 patients to accommodate possible attrition throughout the 12-week study period. Attrition rates are often high in wound studies due to comorbidities associated this patient group particularly when the study period is long, where wounds may deteriorate, and the innate difficulty to adhering to the protocol over many weeks [18]. Even so, based on the community service patient profile, we estimated it would take approximately 12 months to enrol 60 patients assuming a 10% drop out rate [19]; a 20% drop-out is considered acceptable [20].

Randomisation, blinding and allocation concealment

Following eligibility assessment and consent, a simple randomisation method (1:1) was used to randomise
participants to either the intervention (EMLA®) or control group. PASS 2008 Power Analysis and Sample Size software (NCSS, Kaysville, UT) was used to generate the allocation sequence by a researcher not involved with screening patients; the investigator was blinded to the allocations. Patients were allocated to study groups by retrieving the next in a series of sequentially numbered, opaque, pre-prepared sealed envelopes. This method for allocation concealment can achieve a low risk of bias [21].

Similar to other wound care studies [18], it was not possible to blind the participants, treating nurses or the investigators to the treatment allocation as the intervention was compared to usual care and not a placebo. However, the statistician was blinded. To minimise bias, the intervention and control groups were treated as equally as possible apart from the intervention itself. Treating clinicians were required to adhere to the Australian Standards for Wound Management [22] and health service policies and procedures.
Interventions

An intervention period of 4 weeks was selected as healing rates over a 4-week period can determine intervention effectiveness [23-25]. Patients were followed-up over a 12-week period because wound margin advancement, initial healing rate and percentage of wound surface area reduction are strong indicators of complete healing at 12 weeks independent of topical dressing used [25].

**Intervention group**

Participants in the intervention group received a measured dose of EMLA® daily as a primary dressing to their CLUs for 4 weeks followed by 8 weeks of usual care.
EMLA® (Aspen Pharmacare, St Leonards, New South Wales, Australia) is a non-sterile, preservative-free, eutectic mixture of two amide type local anaesthetics lignocaine 2.5% and prilocaine 2.5% and has a good safety profile when used for debridement [26–28]. The EMLA® dose of 1–2 g per 10 cm² to a maximum dose of 10 g was based on manufacturer recommendations [28]. At each dressing change during the intervention period and following wound cleansing, EMLA® was drawn up into a syringe then spread evenly over the wound bed.

To ensure high quality and consistent application of the EMLA®, we developed an intervention protocol and provided education sessions and supervision of nurses to promote intervention fidelity. All treatments were performed by community nurses with previous experience in wound management. To assess the timing and dose of the intervention delivery and effect of the intervention on participants, random quality assurance visits to clinics or patient’s homes, review of the participant’s medical records and follow-up of the data collected were made by the chief investigator.

**Control group**

Initially, we considered using a placebo as the control group intervention however, further consideration identified that a placebo would require daily dressing changes to enable a placebo cream to be applied. The daily dressing change would confer no benefit to the participant and had potential to negatively impact wound healing; such an approach was difficult to ethically justify. Participants in the control group received usual care for 12 weeks where the primary dressing and dressing frequency (daily to weekly) were determined by clinical judgement over the treatment period. Usual care primary dressings could change throughout the study period in line with changes in exudate, non-viable tissue and microorganism levels over the course of treatment. Most common primary dressings used were hydrofibre, hydrogel, enzyme alginogel, povidone iodine mesh, cadexamer iodine and silver impregnated dressings.

Both groups received the same secondary dressing, a soft non-woven, hydrophobic polyamide fibre containing cellulose fluff core (Zetuvit®) [29]. Participants with low exudating CLUs in the intervention and control groups who experienced an increase in WRP during dressing change from secondary dressing adherence had a triglyceride mesh applied over the primary dressing and under the secondary dressing to prevent adherence. All wounds were cleansed with normal saline 0.9%. If clinically indicated, conservative sharp wound debridement and compression therapy were implemented. Regardless of treatment allocation, and in line with standard practice, all participants received EMLA® prior to conservative sharp debridement to eliminate operative pain. EMLA® was removed prior to debridement. Intervention group participants had EMLA® re-applied following debridement.

**Management of adverse events**

Participants recorded any problems or adverse reactions to the intervention in their Pain Diary which was reviewed at each clinic visit. Treating clinicians observed for known reactions to EMLA® such as blanching, erythema, oedema, pruritus, burning, purpura and contact hypersensitivity [28] at each dressing change and documented them in the participant’s electronic medical record. Additionally, a Notification of Adverse Event form was completed followed by immediate notification and discussion with the chief investigator (CI). In the event of any adverse reaction in the intervention group, treatment was ceased immediately and the medical team notified. Notifications of adverse events were mandatory and reported promptly to the NSH HREC and the DSMB by the CI.

**Measurements used to address study aims**

The feasibility of conducting an RCT in a public community health service to prevent unnecessary spending or wasting of resources in a larger study was measured by assessing quantitative and qualitative data to address key study processes, resources, management and scientific feasibility. Quantitative feasibility outcome measures included validation of the recruitment rate and randomisation processes, consent rate, retention rate, and suitability of the eligibility criteria and, data collection instruments. Additionally, to measure intervention adherence, the number of protocol deviations or violations during the study by treating nurses and participants were identified, and the reasons why these occurred were documented. Further quantitative and qualitative measures included the availability and commitment of human resources, the time to perform study processes, availability and quality of study equipment, data management outcomes and challenges and the cost estimates to conduct such a study. The feasibility of the intervention was measured by evaluating the patient’s physiological responses to the intervention and the monitoring of adverse events. Qualitative measures included participant and investigator burden. Scientific feasibility was assessed to address the clinical responses to intervention. Scientific feasibility is reported elsewhere [11, 12].

Additional, patient-specific data were collected. Baseline measurements are detailed in Table 2. Data collection instruments, their psychometric properties, assessment time-points and estimated time to complete are presented in Table 3. When data specific to a leg ulcer were required and if a participant had more than one CLU, the largest ulcer was the reference ulcer; all ulcers were treated as per group allocation.
Table 2 Baseline measurements

<table>
<thead>
<tr>
<th>Participant history</th>
<th>Wound-related pain</th>
<th>HRQoL relating to CLU</th>
<th>CLU Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Socio-demographic history</td>
<td>- WRP at dressing change</td>
<td>- Social life</td>
<td>- Leg ulcer surface area</td>
</tr>
<tr>
<td>-Medical and surgical history</td>
<td>- Before</td>
<td>- Wellbeing</td>
<td>- Aetiology and duration of leg ulcer</td>
</tr>
<tr>
<td></td>
<td>- During</td>
<td>- Physical symptoms</td>
<td>- Ankle Brachial Pressure Index</td>
</tr>
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<td></td>
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<td>- Overall HRQoL[60]</td>
<td>- Leg ulcer measurement:</td>
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<tr>
<td></td>
<td>- Pain type</td>
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Wound photograp

Table 3 Data collection instruments

<table>
<thead>
<tr>
<th>Data collection instrument</th>
<th>Outcome measure</th>
<th>Estimated time of completion</th>
<th>Psychometric properties</th>
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<td>11-point numerical rating scale [62, 63]</td>
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<td>Discriminative power relating to chronic pain. Test, re-test reliability high (r = 0.96); Construct validity—highly correlated with the visual analogue scale for chronic pain conditions (reported range, 0.86 to 0.95) [64]</td>
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<td>Cardiff Wound Impact Schedule [60]</td>
<td>Health-related quality of life</td>
<td>5 to 10 min</td>
<td>Established reliability with internal consistency subscale scores &gt; 0.75, and good reproducibility [60]</td>
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<td>Leg Ulcer Measurement Tool [61]</td>
<td>Chronic leg ulcer appearance</td>
<td>5 to 10 min</td>
<td>Concurrent construct validity high (r = 0.82) with excellent intra-rater/inter-rater reliability for the total LUMT scores (ICC &gt; 0.75) and for many of the 14 domains; some domains were less reproducible; this tool was able to detect change in wound status over time [61]</td>
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<td>Wound-related pain at dressing change assessment tool [56, 65]</td>
<td>Wound-related pain response to intervention over the previous 24 h</td>
<td>5 min</td>
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<td>Wound photography and 2-dimensional photo-digital planimetry [66]</td>
<td>Chronic leg ulcer measurement over time (cm²)</td>
<td>15 min including download onto computer for measurement</td>
<td>Inter-rater reliability and intra-rater reliability is higher than traditional wound tracing methods (94 and 98.3%, respectively) [66]</td>
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Data analysis

Data were entered and checked for missing and invalid values in Microsoft Excel® then imported into Statistical Analysis for Social Scientists (SPSS Version 22, Chicago, USA) for analysis. A random sample (10%) of the data was verified against the original case report form. Quantitative data were analysed using descriptive statistics.

Qualitative data from field notes were analysed using descriptive content analysis [30].

Results

Detailed results for key components of the feasibility assessment are provided below.

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ICC intra-class correlation coefficient, r correlation coefficient, LUMT Leg Ulcer Measurement Tool
Participants considered for inclusion in this study were individuals already referred to a large health district community nursing service New South Wales, Australia. We screened 107 patients with painful CLUs of whom \( n = 70 \) (65%) were eligible. Sixty of the eligible patients (56%) consented to participate in the study. While this met the feasibility objective, the recruitment rate was slower than anticipated and took 30 months (September 2010 to March 2013). In total, 30 patients screened did not meet the eligibility criteria. The most common reasons patients were excluded were insufficient wound-related pain, the presence of wound infection and high wound exudate. Twelve of the screened participants were not eligible due to frailty and chronic disease; seven of these participants were excluded due to the exclusion criteria. In the first 5 months, only three patients were recruited. We recognised that the exclusion criteria were too restrictive and modification took place to improve recruitment rates (Table 1). In addition, the appointment of a research assistant (RA) to assist the chief investigator (CI) also increased the recruitment rate to 2–3 per month. Comparison of groups’ socio-demographic and clinical history at baseline is presented in Table 4. Completed follow-up of all participants took 33 months (September 2010 to June 2013). The trial ended once follow-up for all participants was complete.

Retention
A retention rate of 90% of study participants was achieved. One patient in the intervention group and five in the control group did not complete the study (Fig. 1). One participant required a below knee amputation, another withdrew due to severe back pain and three withdrew as they were unable to maintain a commitment to data collection over the length of the study period. One participant in the control group was lost to follow-up.

Adherence to study procedures
Prior to commencing the study, all treating nurses were assessed as competent in applying the EMLA® dressings. During the study, approximately 30 random quality assurance checks were attended with 100% compliance to intervention protocols. Consistent with current community nursing practice, eight participants performed their own dressing changes (up to three dressings each) when treating nurses or investigators were unavailable during a holiday period. For two participants, EMLA® was continued beyond the 4-week intervention period, at the patient’s request, for management of ongoing pain. EMLA® was ceased for five (16.7%) participants; one participant requested EMLA® to be ceased due to participant burden and four participants reported unchanged or increased WRP following application of EMLA®. There were confounding factors influencing WRP for the participants who reported unchanged or increased WRP such as

![Table 4: Comparison of Groups’ socio-demographic and clinical history at baseline](image-url)

<table>
<thead>
<tr>
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<th>Intervention group (( n = 30 ))</th>
<th>Control group (( n = 30 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.4 (12.5)</td>
<td>73.8 (10.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>CLU duration (weeks)</td>
<td>26.4 (26.0)</td>
<td>20.5 (13.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>CLU surface area (cm(^2)) at baseline</td>
<td>8.01 (10.4)</td>
<td>9.2 (8.9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (43.3)</td>
<td>12 (40.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>17 (56.6)</td>
<td>18 (60.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Ulcer type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>18 (60.0)</td>
<td>22 (73.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Arterial</td>
<td>5 (20.0)</td>
<td>3 (10.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (13.3)</td>
<td>3 (10.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Incompressible</td>
<td>1 (3.3)</td>
<td>2 (6.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetic foot ulcer</td>
<td>1 (3.3)</td>
<td>0</td>
<td>0.31</td>
</tr>
<tr>
<td>Pain medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>17 (56.6)</td>
<td>13 (40.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>4 (13.3)</td>
<td>5 (16.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Other pain meds</td>
<td>21 (70.0)</td>
<td>23 (76.6)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

\( SD \) standard deviation, \( p \) value, CLU chronic leg ulcer, NSAIDS non-steroidal anti-inflammatory drugs
compression therapy applied too early and severe arterial
disease.

Data collection
Data collection instruments and time-points are presented in Table 3. The numerical rating scale (NRS) and the Wound-related Pain at Dressing Change Assessment Tool were quick and easy for both the investigator and the participant to use. The Cardiff Wound Impact Schedule was found to be long and confusing for the frailest of participants. Data from the Pain Diary was inconsistently completed and the diary was not wound specific, thus pain unrelated to CLUs was also documented by the participants. The Leg Ulcer Measurement Tool measured CLU progress; however, there was an overlap with other data collected including WRP intensity, WRP frequency and participant satisfaction with HRQoL. Health service protocols for digital photography were not always adhered to by the community nurses. This contributed to missing data, firstly due to uploading of unclear images, secondly as the computer could not calibrate some images as a ruler was not included in the image thus preventing accurate digital measurement, and finally, some images were not taken at the required time-points (47 out of 266 images). For images that were able to be measured, a specialist wound clinician was required to manually assess accuracy of CLU surface area measurements.

The mean percentage of missing data was 19% (range 8 to 25%) and was missing completely at random [11, 12]. Missing data increased as the study progressed, particularly when nurses trained in data collection were unavailable.

Resource assessment
Human resources required to conduct this study were impacted by availability of the CI and RA who had competing full-time clinical roles. The RA was only available 1 day per week for 17 months to support the study; funding was required for the RA position.

The nurse time required for dressing change and pain data collection was the same in both groups (30 min) as was the added time taken for HRQoL and wound photography data collection at the 2, 4, 8, and 12 week time-points (1 h).

Some participants required home visits during business hours and weekends mostly due to participant frailty, lack of transport options, lack of clinic capacity, and the intervention protocol that is, daily dressings for the intervention period (weekdays: intervention group n = 9 (30%); control group: n = 6 (20%); weekends: intervention group: n = 30 (100%); control group n =4 (33.3%); range: 1 to all visits). Seven participants required all visits in their homes (intervention group: n =5 (16.6%), range: 24 to 77 visits); control group: n = 2 (6.6%), range: 7 to 24 visits).

A limited economic feasibility assessment was informed by a comparison of cost estimates for the intervention and usual care primary and secondary dressings. The intervention group had higher overall costs over the 12-week study period, with increased costs attributed to increased dressing frequency. Throughout the data collection period of 33 months, the intervention group required almost double the number of dressings compared to the control group (intervention group, 1232 dressings (65.4%); control group, 651 dressings (34.6%)). Daily dressings during the intervention period for the intervention group contributed to the considerable difference between groups (intervention group, 741dressings (74.6%); control group 252 dressings (25.3%). The overall cost of dressings per dressing change was less in the intervention group (intervention group, A$6.03; control group A$8.73). However, the intervention group had a 13.2% higher overall cost of primary and secondary dressing consumables over the study period (intervention group A$7441; control group A$5684), due to the increased frequency of dressings compared to the control group.

Management assessment
Participants were initially seen in the community health service clinics. However, as the study progressed, 13 participants had difficulty attending the clinics for treatment. Hire cars were provided for these participants as a short-term solution however, due to budget restrictions, this strategy was not feasible and was discontinued after 20 months. Subsequently, participants unable to attend the clinic were treated in their homes during business hours and weekends as previously reported using existing community nursing resources. This meant that some visits were attended by nurses not educated in the intervention protocols at the beginning of the study; nurse continuity was also an issue. The potential impact on the data collected during home visits was anticipated; the CI attended the visit particularly on week-ends or made phone contact with the nurse to explain the protocols and procedures prior to the home visit.

Participant burden was observed in this study. The length of the eligibility interview, randomisation and recruitment processes (1 to 3 h), the length of the intervention (4 weeks) and study periods (12 weeks), the length of some data collection tools (up to 50 questions), the frequency of the data collection (at each dressing change), the average age and health status of the participants (73 years) and requirement of participants to come to the clinics, all contributed to participant burden.
Scientific assessment
There was no difference in WRP intensity scores between groups before dressing change over the 4-week intervention period (intervention group: mean 4.10 [95% CI 3.55, 4.63] vs control group: mean 4.21 [95% CI 3.66, 4.76]). Nevertheless, there was a statistically significant reduction in WRP for the intervention group compared to the control group during dressing change (intervention group: mean 3.39 [95% CI 2.59, 4.19] vs control group: mean 4.82 [95% CI 3.98, 5.66]) and after dressing change: (intervention group: mean 2.71 [95% CI 1.99, 3.43] vs control group: mean 3.92 [95% CI 3.16, 4.68]) [11]. EMLA® was tolerated well for 4 weeks by 83.3% (n = 25) of the intervention group. The remaining 16.6% (n = 5) of the intervention group had adverse effects from the application of EMLA® to their leg ulcers. Erythema, pallor, itching, oedema, purpuric or petechial lesions, or allergic reaction were not reported by the attending clinicians; however, five participants required EMLA® to be ceased due to increased or unchanged WRP and increased wound size. Usual care was recommenced on all participants. There were no serious adverse events to the intervention during this study.

Interestingly, two participants required recommencement of EMLA® following the 4-week intervention period at their request for the remainder of the 12 week study period due to significant exacerbation of their WRP after cessation of the EMLA® and commencement of usual care. Once EMLA® was recommenced, WRP was reduced.

Discussion
This is the first study to investigate EMLA® used as a primary dressing for relieving wound-related pain for patients with painful chronic leg ulcers. The pilot study was pivotal to assessing feasibility for a larger clinical trial and to determine potential effectiveness. The identification of potential practical problems that may cause breakdown when implementing the research study protocol into clinical practice is crucial for the success of a larger study [31, 32]. By undertaking this feasibility study, we have been able to identify ways in which the study protocol for a future multicentre randomised controlled trial could be refined although the generalisability of our results may be limited due to participant enrolment from a single site. Solutions to manage any challenges during the study and recommendations for protocol modifications to inform a larger RCT are presented in Table 5. The key learnings from this pilot study related to recruitment and retention of participants, establishing resources required and managing data collection to ensure data accuracy and completeness and are presented below.

In terms of the feasibility objectives, although we were able to recruit 100% of the target sample, it was not achieved in the predicted timeframe of 12 months. We were able to meet participant retention and intervention adherence targets of 80%, and the study outcomes suggest that it is feasible to proceed to a larger multisite clinical trial to examine EMLA® as a primary dressing on painful CLUs. However, modifications to the protocol are recommended.

Recruitment
Participant and research process factors influenced recruitment rates in this study. This experience is not uncommon in RCTs [33] where up to two-thirds of trials are unable to successfully recruit their original target [34, 35]. Protracted or ineffective recruitment can have undesirable scientific, ethical and economic consequences [36, 37]. Although random assignment may result in refusal to participate in a study [36, 38], this was not the case in this study. We overestimated the pool of patients with CLUs in the community nursing service that would meet the eligibility criteria. Known as ‘Lasagna’s Law,’ this phenomenon is a common problem in clinical research with the evidence indicating that the incidence of the disease investigated reduces to 10% of the original estimate once the study starts [38]. This is a common threat to the success of clinical research resulting in increased direct costs and challenges the commitment and morale of research staff and participants [38]. Study processes and under resourcing of research personnel contributed to slower than expected recruitment, and it is likely that eligible patients were missed.

Lack of interest, inability to commit, physical and time limitations, change to daily activities and inability to travel to the community nursing clinics were patient-related factors affecting slow recruitment in this study; all of which are frequently cited in the literature [38]. The biggest obstacle to recruitment was patient eligibility at initial screening; we excluded more than we had predicted (34%), thus potential participants with painful CLUs were omitted from the study which may have negatively affected the generalisability of our results. A literature review found that an average of 30% of patients attending eligibility screening in RCTs are ineligible [34]. The majority of potentially eligible participants in this study were older; this was expected since the older person is more likely to succumb to CLUs [39–41].

Considering the prevalence of chronic leg ulcers in society, most chronic wound trials have small sample sizes reflecting the difficulty in recruiting patients if the eligibility criteria are too restrictive [42]. It became apparent that two of the exclusion criteria were considered unnecessary hence amendments were made to the exclusion criteria to increase the recruitment rate previously described. Based on these findings, we acknowledge the importance of understanding the needs and abilities of
Table 5 Feasibility challenges, solutions and recommendations

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>Challenges</th>
<th>Solutions</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment rate</td>
<td>Recruitment was protracted. The reasons were:</td>
<td>- Employment of an RA</td>
<td>- Employment of a dedicated trial manager</td>
</tr>
<tr>
<td></td>
<td>- Insufficient dedicated research personnel coupled with competing full-time workloads</td>
<td>- Community nursing referral screening tool was developed</td>
<td>- A comprehensive screening process to identify potential participants at the beginning of the study</td>
</tr>
<tr>
<td></td>
<td>- Structured screening process prevented identification of all eligible patients</td>
<td>- Transportation was provided for some participants to clinics</td>
<td>- Establish centralised intake system to identify potential patients at first CN contact</td>
</tr>
<tr>
<td></td>
<td>- Exclusion criteria too restrictive</td>
<td>- Amendments to some exclusion criteria</td>
<td>- In-depth review of nursing resources including skill mix prior to commencement of study</td>
</tr>
<tr>
<td>Retention</td>
<td>Participant burden was increased for some frail participants</td>
<td>- Some participants were treated in their homes</td>
<td>- Include home visits for treatments in a larger study</td>
</tr>
<tr>
<td></td>
<td>- There was limited availability of transportation to clinics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resources</td>
<td>Insufficient human resources to conduct the research within the timeframe</td>
<td>Solutions:</td>
<td>Recommendations:</td>
</tr>
<tr>
<td></td>
<td>- Poor continuity of nursing services especially for home visits</td>
<td>- Further institution support was acquired during study</td>
<td>- Ensure funding and equipment for dedicated trial manager</td>
</tr>
<tr>
<td></td>
<td>- Some patients could not attend clinics</td>
<td>- Support from experienced clinical nurses to administer intervention and collect data</td>
<td>- Collaborate with health service management to ensure smooth running of the trial</td>
</tr>
<tr>
<td></td>
<td>- Re-calibration of photo digital planimetry software required for wound measurement accuracy</td>
<td>- The application of the intervention was able to be accommodated within existing clinic schedules.</td>
<td>- Establish uniform data collection processes to ensure quality data collection</td>
</tr>
<tr>
<td>Management</td>
<td>Oversight of the study was difficult for CI and RA due to competing full-time workload</td>
<td>Solutions:</td>
<td>Recommendations:</td>
</tr>
<tr>
<td></td>
<td>- Participant burden was high</td>
<td>- Ensure computer software for data entry and analysis available and appropriate</td>
<td>- Ensure funding and equipment for dedicated trial manager</td>
</tr>
<tr>
<td></td>
<td>- Prolonged consent, randomisation and baseline data collection processes</td>
<td>- Ensured technology to acquire, store and measure wound photography appropriate</td>
<td>- Identify and address competing interests with strategies to promote continuity</td>
</tr>
<tr>
<td></td>
<td>- Poor quality photos of some wounds</td>
<td>- Separated recruitment processes from baseline data collection</td>
<td>- Ensure access to information technology support</td>
</tr>
<tr>
<td></td>
<td>- Existing resources made available by health service for wound size measurements were insufficient</td>
<td>- There was easy access to information technology support</td>
<td>- Ensure accuracy and relevance of wound size measurements by specialist nurses</td>
</tr>
<tr>
<td></td>
<td>- Research data were collected parallel to health service data resulting in some duplication and extended nurse time</td>
<td>- Wound size measurements by wound specialist nurse</td>
<td>- Ensure trial-specific investigators, data collectors and administrative team with no competing interests</td>
</tr>
<tr>
<td></td>
<td>- Data collected by clinicians untrained in study processes resulted in higher rates of missing data</td>
<td>Recommendations:</td>
<td>- Ensure short recruitment processes</td>
</tr>
<tr>
<td>Scientific</td>
<td>Change to intervention protocol required for some participants due to negative clinical response</td>
<td>- Intervention ceased, changed to usual care</td>
<td>- Ensure revise and reduce the size and number of data collection tools and data collection time points</td>
</tr>
</tbody>
</table>

RA research assistant, CI chief investigator, CN community nursing

the prospective study population prior to developing eligibility criteria for a larger study. Prior to recruitment, we over-estimated how many of the potentially eligible patients would qualify for the study. Although recruitment was initially slow, the rate improved when adequate resources for screening and recruitment were in place.

The difficulty in recruiting older individuals has been well identified; however, age itself does not determine an individual’s ability to give consent to research [43]. There are factors however that are associated with age that could impact on an individual’s ability to consent effectively such as frailty, fatigue, cognitive impairment, chronic disease and/or feelings of vulnerability [43]. Nevertheless, in this study, we had a good consent rate (86%) when compared to other RCTs relating to CLUs [44–46].
Community nurses
Most wound care is attended to in the community setting and community nurses are essential for the identification of potential participants in wound care research. They have been described as “effectively the gatekeepers to trial participation” [47]. They are an important link between the investigators and participants and can influence recruitment and retention rates [38]. In this study, community nurses were enthusiastic about being involved in an RCT and could see the benefits to themselves and to the patient. They were provided with criteria to assist them to identify potentially eligible patients however, subsequently, the demands of their clinical workload impacted their ability to undertake patient screening and contributed to delayed or missed participant identification [47].

Chronic leg ulcer types
Patients with venous, arterial, mixed (arterial/venous) and diabetic foot ulcers were recruited so outcomes reflected real-world clinical practice. These ulcer types differ in their underlying aetiology and wound characteristics. To increase the ability to meet our required sample size, patients with any of the above CLU types were included. We acknowledge that such heterogeneity can threaten study validity and usefulness of a clinical trial [42]. Subgroup analysis would be a solution however, a much larger sample size would be required [42] which was not realistic for this single-centre pilot study. Additionally, simple randomisation may not be sufficient to provide well-balanced treatment groups regarding confounders in this broadly defined study; a large, multicentre RCT using stratified randomisation may be appropriate [42].

Attrition
To maintain statistical power, we aimed for less than 20% loss to follow-up. Attrition rates of 20% or more introduce bias and is a serious threat to the internal and external validity by altering the structure of the intervention and control groups [38, 48]. Common predictors for study withdrawal are older age and functional impairment [49]. The attrition rate for this study was only 10% which was encouraging considering the majority of participants were older, frail, in significant pain, had committed to a long study period, were subject to a large amount of data collection and were required to travel to community nursing clinics. To aid retention, some participants required home visits; however, in a larger study, this will require more time allocation plus additional costs [49].

Participant burden
Participant burden is a subjective, multidimensional construct relating to the perception of the participants physiological, physical and/or economic adversity with involvement in the research process [50, 51]. Investigators have traditionally addressed participant burden in clinical trials by focusing on direct risks associated with the intervention or data collection procedures. Nevertheless, it is the indirect burden that can vary due to factors such as study duration, intensity and invasiveness of study procedures [50] that needs to be considered. This pragmatic pilot study has identified direct and indirect factors that contributed to participant burden and will be able to inform a larger study to use a more pragmatic approach to reduce participant burden to maximise research participation and response rates (Table 5).

Missing data
In this study, we had a mean percentage of 19% missing data. The literature does not identify an established cut-off regarding an acceptable percentage of missing data; 5% or less is considered inconsequential, and more than 10% can result in a biased statistical analysis [52]. Additionally, missing data mechanisms and patterns can have a bigger influence on results than the proportion of missing data [52]. To manage missing data in this study, we attempted to follow up all participants, included all available data in the analysis making a plausible assumption about missing data and did a sensitivity analyses that weakened the assumptions about missing data [48]. Missing data was missing completely at random; therefore, systemic attrition did not occur and an unbiased treatment effect estimate was derived from the obtained data [48, 53]. For a definitive effectiveness trial, missing data would need to be minimised to reduce the threat to study validity. Evidence shows that 95% of RCTs report some missing data which can threaten the validity of an RCT, make a true intention to treat analysis difficult to achieve, reduce the power and efficiency of the study and lead to bias [48].

Strengths of the study
The strengths of the study include the recruitment of 100% of the target population, retention of 90% of our sample, assessment of the fidelity of the intervention, inclusion of objective outcome measures, and the ability to refine protocols and procedures. Generalizability of the results of this pilot study may be limited due to participant enrolment from a single health service. Consequently, context-specific issues that may be influenced by local, regional or country specific practices are unknown. Furthermore, there were fewer eligible participants than initially anticipated. The exclusion criteria may have resulted in some patients with painful CLUs being overlooked for inclusion in this study.

Bias could have been introduced since the participants, treating nurses and researchers could not be blinded to
the intervention. Additionally, process evaluation was not attended by a neutral party but by the researchers themselves; therefore, there is the potential that further biases may have been introduced. The study protocols and procedures placed considerable demands on the mostly frail aged participants, the treating nurses and health service resources all contributing to missing data. We recognise the need to minimise the difficulties identified in this study that participants and investigators may encounter when designing a protocol for a larger multisite study. Furthermore, regulations for the use of EMLA® on open wounds such as CLUs and its drug schedule status would have to be ascertained prior to an international study as these factors may differ between countries.

Conclusion
Our goal is to move towards a larger study with wound-related pain as the primary endpoint conducted on individuals with painful chronic leg ulcers. This pilot study provides important feasibility information that can be used to inform a definitive future study. In the interim, this study provides insight into the potential effectiveness of EMLA® on painful chronic leg ulcers, wound healing and health-related quality of life when used as a primary dressing.

Abbreviations
CI: Chief investigator; CLU: Chronic leg ulcer; DSMB: Data safety monitoring board; EMLA®: Eutectic Mixture of Local Anaesthetics; GCP: Good Clinical Practice; HREC: Human Research Ethics Committee; HRQoL: Health-related quality of life; RA: Research assistant; RCT: Randomised controlled trial; WRP: Wound-related pain

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Thank you to the participants and their families for their commitment to this study. Thank you to Jonathan Brinton and Donald Sutherland, Research Assistants, and the CLLHD Community Nursing Service for their contribution to recruitment and data collection. Thank you to Judith Fethney, Biostatistician, University of Sydney, for her assistance with data analysis. Thank you to Wendy White, Director, Wendy White Wound Care, for her role as clinical advisor to the study.

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Availability of data and materials
Ethical approval and associated ethics requirements prevent the sharing of study data.

Authors’ contributions
AP, TB, JK and AM drafted the study protocol and AP analysed the data under the regular supervision of all other co-authors. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Approved by the Northern Sydney Health (NSH) and the Griffith University Human Research Ethics Committees (HREC). Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
4.2.2 Additional feasibility findings not included in Publication 1

Data generated from the primary clinical outcome wound-related pain before, during and after dressing change as measured by the Numerical Rating Scale was used to calculate the sample size for a subsequent study. Given two-sided significance of 0.05, a power of 0.8%, effect size 0.45 +/- 0.3 and variability/standard deviation of 2.2 +/- 0.2, 274 to 306 participants would be required. The sizes have been adjusted upwards based on an estimated dropout rate of 10%.

However, while this effect size was based on the difference between mean pain scores (0.15 to 0.75) and standard deviation of pain scores (2.0 and 2.4) for both groups reported in Publication 2, it would not be used for a subsequent RCT as it would not be clinically meaningful. The evidence suggests that in general, a reduction of approximately two points (30%) on the 11-point pain intensity numerical rating scale, represents a clinically important difference (Farrar, Young, LaMoreaux, Werth, & Poole, 2001). Therefore, recalculation estimated that 52 participants would be needed to detect a difference of at least two in pain scores between the treatment and control groups. In addition, since there was a dropout rate of 10% for this study, this figure was adjusted upwards to 58 to account for potential dropouts as there is a dropout rate of 20% or more in 18% of RCTs (Bell, Kenward, Fairclough, & Horton, 2013).

4.3 The effectiveness of EMLA® as a primary dressing on wound-related pain

This publication addresses the principle clinical outcome of this pilot RCT; whether EMLA® applied daily as a primary dressing on painful chronic leg ulcers over four weeks is effective in reducing wound-related pain compared to standard care. Assessment of wound-related pain has been identified as the most appropriate primary clinical outcome for a future clinical trial. Pain intensity scores were collected before, during and after every dressing change as were data on the quality of the wound-related pain perceived by the participants. The results, published in the following paper, suggest that wound-related pain intensity was similar at baseline and before dressings change for the intervention and control groups. However, there was a statistically
significant difference in wound-related pain during and after dressings with pain being lower in the intervention group. No difference in pain quality was detected between groups. Additional unpublished findings relating to wound-related pain are presented in Section 4.3.2. All findings require further evaluation thus a subsequent definitive study is warranted.

**Statement of Contribution to Co-Authored Publication**

The second co-authored publication in this chapter has been published in the *Advances in Skin and Wound Care Journal*. The details including all authors are:


*My contribution to the paper involved:*

- Critical review of the literature to inform the design of the study
- Study design
- Ethical and governance approvals
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the initial draft paper
- Revision of the paper for important intellectual content
- Approval of the final version
- Dissemination of results

I completed the research and writing of the publication with methodological and editorial advice from my PhD supervisors Professor Andrea Marshall, Associate Professor Tom Buckley, Professor Wendy Moyle and Dr Jennie King, as well as Judith Fethney.

Student: Anne Purcell (Date) 10.12.18

(Date) 9.12.2018

Co-author of publication and primary supervisor: Professor Andrea Marshall
4.3.1 Publication 2: The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers - a pilot randomised controlled trial

**Publication status:** Published

**Publication details:** Purcell, A., Buckley, T., Fethney, J., King, J., Moyle, W. and Marshall, A.P. 2017. The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers - a pilot randomised controlled trial. *Adv Skin Wound Care, 30*(8), 354-363.

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**Institution where work was conducted:**

Griffith University, Gold Coast, QLD and Central Coast Local Health District Community Nursing Service, NSW.
The Effectiveness of EMLA as a Primary Dressing on Painful Chronic Leg Ulcers: A Pilot Randomized Controlled Trial

Anne Purcell, MNurs (Nurs Prac), RN, NP; Thomas Buckley, PhD, RN; Judith Fethney, BA; Jennie King, PhD, RN; Wendy Moyle, PhD, RN; and Andrea P. Marshall, PhD, RN

ABSTRACT
OBJECTIVE: To evaluate the effectiveness of the eutectic mixture of local anesthetics (EMLA; Aspen Pharmacare, St. Leonards, New South Wales, Australia) as a primary dressing on painful chronic leg ulcers.

DESIGN: A pilot randomized controlled trial.

SETTING: The study was conducted across 6 community nursing procedure clinics located in a community nursing service in New South Wales, Australia.

PARTICIPANTS: Sixty participants with painful chronic leg ulcers of varied etiology were recruited into the study.

INTERVENTION: Participants were randomly assigned to an intervention (daily EMLA use for 4 weeks as a primary dressing) or a standard wound care group.

MAIN OUTCOME MEASURE: The effectiveness of EMLA on wound-related pain intensity before, during, and after dressing change.

MAIN RESULTS: Mean pain scores were similar between the 2 groups at baseline ($P = .84$). During dressing change, mean pain scores across the 4-week intervention period were significantly lower in the intervention compared with the control group (intervention group: mean, 3.39 [SD, 2.16]; control group: mean, 4.82 [SD, 2.27]; $P = .02$). Mean pain scores after dressing change were also significantly lower for the intervention group over the 4-week intervention period (intervention group: mean, 2.71 [SD, 1.94]; control group: mean, 3.92 [SD, 2.03]; $P = .03$).

CONCLUSIONS: Data from this pilot study suggest that EMLA as a primary dressing may be effective in reducing chronic leg ulcer pain during and after dressing change and warrant further evaluation.

KEYWORDS: chronic leg ulcers, EMLA, pain, wound dressing

INTRODUCTION

Wound-related pain (WRP) is a major concern for patients with chronic leg ulcers (CLUs), affecting their physical, occupational, social, and psychological well-being. Defined as a lesion of the dermis usually below the knee that persists for 6 weeks or longer, the chronic inflammatory nature of a CLU causes tissue damage resulting in WRP. At least one-third of all people with CLUs report WRP, and the prevalence is as high as 85% in high-risk groups such as older adults. Pain associated with CLUs can be managed with oral pain relief agents and some topical dressings; however, these strategies are ineffective for many people, particularly at dressing change time.

During dressing changes, nearly half of persons with chronic wounds report moderate to severe pain. Wound-related pain can continue after the dressing change. Although the pain may subside for some, the majority of patients experience WRP for an hour or more, with nearly 40% reporting persistent pain for 5 hours or longer following a dressing change.

Best practice for the management of pain associated with CLUs involves multimodal approaches incorporating both nonpharmacologic and pharmacologic pain-relieving strategies. Topical applications can be used to relieve WRP, especially related to wound debridement. Use of eutectic mixture of local anesthetics (EMLA) 5% cream (lignocaine 2.5% and prilocaine 2.5% [Aspen Pharmacare, St. Leonards, New South Wales, Australia]) is recommended for WRP control prior to sharp or mechanical debridement of CLUs. The safety of EMLA when applied to CLUs to CLUs prior to debridement is well established. The recommended dose of EMLA is 1 to 2 g per 10 cm² with a maximum dose of 10 g equating to a maximum wound size of 100 cm². The low concentration of lignocaine and prilocaine combined...
(5%) reduces the potential for systemic toxicity. However, as with any medication, there are possible adverse effects that need to be monitored.

The effectiveness of EMLA during debridement was an indicator that it may also be an effective strategy for patients with persistent pain associated with CLUs. Experimental data suggest that it is effective for some patients and highlight the need for empirical research to evaluate the use of EMLA as a primary dressing. To the authors’ knowledge, the efficacy of EMLA as a primary dressing for CLUs has never been examined. In this article, the authors report a pilot randomized controlled trial (RCT) to evaluate the effectiveness of EMLA applied daily as a primary dressing in reducing WRP in patients with painful CLUs. The effectiveness of EMLA as a primary dressing on healing rates and health-related quality of life was also evaluated in this study; however, presentation of the results is beyond the scope of this article.

METHODS

Study Design

A pilot, parallel-group RCT was conducted. This study was approved by the Northern Sydney Health and Griffith University Human Research Ethics Committees and the Central Coast Local Health District Drug Committee. EMLA 5% cream is approved for use on CLUs in Australia; however, this is not consistent across all countries. The study is registered with the Australian New Zealand Clinical Trials Register (ACTRN 12609001080213) and conducted in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants. The study is reported according to the CONSORT 2010 statement.

Setting

This pilot study was conducted across 6 community nursing procedure clinics located in a community nursing service in New South Wales, Australia.

Participants

Sixty patients with painful CLUs who met the study eligibility criteria (Table 1) and provided informed consent were randomly allocated to either the control (n = 30) or the intervention group (n = 30). There were no published effect size data for EMLA as a primary dressing available to base a sample size calculation on; the sample size was based on other published pilot studies. Although reported sample sizes for pilot studies varied, the median sample size was 30. For this study, a sample size of 60 was selected to accommodate possible attrition throughout the 12-week study period.

Randomization

Patients were randomized to study groups by retrieving the next in a series of prepared envelopes that had been randomized using a computer-generated set of random numbers (PASS 2008; Power Analysis and Sample Size software; NCSS, Kaysville, Utah). A researcher not involved in screening patients conducted the randomization and notified researchers of group allocation following enrollment.

Intervention

Participants in the control group received usual care for 12 weeks where the primary dressing and dressing frequency were determined by individual practitioner’s clinical judgment. Primary dressings, defined as dressings applied directly on the wound bed underneath the secondary dressing, included hydrogel, hydrofiber, alginate, enzyme alginogel, zinc oxide gauze, silver products, and cadexomer iodine. Dressing frequency varied from daily to weekly.

Participants in the intervention group had a daily dressing change with application of a measured dose of EMLA cream (1Y2 g per 10 cm²)³ for 4 weeks before reverting to usual care for the remaining 8 weeks of the trial. The measured dose

Table 1.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>If the patient:</td>
<td>If the patient:</td>
</tr>
<tr>
<td>Had a chronic leg ulcer of at least 5-week duration and wound surface area up to 100 cm²</td>
<td>Was scheduled for leg amputation</td>
</tr>
<tr>
<td>Had low to moderate CLU exudate</td>
<td>Had required the use of EMLA cream for debridement of the wound bed within the previous 1 week</td>
</tr>
<tr>
<td>A numerical rating scale pain score of Q4 at assessment and/or within the previous week</td>
<td>Had a CLU caused by malignancy or pyoderma gangrenosum confirmed by biopsy</td>
</tr>
<tr>
<td>Were currently requiring analgesics due to previously reported wound-related pain</td>
<td>Showed evidence of spreading infection related to the CLU</td>
</tr>
<tr>
<td>Were Q18 years old</td>
<td>Was at end-stage palliative care</td>
</tr>
<tr>
<td>Had the capacity to consent to participation</td>
<td>Had an allergy to EMLA cream and/or history of local anesthetic drug sensitivity</td>
</tr>
<tr>
<td></td>
<td>Had a history of congenital or idiopathic methemoglobinemia, severe hepatic disease, or G6P deficiency</td>
</tr>
</tbody>
</table>

Abbreviations: CLU, chronic leg ulcer; EMLA, eutectic mixture of local anesthetics; G6P, glucose 6-phosphate.

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selected was guided by the recommended dose for CLUs prior to debridement.26 The 4-week intervention period was selected as studies show healing rate during the first 4 weeks of treatment is predictive of wound healing potential.22,23 Reverting to usual care after this period was to evaluate whether the application of EMLA over an extended period would impact on WRP once standard care was resumed. Both groups received the same secondary dressing, a sterile pad with an absorbent core made from chlorine-free bleached smooth cellulose (Zetuvit; Hartmann, Macquarie Park, New South Wales, Australia). All wounds were cleansed with 0.9% sodium chloride solution.

Participants in the intervention group with low-exudate CLUs who experienced dressing adherence had a triglyceride mesh applied to prevent adherence. Those in the control group with low exudate and dressing adherence had application of the triglyceride mesh or a change of the primary dressing. The secondary dressing remained unchanged for both groups.

Conservative sharp wound debridement and/or compression therapy were implemented in both groups when clinically indicated. Regardless of treatment allocation, and in line with standard practice, all participants received EMLA (1 Y2 g per 10 cm2) before conservative sharp debridement to eliminate operative pain. EMLA was removed prior to debridement.

Blinding
Because of the nature of the intervention, patients and nurses applying dressings and those collecting data were not blinded.

Measurement and Data Collection
Data collection commenced in September 2010 and was completed in June 2013. Demographic data, medical history, use of pain-relieving medications, CLU etiology, and data on size and duration were collected at baseline. Data on WRP intensity and WRP quality were collected at baseline before dressing change and initiation of treatment. The patients’ WRP was assessed weekly until week 4 and then again at weeks 8 and 12. The WRP was assessed immediately before the dressing change began, during the dressing procedure, and within approximately 10 minutes after the dressing change.

Instruments
The numerical rating scale (NRS), an 11-point scale, where a higher score indicates greater pain, was used for its discriminative power for patients with chronic pain to describe their pain intensity. A score greater than 0 or equal to 4 is considered clinically significant pain.26 The NRS is a reliable and valid tool for pain assessment that is responsive and has high compliance rates.30,31 The test-retest reliability has been reported as high (r = 0.96), and for the construct validity, the NRS is highly correlated with the visual analog scale for chronic pain conditions (reported range, 0.86 to 0.95).26

Data Analysis
An intention-to-treat principle was applied to data analysis where data from all participants (N = 60) were analyzed in the group to which they were originally allocated. Between-group demographic and clinical data were analyzed using independent t tests for normally distributed data and nonparametric equivalent for data not normally distributed. A W test was used for categorical data. Mean pain scores were analyzed from baseline to week 4 to determine the effect of the intervention compared with usual care, then from weeks 4 to 12 following the cessation of EMLA and resumption of standard care in the intervention group.

To accommodate dependency in the data due to repeated measurements from the same individual over a period, linear mixed-model analysis was used to analyze the change over time in mean pain scores before, during, and after dressing.26,28 This method of analysis was used to accommodate missing data where cases with missing observations at random time points were not automatically excluded from all time points. Assumptions for linear mixed models were assessed and found to be appropriate. Little’s miss- completely-at-random test for pain outcomes was non-significant (P = .318), indicating that data were missing at random. The 2 methods for estimating the parameters in a linear mixed model are maximum likelihood (ML) and restricted ML (REML). In the type of study conducted here, it was the author’s intention to explore the fixed factors of group membership, time, their interaction, and individual subject as the random factor; there would not be much difference between models estimated with ML or REML.32 However, REML is more appropriate for smaller sample sizes, as is the case with this study.

To determine the magnitude of the treatment effect between the intervention and the control groups for pain before, during, and after dressing change, effect sizes between the estimated marginal means were calculated; the phi coefficient was calculated for outcomes analyzed using the W test.33 A medium effect size was considered clinically relevant.

Data were analyzed using the IBM SPSS Statistics version 22 for Windows (Armonk, New York). All P values are 2-sided. Because of the exploratory nature of the study, there was no adjustment for multiple testing because methods to correct for this can be overly conservative and conceal potentially interesting findings.34

RESULTS
The flow of participants through the study is illustrated in the Figure. There were 2 protocol violations identified in the intervention group where participants continued EMLA beyond the 4-week study period for management of ongoing pain; 1 protocol
violation was identified in the control group when a participant applied topical lignocaine to his CLU.

**Demographic and Baseline Values**

Group comparisons at baseline are presented in Table 2. The mean age of participants and duration of CLUs (in weeks) were similar in both groups. All participants were white, and most were retirees not working for income. Data were collected on a range of comorbidities, and there were no significant differences with the exception of asthma (intervention, 36.6% vs control 6.6%, \( P = .005 \)), which was higher in the intervention group. The number of participants who required conservative sharp wound debridement and/or compression therapy during the study period was similar in both groups.
Table 2.

COMPARISON OF GROUPS’ SOCIODEMOGRAPHIC AND CLINICAL HISTORY

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group (n = 30)</th>
<th>Control Group (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>73.4 (12.5)</td>
<td>73.8 (10.1)</td>
<td>.89</td>
</tr>
<tr>
<td>CLU duration, wk</td>
<td>26.4 (26.0)</td>
<td>20.5 (13.4)</td>
<td>.32</td>
</tr>
<tr>
<td>CLU surface area at baseline, cm²</td>
<td>8.01 (10.4)</td>
<td>9.2 (8.9)</td>
<td>.48</td>
</tr>
<tr>
<td>Sex</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (43.3)</td>
<td>12 (40.0)</td>
<td>.79</td>
</tr>
<tr>
<td>Female</td>
<td>17 (56.6)</td>
<td>18 (60.0)</td>
<td>.79</td>
</tr>
<tr>
<td>Ulcer type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>18 (60.0)</td>
<td>22 (73.0)</td>
<td>.27</td>
</tr>
<tr>
<td>Arterial</td>
<td>5 (20.0)</td>
<td>3 (10.0)</td>
<td>.45</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (13.3)</td>
<td>3 (10.0)</td>
<td>.45</td>
</tr>
<tr>
<td>Incompressible</td>
<td>1 (3.3)</td>
<td>2 (6.6)</td>
<td>.55</td>
</tr>
<tr>
<td>Diabetic foot ulcer</td>
<td>1 (3.3)</td>
<td>0</td>
<td>.31</td>
</tr>
<tr>
<td>Conservative sharp wound debridement</td>
<td>14 (46.7)</td>
<td>10 (33.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Compression therapy</td>
<td>16 (53.3)</td>
<td>17 (56.6)</td>
<td>.79</td>
</tr>
<tr>
<td>Pain medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>17 (56.6)</td>
<td>13 (40.0)</td>
<td>.30</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4 (13.3)</td>
<td>5 (16.6)</td>
<td>.72</td>
</tr>
<tr>
<td>Other pain medications</td>
<td>21 (70.0)</td>
<td>23 (76.6)</td>
<td>.56</td>
</tr>
</tbody>
</table>

Abbreviations: CLU, chronic leg ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Five participants were excluded from wound duration analysis (intervention group: n = 2; control group: n = 3). CLU duration beyond 6 weeks could not be determined accurately for 3 participants; 1 participant had CLU duration of 23 years.

Wound-Related Pain

Participants in both the intervention and control groups reported similar levels of WRP at baseline assessment (Table 3). Data were analyzed for the 4-week intervention period before, during, and after dressing change. Pain scores before dressing change decreased in both groups over time, with participants in the intervention group reporting similar pain to the control group throughout the trial, suggesting the intervention did not influence pain before dressing change (Table 3).

Pain reduced significantly during dressing change for both groups over time (Table 4). However, during dressing change, the intervention group reported significantly lower pain over the first 4 weeks (Table 4). Effect sizes (Cohen d) for pain during this period ranged from 0.51 to 0.70 (Table 4). The difference between groups for pain...

Table 3.

COMPARISON OF GROUPS’ MEAN PAIN SCORES OVER THE INTERVENTION AND STUDY PERIODS BEFORE DRESSING

<table>
<thead>
<tr>
<th>Pain Before Dressing¹,²</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P</th>
<th>Effect Size (Cohen d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>7.26 (1.89)</td>
<td>30</td>
<td>7.36 (1.89)</td>
</tr>
<tr>
<td>Week 1</td>
<td>30</td>
<td>4.25 (2.04)</td>
<td>28</td>
<td>4.92 (2.03)</td>
</tr>
<tr>
<td>Week 2</td>
<td>29</td>
<td>3.04 (2.26)</td>
<td>25</td>
<td>3.63 (2.22)</td>
</tr>
<tr>
<td>Week 3</td>
<td>28</td>
<td>3.17 (2.28)</td>
<td>23</td>
<td>2.75 (2.21)</td>
</tr>
<tr>
<td>Week 4</td>
<td>27</td>
<td>2.83 (2.18)</td>
<td>25</td>
<td>2.44 (2.19)</td>
</tr>
<tr>
<td>Week 5</td>
<td>24</td>
<td>2.30 (2.26)</td>
<td>21</td>
<td>2.00 (2.33)</td>
</tr>
<tr>
<td>Week 12</td>
<td>18</td>
<td>1.37 (2.27)</td>
<td>14</td>
<td>1.45 (2.10)</td>
</tr>
<tr>
<td>Combined baseliney, week 4⁴</td>
<td>4.10 (1.45)</td>
<td>4.21 (1.51)</td>
<td>.76</td>
<td>-0.08</td>
</tr>
<tr>
<td>Combined baseliney, week 12⁵</td>
<td>3.46 (1.45)</td>
<td>3.51 (1.51)</td>
<td>.91</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

¹Baseline vs Week 4: type III tests of fixed effects; time P = .001.
²Baseline vs Week 4: type III tests of fixed effects; group P = .76.
³Baseline vs Week 4: type III tests of fixed effects; group × time P = .62.
⁴Baseline vs Week 12: type III tests of fixed effects; time P = .001.
⁵Baseline vs Week 12: type III tests of fixed effects; group P = .91.
⁶Baseline vs Week 12: type III tests of fixed effects; group × time P = .25.
⁷No baseline data were collected after intervention.
Table 4.

**COMPARISON OF GROUPS’ MEAN PAIN SCORES OVER THE INTERVENTION AND STUDY PERIODS DURING DRESSING**

<table>
<thead>
<tr>
<th>Pain During Dressing(^a/b)</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P</th>
<th>Effect Size (Cohen (d))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>30</td>
<td>4.12 (2.19)</td>
<td>28</td>
<td>5.54 (2.22)</td>
</tr>
<tr>
<td>Week 2</td>
<td>29</td>
<td>3.55 (2.47)</td>
<td>25</td>
<td>4.82 (2.46)</td>
</tr>
<tr>
<td>Week 3</td>
<td>28</td>
<td>3.34 (2.59)</td>
<td>23</td>
<td>4.64 (2.48)</td>
</tr>
<tr>
<td>Week 4</td>
<td>27</td>
<td>2.95 (2.60)</td>
<td>22</td>
<td>4.76 (2.53)</td>
</tr>
<tr>
<td>Week 8</td>
<td>24</td>
<td>3.05 (2.99)</td>
<td>20</td>
<td>3.08 (2.90)</td>
</tr>
<tr>
<td>Week 12</td>
<td>19</td>
<td>2.48 (2.65)</td>
<td>13</td>
<td>2.86 (2.52)</td>
</tr>
<tr>
<td>Combined weeks 1–12(^a)</td>
<td>3.39 (2.16)</td>
<td>4.82 (2.27)</td>
<td>.02(^a)</td>
<td>.65</td>
</tr>
<tr>
<td>Combined weeks 1–12(^b)</td>
<td>3.25 (2.18)</td>
<td>4.29 (2.30)</td>
<td>.08</td>
<td>.46</td>
</tr>
</tbody>
</table>

\(^a\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .02\).
\(^b\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .03\).
\(^c\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .01\).
\(^d\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .04\).
\(^e\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .01\).
\(^f\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .05\).
\(^g\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .001\).
\(^h\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .08\).
\(^i\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .30\).

\(^j\)No baseline data were collected after intervention.

During dressing change was not sustained at weeks 8 and 12 after the intervention was ceased (Table 4).

Pain after dressing change was also significantly lower in the intervention group during the 4-week treatment period (\(P = .03\)) and the 12-week study period (\(P = .05\)) (Table 5). The greatest reduction in pain was at weeks 1, 2, and 3 with effect sizes (Cohen \(d\)) ranging from 0.57 to 0.66 (Table 5).

There were no reports of spreading infection, erythema, pallor, itching, edema, purpuric or petechial lesions, allergic reaction, central nervous system reactions, or toxicity from any participant in the intervention group. Three participants in the intervention group reported an increase in WRP following application of EMLA, and the treatment was immediately ceased. In addition, 13 participants with low-exudate CLUs in the intervention and control groups experienced an increase in WRP during dressing change because of the adherence of the secondary dressing; the number of participants was similar in both groups (intervention group: \(n = 7 [23.3\%]\) vs control group: \(n = 6 [20\%], P = 1.00\)). Dressing adherence was not experienced by participants with moderate exudate.

**Effects on Wound-Related Pain Quality**

More than 50% of study participants reported a mix of nociceptive (gnawing, aching, throbbing, tender, sharp) and neuropathic (crawling, burning, stinging, shooting, tingling) pain characteristics at baseline with no difference between groups (intervention...

Table 5.

**COMPARISON OF GROUPS’ MEAN PAIN SCORES OVER THE INTERVENTION AND STUDY PERIODS AFTER DRESSING**

<table>
<thead>
<tr>
<th>Pain After Dressing(^a/b)</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P</th>
<th>Effect Size (Cohen (d))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>30</td>
<td>2.92 (2.12)</td>
<td>28</td>
<td>4.32 (2.12)</td>
</tr>
<tr>
<td>Week 2</td>
<td>29</td>
<td>2.86 (2.16)</td>
<td>25</td>
<td>4.09 (2.13)</td>
</tr>
<tr>
<td>Week 3</td>
<td>28</td>
<td>2.64 (2.36)</td>
<td>23</td>
<td>4.06 (2.29)</td>
</tr>
<tr>
<td>Week 4</td>
<td>27</td>
<td>2.44 (2.38)</td>
<td>24</td>
<td>3.25 (2.36)</td>
</tr>
<tr>
<td>Week 8</td>
<td>23</td>
<td>2.06 (2.68)</td>
<td>20</td>
<td>2.42 (2.65)</td>
</tr>
<tr>
<td>Week 12</td>
<td>17</td>
<td>1.05 (2.36)</td>
<td>13</td>
<td>2.08 (2.28)</td>
</tr>
<tr>
<td>Combined weeks 1–4(^d)</td>
<td>2.71 (1.94)</td>
<td>3.92 (2.03)</td>
<td>.03(^e)</td>
<td>.60</td>
</tr>
<tr>
<td>Combined weeks 1–12(^f)</td>
<td>2.33 (1.96)</td>
<td>3.37 (2.05)</td>
<td>.05</td>
<td>.52</td>
</tr>
</tbody>
</table>

\(^a\)Baseline Y-week 4: type III tests of fixed effects: time \(P = .06\).
\(^b\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .03\).
\(^c\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .71\).
\(^d\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .01\).
\(^e\)Baseline Y-week 4: type III tests of fixed effects: group \(P = .05\).
\(^f\)Baseline Y-week 4: type II tests of fixed effects: group \(P = .75\).

\(^g\)No baseline data were collected after intervention.
DISCUSSION

To the authors’ knowledge, this pilot RCT is the first study to evaluate the effectiveness of daily application of EMLA cream to CLUs as a primary dressing for WRP before, during, and after dressing change. The authors recognize that further research on the effectiveness and safety of EMLA cream as a primary dressing on CLUs is required before this treatment can be considered for routine use in clinical practice. Evaluation of pain interventions is important for patients with CLUs because pain can be severe and difficult to manage in this patient group. Procedural pain from routine interventions, such as dressing removal, wound cleansing, and reapplication, often results in induced, cyclic, inflammatory pain, with anxiety levels before dressing change significantly related to anticipatory pain. The quality of WRP is often variable. Pain can be categorized as nociceptive and neuropathic or have the components of both pain types (mixed). More than half of the participants in this study reported elements of both nociceptive and neuropathic pain at baseline.

In this pilot RCT, the authors demonstrated that the application of EMLA as a primary dressing resulted in a significant reduction in WRP in the intervention group during dressing change for the first 4 weeks of the study. This suggests that the use of EMLA may be an effective strategy for managing WRP for individuals with CLUs. Although there were no differences in pain before a dressing change, WRP was lower in the intervention group during a dressing change. It is possible that EMLA’s rapid onset of action contributed to decreased pain scores during dressing change. EMLA is fast acting, producing effects in the tissues immediately under the application site. Although the depth of effect is greater the longer EMLA is applied, the efficacy of EMLA is dependent on leg ulcer characteristics, location and size, the dose applied, and whether EMLA is occluded, because occlusion of EMLA by a film dressing aids in its diffusion into the tissues. The onset of action can range from 5 to 25 minutes, depending on anatomical location and duration of application, with substantial pain relief for CLUs occurring within 20 minutes. The recommended application time for EMLA when occluded prior to a procedure is 1 to 2 hours for maximum lasting effect, with several clinical trials reporting adequate dermal analgesia at 60 minutes lasting up to 4 hours after removal. Alternatively, it is also possible that the 24-hour application of EMLA maintained enough anesthetic effect to reduce anticipatory and/or procedural pain experienced from removal of the dressing, cleansing, and reapplication. People can anticipate pain at a central nervous system level if they perceive the wound treatment will be painful. Because participants in the intervention group were not blinded to receiving EMLA, they may not have anticipated an increase in pain; thus, their pain was less.

This study also demonstrated a significant reduction in WRP in the intervention group after dressing change during the intervention period. This is important because as many as 60% of patients experience WRP for an hour or more following dressing change, with 1 in 6 patients experiencing WRP for more than 3 hours. The length of time taken for WRP to subside after dressing change is an indicator of the success of a dressing regimen. In this pilot study, the majority of pain data were collected within a 30-minute timeframe; thus, it is unknown how long pain relief extends beyond this period. Others, however, have reported that postprocedural analgesia from EMLA can last for at least 4 hours, even after removal of EMLA. It is possible that those patients in the control group who required application of EMLA prior to debridement may have experienced a reduction in pain during and after dressing change. Although EMLA was removed prior to debridement, it is possible that continued analgesic effect was experienced. Nevertheless, WRP still remained significantly lower in the intervention group over the entire intervention period.

When pain was assessed before the dressing change, a clinically meaningful or statistically significant difference in WRP between the intervention and control group was not observed. This may have been due to the vascularity of the local area of the CLU, which influenced the duration of the anesthetic effect of EMLA, with increased vascularity resulting in greater clearance and shorter duration of anesthetic effect. Consequently, similar pain scores before the dressing change may have been observed. In addition, the elimination half-life of lignocaine and prilocaine may be another reason for similarities in pain scores before dressing change. Some literature describing topical use of these local anesthetics reports a half-life of 65 to 150 minutes and 10 to 150 minutes, respectively, a similar half-life of their intravenous counterparts. It is also possible that the anesthetic effect was no longer present before dressing change.

Pain intensity can be suggestive of leg ulcer type, with arterial ulcers associated with the highest average pain scores. In this study, the intervention group had more arterial leg ulcers than did the control group. This may have influenced the level of WRP; however, pain scores remained lower in the intervention group compared with the control group at almost all time points.
throughout the entire study period except for weeks 3, 4, and 8 before dressing change (Tables 3Y5).

Daily dressings have been associated with increased WRP particularly at dressing removal.\textsuperscript{1,8} In this study, EMLA performed better as a primary dressing despite the fact that the dressings were attended daily. In line with current evidence,\textsuperscript{17} daily dressings were not generally required for the control group as the wound exudate was low to moderate. The reduced frequency of dressing changes in the control group would have resulted in decreased exposure to noxious stimuli. Nevertheless, the intervention group had a greater reduction in WRP during the intervention period.

The use of EMLA as a primary dressing applied daily over 4 weeks prompted important consideration of the potential systemic toxicity from repeated applications of EMLA to CLUs as a primary dressing over an extended period. Although there is no evidence regarding the toxicity of EMLA when used as a primary dressing, research to date suggests that repeated applications of EMLA prior to sharp debridement for 30 to 60 minutes over 4 weeks result in no accumulation in plasma levels.\textsuperscript{14} In addition, EMLA applied to wounds measuring 50 to 100 cm\textsuperscript{2} over 24 hours or large doses of EMLA applied directly to buccal mucosa (8 g to 18 cm\textsuperscript{2} for 30 minutes) shows plasma levels well below toxic levels with no adverse effects.\textsuperscript{1,8}

In this pilot study, the authors compared EMLA with standard care on painful CLUs and found that it was effective in reducing WRP during and after dressing change when pain is often at its worst. The effect sizes also show there was a clinically significant effect for the intervention group compared with the control group. In the absence of any previous research regarding the effectiveness of EMLA as a primary dressing on painful CLUs, the authors conducted this pilot study to evaluate the feasibility of the research protocol and to provide data for determining the effect size and sample size calculations for a larger, multisite RCT designed to test the effectiveness of the intervention.

Limitations of Study

An RCT study design was used in this pilot work to minimize bias. Because of the nature of the intervention, the authors were unable to blind participants or the community nurses providing the treatment and collecting outcome data. It is possible that participant awareness of being allocated to the treatment group may have introduced participant bias and resulted in lower pain scores being reported. Likewise, treating clinicians may have influenced participants (either positively or negatively), depending on their views of the intervention.\textsuperscript{19}

The authors acknowledge that a single or double-blind trial design using a placebo as the primary dressing for the control group would have been optimal to minimize bias. They originally considered a control group where patients would receive daily dressing changes during the first 4 weeks of the intervention, but were unable to source a placebo cream that could be applied directly to the wound and had similar properties to EMLA. The authors also considered the issue of introducing daily dressing changes with a placebo cream that the authors knew would confer no benefit to the patient and may have negatively impacted wound healing, which the authors and wound specialists they consulted believed to be difficult to ethically justify. The difficulty in blinding interventions in wound product evaluations has also been noted in the literature.\textsuperscript{19}

Secondary dressing adherence also prompted use of a triglyceride mesh for patients in both the intervention and control groups, when patients had low-exudate wounds. In the intervention group, the triglyceride mesh was placed between the EMLA and secondary dressing. The inconsistent use of the triglyceride mesh within both groups may have introduced a confounding factor. In future studies, the authors would use a standardized secondary dressing, for example, a silicone foam or triglyceride mesh for all patients to prevent dressing adherence. They also acknowledge that the subjective nature of pain as an outcome measure contributes to an increased chance for bias.\textsuperscript{19}

An important challenge in this study was the collection of data across multiple time points, and the authors acknowledge the limitation associated with missing data. Throughout the study, there were challenges in obtaining data for each of the data points. The study was conducted in a group of patients, most of whom were older and many of whom were frail. This may have contributed to challenges in collecting complete data for all participants. In addition, clinicians normally responsible for direct patient care assisted with data collection, and it is possible that competing priorities caused some data collection to be overlooked. It was not possible to standardize data collection points, particularly those obtained during and after dressing change. This variability may have influenced data. If possible, future clinical trials should standardize data collection time points. Also, a third of participants in the control group had EMLA applied prior to debridement. The authors are unclear whether this may have impacted the reporting of pain scores. They note that a significant difference in pain scores was achieved during and after dressing change during the 4-week intervention period, suggesting that the application of EMLA in the control group for debridement did not influence these results. This limitation could not be avoided as debridement of nonviable tissue is a fundamental component of CLU management and cannot be attended without the application of EMLA, the topical anesthetic available in the authors' health service.

The authors report that 2 participants, for whom EMLA was effective at reducing WRP before, during, and after dressing change,
required EMLA treatment beyond the 4-week intervention period. The cessation of EMLA at the end of the intervention period and transition to usual care resulted in increased pain, which, through shared decision making, resulted in the reintroduction of EMLA. Ongoing use of EMLA may have influenced the results obtained after the 4-week treatment period.

In this pilot study, the authors also included participants with CLUs of different etiologies. Although the majority of the participants had venous leg ulcers, inclusion of other ulcer types may have contributed to confounding of ulcer type. By identifying the above limitations, however, this pilot study can inform a larger multisite RCT in the future.

**Implications for Practice**

This pilot work suggests that EMLA may be a promising strategy for managing WRP in patients with CLUs; however, further research is required to more comprehensively evaluate the effectiveness of this treatment.

**CONCLUSIONS**

Painful CLUs are a substantial healthcare problem and cause considerable negative physical and psychosocial problems, especially in the older adult population. This pilot study indicates that topical application of EMLA as a primary dressing is a potentially effective treatment for reducing WRP for patients with chronic CLUs, particularly during and after dressing change, and warrants further investigation.

**REFERENCES**

28. Hawker GA, Mian S, Kedzierska T, French M. Measurements of adult pain: visual analogue scale for pain (VAS pain), numerical rating scale for pain (NRS pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOP). Arthritis Care Res (Hoboken) 2011;63(S1):S240-S2.
4.3.2 Additional wound-related pain findings not included in Publication 2

Beyond what was reported in Publication 2 (Purcell et al., 2017a), additional data were analysed to understand how EMLA® when used as a primary dressing, affected the consumption of pain-relieving medications for wound-related pain. In this study, the consumption of pain-relieving medications was recorded in the American Geriatric Society Pain Diary (American Geriatric Society Panel on Persistent Pain in Older Persons, 2002). A summary of these additional data is provided below.

The number of occasions participants consumed oral pain-relieving medications per day was fewer in the intervention group (intervention group: mean 0.97 (SD 0.728) vs control group: mean: 1.49 (SD 1.12); (t = 2.0; \( p = 0.05 \)). The cumulative number of occasions pain-relieving medications were consumed over the 12-week study period was also lower in the intervention group [intervention group: mean 56.59 (SD 52.34) vs control group 92.13 (SD 89.97); (t = 1.75; \( p = 0.09 \)]. However, there were no data to indicate whether these medications were taken for treating wound-related pain or other bodily pain not associated with the chronic leg ulcer.

Additional data were also obtained from the Wound-Related Pain at Dressing Change Assessment Tool, which is unvalidated. These data were specifically related to the location of pain and the impact on participant’s sleep and activities of daily living. For location of pain, there were no differences between groups at baseline, week 4 or week 12. However, at baseline, both the control and intervention groups more frequently reported pain to be in both the wound and surrounding skin, a finding that was not sustained at week 4 or 12 (Table 4.1).
Table 4.1 Comparison of groups’ - Location of wound-related pain experienced

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>6 (20.0%)</td>
<td>9 (30.0%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Surrounding skin</td>
<td>3 (10.0%)</td>
<td>3 (10.0%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Both locations</td>
<td>19 (63.3%)</td>
<td>17 (56.7%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>6 (20.0%)</td>
<td>8 (26.7%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Surrounding skin</td>
<td>3 (10.0%)</td>
<td>3 (10.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Both locations</td>
<td>5 (16.7%)</td>
<td>5 (16.7%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>8 (26.7%)</td>
<td>4 (13.3%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Surrounding skin</td>
<td>6 (20.0%)</td>
<td>3 (10.0%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Both locations</td>
<td>2 (13.3%)</td>
<td>0 (0%)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Data regarding when pain was experienced has not been included for analysis because there were also no corresponding reports of pain intensity when using this tool. The measurement of pain before, during and after dressing change as reported in Publication 2 provides a clearer description of the impact of EMLA® in the management of wound-related pain.

The impact of wound-related pain on sleep and ADLs (Table 4.2) was also explored and no difference between the intervention and control groups regarding the effect of wound-related pain on participants’ ability to sleep was observed at any time point. However, at baseline, the control group more frequently reported an impact on ADLs, although this was not sustained at weeks 4 and 12. Over the 4-week intervention and 12-week study periods the frequency at which wound-related pain influenced ADLs decreased for both the intervention and control groups.
Table 4.2. Comparison of Groups’ effects of wound-related pain on sleep and activities of daily living

<table>
<thead>
<tr>
<th>WRP effect on sleep</th>
<th>Intervention group n (%)</th>
<th>Control group n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20 (66.6%)</td>
<td>22 (73.3%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Week 4</td>
<td>8 (26.6%)</td>
<td>9 (30%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Week 12</td>
<td>2 (6.7%)</td>
<td>5 (16.7%)</td>
<td>0.23</td>
</tr>
<tr>
<td>WRP effect on ADLs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14 (46.6%)</td>
<td>22 (73.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Week 4</td>
<td>12 (40%)</td>
<td>15 (50%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Week 12</td>
<td>8 (26.6%)</td>
<td>6 (20%)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: WRP, wound-related pain; ADLs, activities of daily living

4.3.3 Discussion of unpublished wound-related pain findings

It is the response to noxious stimuli and tissue damage that is identified as the origin of pain perception for chronic leg ulcers (Zhao et al., 2017). Dressing change can cause such stimuli and is considered to be a major cause of wound-related pain (Butcher & White, 2014; Moffatt et al., 2002; Price et al., 2008). Wound-related pain does not resolve immediately after dressing change and can be experienced for a variety of reasons in different locations such as the wound itself or surrounding tissues (Hopman et al., 2013; Price et al., 2008; Vandenkerkhof et al., 2013). Wound-related pain can also continue after dressing change for more than five hours and in some cases, oral pharmacological pain management strategies may not be effective and can impact an individual’s ability to sleep and perform ADLs (Price et al., 2008). In this study a difference in the number of oral pain-relieving medications consumed by the participants over the study period was not observed. Analysis of these data is problematic as the American Geriatric Society Pain Diary (Appendix 14) did not allow for explanation of why oral pain-relieving medications were being taken so consequently it was unclear whether the oral consumption of pain-relieving medication was specifically for the management of wound-related
pain associated with the chronic leg ulcer or for another reason. Many of these participants had additional comorbidities therefore, it is possible that the oral medications were taken to alleviate other sources of bodily pain.

EMLA® can provide local anaesthesia for four hours even after removal from a chronic leg ulcer (Hansson et al., 1993) however, its effectiveness when retained on the leg ulcer as a primary dressing on pain perceived at the wound site and surrounding skin as well as effects on an individual’s sleep and ADLs had not previously been explored. In this study, although applying EMLA® as a primary dressing on chronic leg ulcers did demonstrate statistically significant improvements in wound-related pain during and after dressing change for the intervention group, there were no differences between the intervention and control groups regarding where wound-related pain was experienced or its effects on participant’s sleep or ADLs. The lack of difference observed between the intervention and control groups could possibly be attributed to Type II error.

However, over the 4-week intervention and 12-week study periods, the frequency at which pain was experienced in both the wound and surrounding tissues decreased as did the number of participants whose sleep and ADLs were impacted by wound-related pain. Pain in the wound and surrounding tissues may have decreased over time because the wound environment was conducive to healing. Wounds that are not healing well can have an exudate level that is either too high or too low resulting in desiccation and/or maceration of the wound and a high microorganism load contributing to increased inflammation or infection. When these factors are present pain intensity can be increased (Bechert & Abraham, 2009). Recommendations from a critical review on the impact of topical treatments on the wound microenvironment in wounds such as chronic leg ulcers, highlights that dressings need to provide a moist wound environment, and when necessary, modulate the microenvironment with antimicrobials and analgesics which
will control wound-related pain and accelerate wound healing (Junker, Kamel, Caterson, & Eriksson, 2013). Good pain control can influence an individual’s ability to sleep and cope with their ADLs therefore positively modulating the healing response (Guo & Dipietro, 2010). The relief of wound-related pain as a result of using topical anaesthetics could theoretically improve sleep and ADLs as indicated in the case report (Appendix 1). However, this would need to be investigated further in a subsequent study that was appropriately powered to detect a difference in these specific clinical outcomes.

4.4 The effectiveness of EMLA® used as a primary dressing on health-related quality of life and wound healing

This publication presents the secondary clinical results of this pilot RCT; whether the effect EMLA® may have on painful chronic leg ulcers when applied daily as a primary dressing is associated with improvements in wound healing and/or HRQoL. The results showed that there was no difference in wound healing trajectories between the intervention and control groups at baseline or over the 12-week study period. Similarly, there was no difference in any of the HRQoL subgroups at baseline or over the study period except for a statistically and clinically significant improvement in the subgroup Wellbeing at the end of the 4-week intervention period. This publication reports that the intervention did not negatively impact wound healing or health-related quality of life compared to standard care. However, a subsequent definitive study is warranted to determine more conclusively. Unpublished data relating to leg ulcer measurement is presented in Section 4.4.2.

Statement of contribution to co-authored publication

The first co-authored publication in this chapter has been published in Pilot and Feasibility Studies. The details including all authors are: Purcell, A., et al. (2017). The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers: effects on wound healing and health-related quality of life. International Journal of Lower Extremity Wounds 16(3): 163-172
My contribution to the publication involved:

- Critical review of the literature to inform the design of the study
- Study design
- Ethical and governance approvals
- Enrolment of participants
- Data collection
- Data analyses
- Data interpretation
- Writing of the initial draft of the paper
- Revision of the paper for important intellectual content
- Approval of the final version
- Dissemination of results

I completed the research and writing of the publication with methodological and editorial advice from my PhD supervisors Professor Andrea Marshall, Associate Professor Tom Buckley, Professor Wendy Moyle and Dr Jennie King.

Student: Anne Purcell (Date) 10.12.18

(Date) 9.12.2018

Co-author of publication and primary supervisor: Professor Andrea Marshall

(Date) 9.12.18

Co-author of publication and external supervisor: Associate Professor Tom Buckley

(Date) 10.12.18

Co-author of publication and associate supervisor: Professor Wendy Moyle

(Date) 10.12.18

Co-author of publication and external supervisor: Dr Jennie King

(Date) 11.12.18

Co-author of publication and biostatistician: Judith Fethney
4.4.1 Publication 3: The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers: effects on wound healing and health-related quality of life.

Publication status: Published.


The effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers: effects on wound healing and health-related quality of life. *International Journal of Lower Extremity Wounds*. 16(3), 163-172.

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Institution where work was conducted:
Griffith University, Gold Coast, QLD and Central Coast Local Health District Community Nursing Service, NSW
The Effectiveness of EMLA as a Primary Dressing on Painful Chronic Leg Ulcers: Effects on Wound Healing and Health-Related Quality of Life

Anne Purcell, RN, MNurs (Nurs Prac)1,2, Thomas Buckley, RN, PhD3, Judith Fethney, BA3, Jennie King, RN, PhD2,3, Wendy Moyle, RN, PhD1, and Andrea P. Marshall, RN, PhD1,4

Abstract
This study aimed to evaluate the effect of EMLA 5% cream applied to painful chronic leg ulcers (CLUs) as a primary dressing on wound healing and health-related quality of life (HRQoL). A pilot, parallel-group, nonblinded, randomized controlled trial was conducted in 6 community nursing procedure clinics in New South Wales, Australia. A total of 60 participants with painful CLUs of varied etiology were randomly assigned to the intervention (EMLA daily for 4 weeks as a primary dressing, followed by usual care) or usual care only. Wound size and HRQoL were measured at baseline, end of the intervention period (week 4), and week 12. At baseline, wound sizes were similar for both the intervention and control groups. During the intervention period, there was no significant difference in wound sizes between groups (intervention group: mean = 52.41, SD = 21.25; control group: mean = 38.15, SD = 21.25; P = .03; d = 0.62). The trial findings suggest that daily applications of EMLA as a primary dressing do not inhibit wound healing and may improve patient well-being. Studies with larger samples are required to more comprehensively evaluate the impact of this treatment on wound healing and HRQoL.

Keywords
chronic leg ulcers, pain, EMLA, healing, health-related quality of life

A chronic leg ulcer (CLU) is defined as a lesion that deviates from the normal healing process regarding time, appearance, and response to treatment and does not demonstrate significant signs of healing, such as an advancing wound edge in 6 weeks.1,2 A CLU is a symptom of underlying disease that directly and indirectly challenges wound healing potential3 and is associated with considerable reduction in an individual’s health-related quality of life (HRQoL).4

Wound healing is an exceedingly complex process involving a cascade of overlapping and interdependent events, which, in normal circumstances, would result in wound healing.5 However, when the wound environment becomes hypoxic and has poor lymph drainage, a heavy bio-burden, the presence of necrotic tissue, and elevated levels of proinflammatory cytokines and proteases, wound healing is delayed, and a chronic wound such as a leg ulcer develops.6 CLUs provide a perfect environment for micro-organisms to proliferate, placing greater demands on the immune system. The more diverse the microbiology, the more unmanageable the micro-organisms, which increases the risk for wound infection, pain, and delayed wound healing.7

The presence of a CLU can affect HRQoL,8 with pruritus, exudate, malodor, edema, poor mobility, sleeplessness, and wound-related pain affecting psychological, occupational, and social quality of life considerably.4 The relationship between physiological stress and wound healing can indirectly promote health-damaging behaviors.9,10

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Central to good healing trajectories and improved HRQoL is control of wound-related pain.\textsuperscript{11-15} Patients associate reduction in pain with wound healing, and the anticipation of healing can contribute to improved HRQoL.\textsuperscript{4} Rectifying the physiological changes that lead to wound chronicity and wound-related pain, such as poor blood supply, bacterial burden, edema, and inflammation, together with pharmacological and nonpharmacological pain relieving strategies and appropriate wound management will likely reduce wound-related pain and improve healing and HRQoL.\textsuperscript{2,14} However, effective pain relief may be difficult to achieve using conventional strategies.\textsuperscript{16}

Topical analgesia can be used when oral analgesia is ineffective as an adjunct or alternative pain relieving strategy. In Australia, the use of the topical anesthetic cream EMLA (Aspen Pharmacare, St Leonards, NSW, Australia) a eutectic mixture of 2 amide-type local anesthetics—lignocaine 2.5% and prilocaine 2.5%—on CLUs to manage pain associated with debridement is part of usual care.\textsuperscript{17} However, the use of EMLA as a method of managing wound-related pain for patients with CLUs outside the context of debridement has not been previously evaluated.\textsuperscript{18} Only 1 small-sample study examines repeated applications of EMLA on CLUs and wound healing when used prior to debridement.\textsuperscript{19} A few small-sample animal studies and 1 human study have evaluated the effects of EMLA on wound healing; however, these studies are limited by their use of an acute wound model\textsuperscript{20,22}; acute wound pathophysiology is considerably different to that of a chronic wound.\textsuperscript{25}

We evaluated the effectiveness of EMLA as a primary dressing for painful CLUs using the Numerical Rating Scale to assess pain intensity and demonstrated that daily use does significantly reduce wound-related pain, particularly during and after dressing change.\textsuperscript{26} Although the effect of EMLA on pain was the primary objective of the trial, we also wanted to consider whether EMLA used in this way would affect other important patient outcomes. Consequently, we purposely evaluated wound healing and HRQoL as important secondary outcomes. In this article, we report the analysis of data relating to the daily application of EMLA on painful CLUs and its effect on wound healing and HRQoL.

Methods

Study Design

A pilot, parallel-group, nonblinded, randomized controlled trial (RCT) design was used to conduct this study. Although not consistent across all countries, in Australia, EMLA 5% cream is approved for use on CLUs for wound debridement only.\textsuperscript{27} Institutional ethics approval was obtained from Northern Sydney Health and Griffith University Human Research Ethics Committees (AU RED Ref. HREC/09/HARBR/162) and the Central Coast Local Health District Drug Committee. The study was conducted in accordance with the Declaration of Helsinki (revised 2013) and reported according to the CONSORT 2010 statement.\textsuperscript{28} Written informed consent was obtained from all participants.

Participants and Randomization

Prospective study participants included all patients from 6 community nursing clinics in New South Wales, Australia, with painful CLUs of varied etiology who met the eligibility criteria (Table 1). A total of 60 patients who met the criteria were randomly allocated to either the control (n = 30) or the intervention group (n = 30). Because this is the first study we know of to examine EMLA as a primary dressing on CLUs, there were no published data available to inform a sample size calculation for this work. A sample size of 60 was

### Table 1. Inclusion and Exclusion Criteria.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>The patient had a chronic lower-leg ulcer of at least 6 weeks’ duration and wound surface area up to 100 cm(^2)</td>
<td>The patient was scheduled for leg amputation.</td>
</tr>
<tr>
<td>Low to moderate CLU exudate</td>
<td>Had or required the use of EMLA cream for debridement of the wound bed within the previous 1 week.</td>
</tr>
<tr>
<td>A Numerical Rating Scale pain score of 4 or greater at assessment and/or within the previous week</td>
<td>Had a CLU caused by malignancy or pyoderma gangrenosum confirmed by biopsy.</td>
</tr>
<tr>
<td>Wound-related pain that required oral analgesics</td>
<td>Showed evidence of spreading infection relating to the CLU.</td>
</tr>
<tr>
<td>An age of 18 years or more</td>
<td>Was in end-stage palliative care.</td>
</tr>
<tr>
<td>Capacity to consent to participation</td>
<td>Had an allergy to EMLA cream and/or history of local anesthetic drug sensitivity.</td>
</tr>
<tr>
<td></td>
<td>Had a history of congenital or idiopathic methemoglobinemia, severe hepatic disease, or G6P deficiency.</td>
</tr>
<tr>
<td></td>
<td>Was prescribed class III antiarrhythmic drugs or sulfonamides.</td>
</tr>
<tr>
<td></td>
<td>Was lactating, pregnant, or aiming to fall pregnant.</td>
</tr>
</tbody>
</table>

Abbreviation: CLU, chronic leg ulcer.
selected because this is consistent with that of other pilot studies and allowed for attrition, given our sample was of older adults. Participant flow through the study is illustrated in Figure 1. To ensure the validity of the RCT for this pragmatic pilot study, patients were randomized into study groups using a computer-generated set of block random numbers (PASS 2008 [Power Analysis and Sample Size software], NCSS, Kaysville, UT); then, the randomization sequence was placed into consecutive pre-prepared opaque envelopes. The envelopes were secured by a researcher who was not involved in screening patients. After enrollment, the Chief Investigator (CI) or Research Assistant (RA) contacted the researcher by telephone, who then notified the CI or RA of group assignment after enrollment.
**Intervention**

Participants and nurses applying dressings and those collecting data were not blinded to group allocation because of the nature of the intervention. Participants in the intervention group had a daily application of a measured dose of EMLA cream (1-2 g per 10 cm²) to the CLU (wound bed only) as the primary dressing: that is, directly on the wound bed underneath the secondary dressing for 4 weeks. For the remaining 8 weeks, participants received usual care. In this study, usual care is defined as current evidence-based wound management strategies appropriate to the patient’s condition as judged by the treating clinician. Although daily dressings for low to moderate exudating wounds is not usually advocated, there is no known evidence regarding the use of EMLA as a primary dressing on CLUs; therefore, patient safety was the rationale for this decision. As demonstrated in our published case report, daily dressings are possible even when compression therapy is required. This method was chosen because there was significantly less interobserver variation when compared with contact tracings.

HRQoL data were collected during a scheduled treatment visit where patients scored their HRQoL for the previous 24 hours. HRQoL was assessed using the Cardiff Wound Impact Schedule (CWIS; Wound Healing Research Unit, Cardiff University). The CWIS has been previously reported to have good internal consistency reliability (Cronbach $\alpha = .77-.96$) and reproducibility and is sensitive enough to discriminate between health states. In our study, the Cronbach $\alpha$ of all CWIS subscales were as follows: Social Life, $\alpha = .82$; Wellbeing, $\alpha = .92$; Physical Symptoms and Daily Living, $\alpha = .81$; Overall Quality of Life (How good is your quality of life: $\alpha = .91$; How satisfied are you with your overall quality of life: $\alpha = .82$).

**Data Analysis**

Data were analyzed using the IBM SPSS Statistics version 22 for Windows (Armonk, NY). An intention-to-treat principle was applied to data analysis, where data from all participants ($n = 60$) were analyzed in the group to which they were originally allocated. Categorical data were analyzed using the $\chi^2$ test of independence. Because of the exploratory nature of the study, there was no adjustment for multiple testing because methods to correct for this can be overly conservative and conceal potentially interesting findings.

Between-groups demographic and clinical data were analyzed using 2-sided independent $t$-tests for normally distributed data and the Mann-Whitney $U$ test for data not normally distributed. Wound sizes were analyzed at baseline and weeks 4 and 12. To test for differences between the groups at each time point the Mann-Whitney $U$ test was used.

HRQoL data were analyzed from baseline and week 4 (conclusion of the intervention period) to determine the effect of the intervention on HRQoL compared with usual care. Data were analyzed from week 4 to week 12 to determine any changes to HRQoL in the postintervention period. A linear mixed-model analysis was used to accommodate dependence in the data arising from repeated measurements from the same individual over a period of time. All subscales for HRQoL were analyzed separately and were normally distributed over the study period. Data were missing at random as assessed using Little’s Missing Completely at Random test, and this was nonsignificant ($P = .318$).

For all HRQoL subscales, effect sizes between the estimated marginal means were calculated to determine the magnitude of treatment effect between the intervention and control groups. In our study, a medium effect size was considered clinically relevant because the evidence shows that a mean effect size of 0.495 has been calculated for generic and disease-specific HRQoL instruments.
Table 2. Comparison of Sociodemographic and Clinical History Between Groups.

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group (n = 30)</th>
<th>Control Group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>73.4 (12.5)</td>
<td>73.8 (10.1)</td>
</tr>
<tr>
<td>CLU duration (weeks), a mean (SD)</td>
<td>26.4 (26.0)</td>
<td>20.5 (13.4)</td>
</tr>
<tr>
<td>CLU surface area (cm²) at baseline, mean (SD)</td>
<td>8.01 (10.4)</td>
<td>9.2 (8.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (43.3)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (56.6)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td>Ulcer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous</td>
<td>18 (60.0)</td>
<td>22 (73.0)</td>
</tr>
<tr>
<td>Arterial</td>
<td>5 (20.0)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (13.3)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Incompressible</td>
<td>1 (3.3)</td>
<td>2 (6.6)</td>
</tr>
<tr>
<td>Diabetic foot ulcer</td>
<td>1 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Conservative sharp wound debridement</td>
<td>14 (46.7)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Compression therapy</td>
<td>16 (53.3)</td>
<td>17 (56.6)</td>
</tr>
<tr>
<td>Pain medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>17 (56.6)</td>
<td>13 (40.0)</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>4 (13.3)</td>
<td>5 (16.6)</td>
</tr>
<tr>
<td>Other pain medications</td>
<td>21 (70.0)</td>
<td>23 (76.6)</td>
</tr>
</tbody>
</table>

Abbreviations: CLU, chronic leg ulcer; NSAID, nonsteroidal anti-inflammatory drug.

A total of 5 participants were excluded from wound duration analysis (intervention group: n = 2; control group: n = 3). CLU duration beyond 6 weeks could not be determined accurately for 3 participants; 1 participant had a CLU duration of 23 years.

Results

Demographic and Baseline Values

Sociodemographic and clinical histories were similar between the intervention and control groups at baseline (Table 2). The average age of study participants was 73 years, with the majority being female (n = 35, 58%). All participants were Caucasian and had retired from paid employment. More than 65% of the CLUs were caused by venous insufficiency, and the average CLU duration was >20 weeks, with an average wound size <10 cm². Half of the participants were taking oral opiates for relief of wound-related pain; 41% (n = 25) combined opiates with other pain-relieving medications. Data were collected for a range of comorbidities; there were no significant differences between the intervention and control groups, with the exception of asthma, the incidence of which was higher for the intervention group (intervention: n = 11, 36.6%; control: n = 2, 6.6%; P = .005). During the study period, the number of participants requiring conservative sharp wound debridement and compression therapy was similar.

Two protocol violations were identified in the intervention group, where participants continued EMLA beyond the 4-week study period for management of ongoing pain; 1 protocol violation was identified in the control group, where a participant applied topical lignocaine to the wound. Data from participants who withdrew were included in the analysis up to the time of their withdrawal.

The results from our study suggest that daily application of EMLA as a primary dressing to painful CLUs repeatedly over an extended period does not inhibit wound healing or reduce HRQoL when compared with usual wound care.

Wound Healing

Throughout the study period, 228 from a potential 300 photographs were collected and the surface areas digitally measured by a wound management nurse practitioner who was not blinded to group allocation. Wound size data for both groups were not normally distributed at any time point. Wound sizes were equivalent at baseline in both groups (P = .11). There were no statistically significant differences in wound size between groups at week 4 (P = .50) or week 12 (P = .78). Overall, wound sizes decreased in both groups from baseline to week 4 and continued to decrease in both groups to week 12 (Table 3). Some wounds increased in size in both groups during the intervention period; however, there was no difference between groups in the number of participants where this occurred: intervention group, n = 10 (33.3%); control group, n = 7 (23.3%); P = .46.

For 7 (12%) participants, complete wound closure was achieved by the end of the intervention period (intervention group, n = 3; control group, n = 4). The average size of these wounds on enrolment into the study was 2.2 cm² (intervention group, mean = 1.9 cm²; control group, mean = 2.1 cm²), which was below the wound size median in both groups at baseline. By the end of the 12-week study period, 12 (20%)
participants had achieved complete wound closure (intervention group, n = 5; control group, n = 7).

Health-Related Quality of Life

Participants in both the intervention and control groups reported similar levels of HRQoL in all CWIS subscales at baseline assessment (Table 4). Mean HRQoL scores in all subscales increased throughout the 12-week study period in both groups. In the intervention group, there was a trend toward improved HRQoL, but this only reached significance for the subscale Wellbeing from baseline to week 4 (intervention period) compared with the control group (intervention group: mean = 52.41; SD = 24.50; control group: mean = 38.15; SD = 21.25; P = .03; d = 0.62), although this significance was not sustained after the intervention period. Additionally, there was a trend toward improved perceptions for participants in the intervention group for how they rated their overall HRQoL at week 12 compared with the control group. Although not statistically significant, there was clinical significance based on the prestated criterion of a medium effect size as clinically relevant (intervention group: mean = 7.37, SD = 2.06; control group: mean = 6.19, SD = 2.04; P = .09; Cohen’s d = 0.58). All other effect sizes were less than medium (Table 4).

Discussion

This is the first study we know of that evaluates EMLA as a primary dressing on painful CLUs. Chronic pain is thought to be a biopsychosocial disorder and is often viewed by the individual as a stressor that directly affects wound healing. 38 We, therefore, considered wound healing and HRQoL as 2 important secondary outcomes of this pilot RCT.

Evidence shows that 3 criteria indicate whether a wound will completely heal by 12 weeks or not: initial healing rate, percentage of wound surface area reduction, and wound healing trajectories.39 Using these criteria, wounds that have not healed in a timely fashion at 4 weeks are highly unlikely to heal after 8 additional weeks of wound care independent of the topical dressing used.39 Although our initial case study suggested that improved CLU healing was possible using EMLA daily as a primary dressing,18 we were uncertain whether this would be the case for all patients and were concerned that daily removal of the dressing might disrupt the healing process.16,40,41 For both the intervention and control groups, wound size reduced throughout the study in a similar fashion, suggesting that EMLA used daily as a primary dressing neither improved nor impaired healing compared with usual wound management. This is in line with the evidence indicating that EMLA is unlikely to delay wound healing.19,21,42 Only 1 small-sample study examines repeated applications of EMLA on CLUs and wound healing, although this is in the context of debridement.19 Nevertheless, evidence shows that EMLA has no effect on blood flow or vascular reactivity,43 can increase wound tensile strength,22 has a positive effect on the inflammatory cascade, preventing ischemia, edema, and pain;44 increases cell multiplication,5; and has a powerful and rapid-acting antibacterial effect on common bacteria found in chronic wound cultures, such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Streptococcus pyogenes.45

Because of the different local, systemic, and psychological factors influencing wound healing,10,46 a regression analysis was not possible to determine which factors were most important in wound healing. Leg ulcer characteristics, location and size, vascularity of the local area, and the dose of EMLA applied may have also influenced the results. This is an area that needs to be investigated in a larger study.

The physical, psychological, and social problems relating to CLUs are abundant.4,48,49 It is the relentless severity of pain associated with CLUs that is the most debilitating symptom affecting an individual’s HRQoL, especially at dressing change.16,50 Dressing removal is identified as the time of greatest pain for those with wounds.51 Even though our previously published findings indicate that the use of EMLA as a primary dressing reduced pain intensity significantly compared with usual wound management during and after dressing change,26 we did not observe an improvement in HRQoL during the intervention period. Reduction in wound-related pain at the time of dressing may not be enough to affect HRQoL and the 4-week intervention period may not have been sufficient to identify an improvement in

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**Table 3. Comparison of Wound Size Between Intervention and Control Groups.**

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group (I)</th>
<th>Control Group (C)</th>
<th>I vs C, P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Median (cm²) (IQR)</td>
<td>n</td>
</tr>
<tr>
<td>Increase in wound size</td>
<td>Baseline</td>
<td>29</td>
<td>3.7 (2.2-10.4)</td>
</tr>
<tr>
<td></td>
<td>Week 4</td>
<td>22</td>
<td>2.4 (1.3-12.7)</td>
</tr>
<tr>
<td></td>
<td>Week 12</td>
<td>20</td>
<td>0.7 (0.1-5.0)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
HRQoL. Other factors may have influenced our results, especially because the majority of participants did not have complete wound closure by study completion. For both groups, life restriction, dressing adherence, exudate leakage, malodor, loss of control, altered body image, self-loathing, and social isolation are just some of the factors that may have influenced participants’ HRQoL. For the intervention group, daily dressings during the intervention period may have also influenced HRQoL.

Pain management for CLUs is difficult because of the limited effectiveness of analgesics and their systemic effects. There are many available strategies to relieve wound-related pain to improve HRQoL, such as the administration of oral opiates; however, 21% of patients with chronic wounds find pain relief ineffective. Overall, opioid therapy does not seem to accomplish outcome goals, such as sufficient pain relief, improved function, or improved HRQoL, and can be fraught with problems relating to cognitive impairment and other physical side effects. The discovery of opiate receptors on peripheral nerve terminals opened up the possibility of using topical pain relieving applications without decreasing the efficacy of the analgesia. Studies of topical opiates to relieve wound-related pain, such as morphine mixed with hydrogel, have shown a negative impact on wound healing, whereas our study found no such effect.

There are many advantages to the topical delivery of anesthetics such as EMLA. Administration is noninvasive, resulting in patient acceptability; gastrointestinal irritation is avoided, and there is first-pass metabolism, sustained delivery, and reduced systemic side effects, many of which have the capacity to improve an individual’s HRQoL. Additionally, a systemic drug may be used concurrently with a topical drug more safely; also, they are easier to use because topical analgesic drugs do not require titration. Nevertheless, when applying a topical anesthetic preparation, it is important to consider the variability of the tissue it is applied to because this may influence the absorption and distribution of the drug; the therapeutic effects, which depend on the amount, depth, and rate of penetration; and potential toxicological hazards. However, the overall safety profile of EMLA and other topical anesthetic preparations is good, and increasing evidence supports their efficacy for relieving nociceptive and neuropathic localized

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**Table 4. Comparison of Cardiff Wound Impact Schedule Subscales Between Intervention and Control Groups.**

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Effect Size (Cohen’s d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>Social Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29</td>
<td>63.15 (25.44)</td>
<td>29</td>
</tr>
<tr>
<td>Week 4</td>
<td>25</td>
<td>69.66 (26.72)</td>
<td>22</td>
</tr>
<tr>
<td>Week 12</td>
<td>24</td>
<td>74.32 (26.98)</td>
<td>18</td>
</tr>
<tr>
<td>Type III tests of fixed effects: Time, P = .03; Group, P = .17; Group × Time, P = .77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wellbeing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29</td>
<td>40.86 (21.35)</td>
<td>29</td>
</tr>
<tr>
<td>Week 4</td>
<td>26</td>
<td>52.41 (24.50)</td>
<td>23</td>
</tr>
<tr>
<td>Week 12</td>
<td>24</td>
<td>59.04 (21.56)</td>
<td>17</td>
</tr>
<tr>
<td>Type III tests of fixed effects: Time, P ≤ .001; Group, P = .11; Group × Time, P = .22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28</td>
<td>56.57 (18.37)</td>
<td>29</td>
</tr>
<tr>
<td>Week 4</td>
<td>26</td>
<td>67.64 (24.86)</td>
<td>22</td>
</tr>
<tr>
<td>Week 12</td>
<td>24</td>
<td>73.82 (24.45)</td>
<td>17</td>
</tr>
<tr>
<td>Type III tests of fixed effects: Time, P ≤ .001; Group, P = .20; Group × Time, P = .75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How good is QoL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27</td>
<td>5.71 (2.34)</td>
<td>28</td>
</tr>
<tr>
<td>Week 4</td>
<td>23</td>
<td>6.28 (2.16)</td>
<td>20</td>
</tr>
<tr>
<td>Week 12</td>
<td>20</td>
<td>7.37 (2.06)</td>
<td>16</td>
</tr>
<tr>
<td>Type III tests of fixed effects: Time, P ≤ .01; Group, P = .11; Group × Time, P = .58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction with QoL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>27</td>
<td>5.64 (2.38)</td>
<td>28</td>
</tr>
<tr>
<td>Week 4</td>
<td>23</td>
<td>6.48 (2.25)</td>
<td>21</td>
</tr>
<tr>
<td>Week 12</td>
<td>20</td>
<td>7.22 (1.92)</td>
<td>15</td>
</tr>
<tr>
<td>Type III tests of fixed effects: Time, P ≤ .01; Group, P = .18; Group × Time, P = .75</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: QoL, quality of life.

*Social life, Wellbeing, and Physical symptoms: possible score range, 1 to 100. How good is QoL and Satisfaction with QoL: possible score range, 0 to 10.
peripheral pain. These advantages may enhance analgesic medication adherence, particularly in the frail and older populations, and thus improve some aspects of HRQoL.

At the end of the intervention period, participants who received EMLA daily as a primary dressing reported a statistically and clinically significant improvement in Wellbeing, 1 of the 4 CWIS subscales. This significant improvement between the 2 groups was not sustained; whether this was a result of the intervention group changing over to usual care after the intervention period is unknown. Additionally, we did not control for the effects of the other factors known to influence HRQoL, such as debridement, compression therapy, arthritis, and cardiac disease. Consequently, in the context of this innovative pain management strategy, the influence of these other factors on Wellbeing requires further exploration. Our results also show that there was no difference between groups regarding the remaining 3 CWIS subscales—Social Life, Physical Symptoms and Daily Living, and Overall Quality of Life—although there was a clinically significant difference in the latter subscale at week 12. The complexity of HRQoL may mean that improved management of pain alone is inadequate to contribute to a meaningful improvement. A larger study is needed to confirm this.

Wellbeing, a component of HRQoL, has an interdependent and dynamic connection to HRQoL. Both HRQoL and Wellbeing can be influenced by the wound, its symptoms, treatment, and any alterations in physical (pain), psychological, and social functioning, with each of these factors influencing the other in a continual feedback loop. HRQoL refers to the individual’s cognitive evaluation of their situation and assesses the negative impact of the wound and its management, whereas Wellbeing refers to their emotional evaluation and assesses the positive physiological variables. Historically, emotion and cognition were viewed separately; more recently, they are considered interdependent. The CWIS Wellbeing subscale focuses on anxiety levels in relation to wound outcomes. There may be a gap in the assessment process, however, because the Wellbeing questions only focus on the negative effect of anxiety. The CWIS has been criticized as being too broad because it was designed for all chronic wound types; so differences in wound types may limit the sensitivity of the instrument. Whether our results indicate that the intervention group may have had less anxiety than the control group while they were receiving EMLA because their wound-related pain was less is unknown because anxiety was not specifically assessed.

The influence of CLU pain on HRQoL is well established as is the successful use of the topical application of EMLA for pain relief in the context of debridement. This pilot study has shown that when EMLA is applied daily as a primary dressing over an extended period of time on painful CLUs, wound-related pain is significantly reduced during and after dressing change. Consequently, wound healing was not adversely affected when compared with usual evidence-based wound management, with no difference in wound sizes at any time point over the study period. Likewise, HRQoL was also not adversely affected, in that all CWIS subscale scores were higher in the intervention group with statistical significance in Wellbeing at week 4 and clinically meaningful improvement for how good participants thought their HRQoL was at the end of the study period. However, further research with a larger sample size is needed to fully ascertain the effects of this intervention.

We conducted a RCT pilot study to minimize bias but were unable to blind participants and those collecting the data to group allocation and acknowledge that the lack of blinding may have introduced some bias. In addition, the subjective nature of HRQoL as an outcome measure and the self-administration of the questionnaire may have increased the chance for bias, particularly because participants were older adults with a large number of comorbidities. This may have resulted in distorted data. The study was conducted in a group of patients most of whom were older and frail, which may have contributed to challenges in collecting complete data for all participants over the multiple timepoints.

The following factors may have influenced the results in both groups: HRQoL data were not collected at a specific time during the treatment session; participants requested to continue the intervention beyond the 4-week treatment timeframe because of the considerable increase in their wound-related pain once the EMLA was stopped and usual care commenced; participants were treated in dedicated community nursing clinics, and the Hawthorne effect and enhanced therapeutic alliance may have influenced the psychological measures. Additionally, the inclusion of participants with varied CLU etiology may have contributed to the confounder of ulcer type.

The results of this pilot study suggest that EMLA is a promising pain-relieving strategy that does not inhibit healing potential and may improve HRQoL for patients suffering from CLU pain. Further larger studies are warranted to comprehensively evaluate the effectiveness of this treatment. This pain-relieving strategy could potentially be used by all clinicians practicing wound care, either on its own or in combination with other pharmacological or nonpharmacological strategies.

**Authors’ Note**

Study registered with the Australian and New Zealand Clinical Trials Registry: ACTRN 12609001080213.

**Declaration of Conflicting Interests**

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References
32. Samad A, Hayes S, French L, Dodds S. Digital imaging versus conventional contact tracing for the objective


4.4.1 Additional findings not included in Publication 3

In the third publication, the secondary clinical results of this pilot RCT were presented and focused on the daily application of EMLA® as a primary dressing to painful chronic leg ulcers and whether it is associated with improvements in wound healing and/or HRQoL. In addition to what was reported in Publication 3, data were analysed to measure how EMLA® affected leg ulcer appearance over time when used as a daily primary dressing. Data were collected at baseline and weeks 2, 4, 8 and 12 using the Leg Ulcer Measurement tool (LUMT) (Woodbury et al., 2004) (Appendix 16) designed to evaluate chronic leg ulcer appearance over time. LUMT scores were analysed at baseline and weeks 4 and 12 using the mixed linear model analysis. To determine the magnitude of the treatment, effect sizes between the estimated marginal means were calculated. Comparison of groups’ mean LUMT scores over the intervention and study periods are presented in Table 4.3.

**Table 4.3.** Comparison of groups’ mean Leg Ulcer Measurement (LUMT) scores over the intervention and study periods

<table>
<thead>
<tr>
<th></th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>Baseline Baseline</td>
<td>29</td>
<td>35.72 (7.31)</td>
<td>30</td>
</tr>
<tr>
<td>Week 4</td>
<td>26</td>
<td>28.54 (10.31)</td>
<td>27</td>
</tr>
<tr>
<td>Week 12</td>
<td>28</td>
<td>20.57 (14.75)</td>
<td>20</td>
</tr>
</tbody>
</table>

Based on the LUMT, the appearance of participants’ chronic leg ulcers in both the intervention and control groups presented similarly at baseline assessment. As reported in Publication 3, there were seven participants whose chronic leg ulcers healed by week 4 and 12 by the end of the 12-week study period. Even if wounds were healed a LUMT score, albeit a low score, was able to be recorded, so data from all wounds were included regardless of wound healing. There was a reduction in mean LUMT scores in both groups by the end of the intervention period (week 4).
indicating an improvement in chronic leg ulcer appearance although there was no difference between groups. Mean LUMT scores reduced significantly in both groups over time from baseline to 12 weeks, however, did not differ significantly between groups. Similarly, chronic leg ulcer appearance for both groups continued to improve with LUMT scores again lower at week 12 with no difference observed between groups ($p = 0.39$).

4.4.2 Discussion of unpublished leg ulcer appearance data
As identified in the LUMT there are other aspects of a wound apart from wound size that can determine whether the wound is progressing well or not (Woodbury et al., 2004). The findings suggest that the daily application of EMLA® as a primary dressing may not negatively impact chronic leg ulcer healing rate, exudate, tissue type, oedema, and/or bioburden any differently to usual wound care, although this study was not powered to detect a difference between groups.

4.5 Conclusion
Primarily, this study aimed to examine the feasibility of the study design to inform a subsequent multicentre RCT. Primary feasibility objective were met with 100% recruitment, 90% retention rate and 100% adherence to study procedures following random quality checks, therefore, the feasibility of undertaking a subsequent effectiveness trial has been established. Recruitment was slow particularly at the beginning of the study owing to community nurses not identifying potential study participants, competing health service responsibilities for the chief investigator and the strict participant exclusion criteria. With the addition of a part-time research assistant, additional promotion of the study to the community nurses and amendments to exclusion criteria, the recruitment rate doubled. Dedicated research personnel would be beneficial in a subsequent study. Even though 90% of the sample was retained throughout the study it became evident that strategies to better accommodate frail participants should be incorporated into a subsequent study.
Although a sample size for a subsequent RCT was calculated, sample size calculations from pilot studies should be used cautiously as they can potentially be misleading. Pilot studies do not provide meaningful effect size estimates for planning a subsequent study (Arnold et al., 2009; Leon et al., 2011; Thabane et al., 2010). It is advised to consider clinical meaningfulness if using the potentially unstable effect size estimates of pilot studies in power calculations (Duan, 2013).

Clinical findings from this study indicate that using EMLA® as a primary dressing significantly improves wound-related pain during and after dressing change, significantly improves participant wellbeing and would not negatively impact wound healing or health-related quality of life. Other unpublished clinical data from this study associated with wound-related pain and leg ulcer status showed mostly no difference between groups indicating that EMLA® was comparable with usual wound care. Additionally, participants in this study seemed to tolerate EMLA® well although this study was not designed to comprehensively assess safety and could only report on cases of severe adverse events or death, neither of which was reported.

Overall, the study findings support the feasibility of conducting a subsequent multi-centre RCT which would fully evaluate the effectiveness of EMLA® as a primary dressing on painful chronic leg ulcers as a pain-relieving strategy. This would be the primary outcome for the subsequent study, however, some modifications to the study design would be essential to ensure its success. The modifications are discussed in the next chapter.
Chapter 5 Recommendations and Conclusion

5.1 Introduction

In this thesis, the effectiveness of EMLA® on wound-related pain, wound healing and health-related quality of life (HRQoL) when used as a primary dressing on painful chronic leg ulcers was examined to assess the feasibility of conducting a subsequent randomised, controlled study (RCT). In Australia, chronic leg ulcers account for 16% of all chronic wounds and 94% of people with chronic leg ulcers report significant wound-related pain especially at dressing change (Price et al., 2008; Queensland Government et al., 2017). Chronic leg ulcers cause physiological and psychological stress which impacts wound healing leading to reduced HRQoL. There are a variety of pharmacological and non-pharmacological strategies to manage wound-related pain with oral pharmacological agents used most often to alleviate wound-related pain despite these not always being successful. Evidence suggests that topical local anaesthetic and topical analgesic agents can reduce pain associated with chronic leg ulcers.

A clinical case was the catalyst for this study. Significant pain associated with a chronic venous leg ulcer resulted in an individual consuming high levels of oral opioid medications for pain management despite their ineffectiveness. The ongoing pain experienced by the patient had a negative impact on her HRQoL and wound healing. In an attempt to manage this ongoing pain, EMLA® was applied daily as a primary dressing on the leg ulcer resulting in marked reduction in wound-related pain within 24 hours. Pain continued to subside leading to a reduction in the oral opioid intake and further improvements in their HRQoL. Additionally, optimum wound management strategies were instigated leading to complete wound healing (Purcell et al., 2012). This case, together with the ever-increasing consumption of opioid medications in Australia, provided the impetus for evaluating the evidence for the use of topical pain management strategies and the formulation of a research question: Are topical local anaesthetics and topical analgesics effective in reducing chronic leg ulcer pain?
Twenty-two studies met the inclusion criteria and were included in the literature review (Chapter 2). Following critical analysis and synthesis of this body of literature, the majority of studies included were RCTs although overall, the level of risk of selection, performance, detection and attrition biases was unclear due to poor reporting.

The findings from this review identified that topical local anaesthetic agents used to control acute operative pain associated with chronic leg ulcer debridement is well-established. Topical analgesics morphine gel and ibuprofen foam, were the predominant topical analgesic agents investigated. These agents were used as primary dressings for chronic pain associated with leg ulcers. Findings show that topical morphine gel has not been successful in managing chronic leg ulcer pain however, ibuprofen foam has been successful. At the time of commencing this study, ibuprofen foam was not available in the health service.

Reports suggest that EMLA® has a good safety profile after repeated applications for debridement, the capacity to kill micro-organisms that commonly reside on chronic leg ulcers, can reduce wound inflammation and is not detrimental to wound healing. Additionally, the evidence has indicated that application of EMLA® for debridement results in low systemic uptake of lignocaine or prilocaine and only local adverse effects. To date, there have been no studies which have investigated EMLA® or any other local anaesthetic as a daily primary dressing over an extended period on chronic leg ulcers to manage chronic wound-related pain.

This led to the research question for this study: *Is the eutectic mixture of local anaesthetics (EMLA®) effective for reducing wound-related pain when used as a primary dressing on painful chronic leg ulcers and what impact does this pain-relieving strategy have on wound healing and health-related quality of life?*

The results of this pragmatic, parallel group, non-blinded, superiority, pilot, randomised, controlled trial were provided in Chapter 4. The primary aim of this pilot study was to assess feasibility using a framework which included four broad classifications: processes, resources,
management and scientific aspects of the study (Thabane et al., 2010) to generate data to inform the development of a protocol for a future subsequent study. The design used in this pilot study was an RCT with wound-related pain identified as the most appropriate primary clinical outcome for a subsequent trial. The impact on HRQoL, wound healing and the associated reduction in oral analgesia were identified as appropriate secondary clinical outcomes for the study. Data generated from the primary clinical outcome wound-related pain was used to calculate the sample size for a subsequent study.

In this chapter, a summary of the study methods and findings is provided and the implications of the findings for wound management practice and recommendations for future research are suggested. Finally, the conclusions for this study are stated.

5.2 Summary of study findings

To examine the feasibility of conducting a future multisite trial, this pilot study was conducted in a large community nursing service. It was necessary to use the same design that would be used in a subsequent study to ensure methodological rigour and scientific validity of the study procedures that would appropriately inform a subsequent RCT (Schulz et al., 2010). Feasibility assessment including recruitment and retention, the establishment of necessary resources, management of data collection to ensure data accuracy and completeness, intervention fidelity and statistical analysis are critical before conducting a subsequent study which tests intervention effectiveness (Eldridge et al., 2016; Thabane et al., 2010).

In this study, feasibility was judged by pre-determined criteria; the recruitment of at least 80% of eligible patients within 12 months, retention of 80% of participants during the study period and at least 80% adherence to the intervention protocols. The study objective to inform the planning of a subsequent study was achieved. There were a number of process, resource, management and scientific challenges identified while conducting this study. Key learnings were related to recruitment and retention of participants, establishing resources required and managing data
collection. Solutions were required for all framework classifications which guided the recommendations for amendments to procedures in a subsequent study (Publication 1). The study outcomes suggest that it would be feasible to progress to a subsequent, multisite RCT. One hundred percent of the sample was able to be recruited. The study processes were considered adequate to retain most participants and maintain compliance to the intervention protocols with a 90% retention rate and 100% intervention compliance.

Although recruitment took 18 months longer than anticipated this is not uncommon in RCTs (Caldwell, Hamilton, Tan, & Craig, 2010). As is often the problem in clinical research (Gul & Ali, 2010), the overestimation of the patient pool that would meet the eligibility criteria was responsible for the slow recruitment rate. Since the actual number of eligible patients in this single site study was not known, initial clinical screening was done by community nurses who may have overlooked patients and may have contributed to the slow recruitment rate and potentially eligible patients being missed. Consistent with the evidence where an average of 30% of patients attending eligibility screening are found to be ineligible in RCTs (Toerien et al., 2009), more patients than had been predicted were excluded (34%) in this study. One hundred and seven patients with painful chronic leg ulcers were screened of whom 70 (65%) were eligible.

We were able to identify the reasons for the delay and implement strategies to facilitate recruitment. This included modifications to the exclusion criteria such as, the inclusion of participants with painful peripheral neuropathy and those who required EMLA® for debridement within the week prior to recruitment, as opposed to the initial criteria which excluded those individuals who had received EMLA® within a 4-week period prior to recruitment. Another strategy was the employment of a research assistant. Recruitment rates doubled once a research assistant was added to the research team. For a subsequent study, a dedicated investigator for the preliminary screening process could potentially capture more potential eligible patients.
The simple randomisation technique used for this pilot study, a common technique used for chronic wound trials (Vollenweider et al., 2012), was appropriate and effective for producing a balance between the study groups. To maintain good balance, block randomisation could be used although this can lead to allocation becoming unconcealed (Suresh, 2011; Vickers, 2006). A central randomisation service would cater more effectively for a subsequent multisite study (Suresh et al., 2016). The consent rate (86%) for this study was good in comparison to other RCTs where participants had chronic leg ulcers (Harrison et al., 2008; Nikolovska, Arsovski, Damevska, Gocev, & Pavlova, 2005; Weller, Evans, Staples, Aldons, & McNeil, 2012).

Direct and indirect factors influencing participant burden were identified in this study. The majority of participants were older with a number of co-morbidities and functional impairment, common predictors for study withdrawal (Peterson, Pirraglia, Wells, & Charlson, 2012). Participant burden was impacted by the length of the intervention and study periods, the number of data collection tools (six) and frequency and duplication of data collection resulting in 50% of the participant withdrawals. Even so, our aim of at least 80% retention was achieved.

The study protocol required participants to be seen in the community nursing clinics, however, this was not possible for some participants mostly due to frailty, lack of transport options, lack of clinic capacity and the intervention protocol that is, daily dressings for the 4-week intervention period. Use of hire cars provided some assistance but did not remain feasible due to budget restrictions, therefore, some participants required home visits which impacted on investigator burden. Additionally, a lack of clinical resources meant that some participants in both groups (13%) attended to their dressings independently for short periods of time. Random checks for adherence to the intervention protocols showed 100% adherence from treating clinicians. To maintain this consistency, participants who attended their own dressings were given instructions, however, they were not monitored during the procedures, thus adherence may have been compromised. Nevertheless, this approach is consistent with person-centred care and could be a consideration for future wound management strategies.
The primary clinical findings showed that EMLA® used daily as a primary dressing did not significantly improve wound-related pain intensity scores before dressing change in comparison to standard care. However, during the 4-week intervention period, lower wound-related pain intensity scores were statistically and clinically significant during and after dressing change in the intervention compared to the standard care group. After the intervention was ceased there was no difference between groups at week 12. For two participants, EMLA® was so successful at relieving wound-related pain participants independently continued using EMLA® (which is available over the counter and without prescription) after the intervention period was completed.

Although protocols were in place at the beginning of the study to maintain intervention fidelity, this unplanned ‘drift’ regarding the duration of the intervention may have impacted the internal validity of the study (Siedlecki, 2018). There was no difference between groups for the amount of pain-relieving medications consumed per day and cumulatively over the 12-week study period. Similarly, at the end of the intervention period, there was no difference between groups for where pain was experienced (wound, surrounding skin or both locations), pain quality and effects of pain on sleep and ADLs. These results do not reflect pain intensity only that pain was experienced. Wound-related pain increased or was unchanged on some participants in the intervention group therefore, EMLA® was ceased. Confounding factors may have influenced this result.

Clinical findings also showed that participant wellbeing was significantly improved, however, for the other HRQoL subgroups, EMLA® did not have a significant impact. Finally, findings showed that EMLA® did not impact wound healing or the appearance of the chronic leg ulcers compared to standard care. There was a concern that daily dressings would interrupt wound healing, but this was not evident although there are limitations to this data due to the sample size. The study intervention EMLA® was well tolerated by the intervention group however, the small sample size limited accurate evaluation. A subsequent RCT would reduce the chance of
Type 1 or Type II error (Leon et al., 2011). A multi-site study will provide greater statistical power (Weinberger et al., 2001).

There are two reasons for caution before conducting a subsequent RCT due to the sample size of this pilot study. Firstly, even though calculating a sample size from the pilot study seems reasonable especially since there are no other data to inform the process, pilot studies can mislead sample size calculations for a subsequent RCT as they cannot estimate the effect size with sufficient accuracy (Arain et al., 2010; Kraemer et al., 2006; Thabane et al., 2010).

Secondly, implementing clinical results into practice until a more definitive subsequent study is conducted investigating the use of EMLA® or any other topical local anaesthetic as a primary dressing on chronic leg ulcers, is not recommended (Thabane et al., 2010). Nevertheless, in line with most pilot studies where hypothesis tests are performed to comment on the statistical significance of results (Arain et al., 2010), in this study, $p$-values for the secondary clinical outcomes have been provided and interpreted.

The findings from this pilot study are unique as this is the first study examining EMLA® as a primary dressing on chronic leg ulcers. This study was not intentionally powered to detect a difference between groups. It is the feasibility results from this study that will inform subsequent studies not the safety or efficacy results (Leon et al., 2011). This pilot study fulfilled its aims and the research question has been answered. It showed that it is feasible for a subsequent study to be conducted to investigate the effectiveness of EMLA® as a primary dressing on painful leg ulcers. The clinical outcomes also indicate that EMLA® used in this way may improve chronic leg ulcer pain, would not be detrimental to wound healing and may improve an individual’s HRQoL.

5.3 Recommendations for future research

During the course of this research, it was identified that EMLA®, when applied as a primary dressing on chronic leg ulcers, is effective in reducing wound-related pain during and after dressing change. Furthermore, EMLA® did not impact wound healing, improved wellbeing
but did not reduce other physiological and psychosocial aspects of health-related quality of life when compared to standard wound care. However, a subsequent, adequately powered clinical trial is needed to definitively assess intervention effectiveness. The reduction of wound-related pain would be an appropriate outcome measure for an RCT with a shorter intervention phase as the reduction in pain levels in the intervention and control groups subside the longer the intervention period (Franks, et al., 2006). However, a longer intervention period may provide better evidence on the effect of the intervention on all aspects of HRQoL (Franks, et al., 2006).

This study has shown that it is possible to undertake an RCT investigating EMLA® in a community nursing setting however, there are several key areas which should be considered in future research. Firstly, the different chronic leg ulcer aetiologies included in this study, was a potential confounding factor, and may have distorted the true relationship between leg ulcer pain and EMLA®, introduced bias and influenced conclusions (Skelly, Dettori & Brodt, 2012). Therefore, in a future RCT, leg ulcer aetiology would need to be considered when undertaking sample size calculation and stratified sampling used to ensure equal representation of patients with venous, arterial and mixed leg ulcers (Pannucci & Wilkins, 2010). Dedicated research personnel with no competing workloads would be necessary to oversee a subsequent study. The training of a broad range of people cross multiple sites would be required to enhance intervention fidelity. Consent, randomisation and baseline data collection processes and the frequency and duration of follow-up would need to be reduced to prevent missing data, clinician and participant burden and unnecessary spending on human and other resources. Data collection would need to be more focused and duplication avoided by ensuring the most efficient and validated tools are used. For example, although the Cardiff Wound Impact Schedule questionnaire is a validated tool, its length and structure were confusing and laborious for participants. A short version could be developed and validated before a subsequent study. Similarly, the Leg Ulcer Measurement Tool, also a validated tool, could be shortened by omitting the patient-rated domains to prevent data duplication relating
to pain intensity and HRQoL and retain the items which focus specifically on wound appearance.

Before a subsequent RCT is conducted, smaller studies are required that will enhance the methodology resulting in a more robust, economical, multisite RCT. The recommendations for further studies are presented in Table 5.1.

**Table 5.1** Recommendations for further studies prior to conducting a subsequent RCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment of participants</td>
<td>To investigate the number of potentially eligible patients to get a true estimate of the ability to recruit for a subsequent RCT</td>
</tr>
<tr>
<td>Treatment duration of EMLA®</td>
<td>To investigate the sustainability of the anaesthetic capabilities of EMLA® on chronic leg ulcer pain beyond 24 hours. This would decrease the need for daily dressings which is not ideal due to several patient and health resource issues.</td>
</tr>
<tr>
<td>Plasma concentrations of EMLA® following repeated applications over an extended period</td>
<td>Studies have demonstrated that plasma concentrations of the active ingredients of EMLA®, lignocaine and prilocaine, are well below toxic levels following multiple applications of EMLA® to chronic leg ulcers for debridement, however, plasma concentrations following repeated and extended applications have never been examined. For patient safety, this data is important if EMLA® is used as a primary dressing.</td>
</tr>
<tr>
<td>Validation of data collection tools</td>
<td>The Wound-related Pain at Dressing Change Monitoring and Evaluation and Assessment Tools used in this study have never been validated (Appendix 12 and 13). There are no other known wound-related pain specific tools available that capture this comprehensive wound-related pain data, therefore, it is essential that a study is conducted to validate these tools before a subsequent study so researchers can use them in the future.</td>
</tr>
<tr>
<td>The effect of EMLA® on non-viable tissue, bioburden including biofilm and granulation tissue.</td>
<td>The evidence shows that EMLA® has anti-inflammatory and antimicrobial organism capabilities. Management of bioburden and non-viable tissue and protection of granulation tissue are key to the successful management of chronic leg ulcers.</td>
</tr>
</tbody>
</table>
5.4 Recommendations for clinical practice

Even though this study included assessment of clinical outcomes, the primary aim of this pilot study was to assess feasibility rather than to examine intervention effectiveness. The pilot study was designed to explore study feasibility which would help inform a subsequent clinical trial. Specific aspects of feasibility included recruitment, retention and adherence to the study protocol. The sample size was not determined a priori for the secondary outcomes because relevant data were unavailable. There was a statistically significance difference between the intervention and control group for wound-related pain intensity during and after dressing change. Although there was no difference in most measures of quality of life, wellbeing was higher for the intervention group, and this difference was statistically significant. Despite the positive results observed for reduced pain during and after dressing change recommendations for using this intervention in clinical practice are premature. Learning from this feasibility study would help inform a robustly designed effectiveness trial where primary and secondary outcomes could be more comprehensively investigated (Lee et al., 2014; Leon et al., 2011; Thabane et al., 2010; Tickle-Degnen, 2013).

5.6 Conclusion

The question for whether it is feasible to undertake a subsequent, multisite RCT to examine the effectiveness of EMLA® used as a primary dressing on painful chronic leg ulcers and its associated effects on HRQoL and wound healing has been answered by conducting this pilot study. This study has shown that it would be feasible to undertake a subsequent RCT.

The recommendations from this pilot study need to be put in place at the beginning of a subsequent RCT to prevent or limit participant, researcher, resource and economic burden thus enhancing the success of a subsequent study. It would be challenging to recruit an adequate number of participants for a subsequent multisite RCT unless it was conducted over a larger sample of wound clinics. A subsequent RCT may build on findings from this study thus ensuring
definitive clinical findings to support clinicians and patients regarding the safe and effective use of EMLA® and other topical anaesthetics as primary dressings on wounds of varied aetiology.
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Appendices

Appendix 1: Impetus for study - Publication 4: Case report

Eutectic mixture of local anaesthetics (EMLA) 5% cream as a primary dressing on a painful lower leg ulcer

Patients living with chronic leg ulceration may frequently experience moderate to severe wound-related pain, which may not be alleviated by oral analgesics alone. Poorly controlled leg ulcer pain can prevent timely and effective wound management strategies being implemented, and increase wound healing times. Furthermore, patients with poorly controlled leg ulcer pain can experience continuous pain, which significantly affects quality of life. This case report introduces an innovative way of using the eutectic mixture of local anaesthetics (EMLA) 5% cream to reduce wound-related pain, reduce oral analgesic intake, and improve health-related quality of life for a patient with a painful, chronic lower leg ulcer.

Leg ulcer; wound-related pain; eutectic mixture of local anaesthetics (EMLA)

Wound-related pain (WRP) has been identified as a major limiting factor in the daily life of patients with chronic leg ulcers.1 A study of patients with leg ulcers of venous or mixed aetiology reported that 85% of participants experienced WRP, with a mean pain score of 4.6 on the numerical rating scale (NRS; range 1–10).2 A score of ≥4 is considered significant pain.3

Scores that are persistently ≥4 can indicate uncontrolled WRP, and WRP may increase significantly during and between dressing changes, and throughout wound debridement.4 Strategies for reducing WRP are to treat the underlying cause, address local factors such as ischaemia, infection, wound desiccation, excessive exudate, oedema and maceration of the surrounding skin, and to consider analgesic and co-analgesic options.3

Recommended analgesic pain intervention generally includes non-opioid analgesia, such as non-steroidal anti-inflammatory drugs and/or paracetamol, as well as opioids with adjuvant drugs recommended for severe pain.3 However, evidence suggests that WRP is frequently under-treated, with many patients taking minimal analgesics or none at all.4 Even with appropriate pain management strategies in place, some patients may experience persistent pain at the wound site and/or the surrounding tissues.4 This persistent WRP may reduce their ability to tolerate appropriate wound treatment, such as the application of compression therapy, and thus contribute to delayed or reduced wound healing potential.3

To date, literature regarding topical analgesic/anaesthetic treatments for leg ulcer WRP has focused primarily on morphine gel, lignocaine gel, slow release, low-dose ibuprofen in a foam dressing, and the eutectic mixture of local anaesthetic 5% cream (EMLA).5 A recent systematic review found no evidence to support one agent as being most effective in relieving WRP; however, EMLA was found to reduce WRP when applied to the wound bed of chronic leg ulcers before debridement.6

The Australia and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers,7 and World Union of Wound Healing Societies (WUWHS) guidelines recommend the use of EMLA for the debridement of venous leg ulcers, but make no recommendation for its use as a primary dressing.

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In this case report, we demonstrate how EMLA, when used as a primary dressing on a chronic lower leg ulcer, reduced WRP, improved quality of life, reduced the patient’s oral analgesic intake, and did not interfere with the healing potential of the wound, resulting in wound closure.

Case presentation
A 49-year-old woman with a 9-month history of an extremely painful, right medial lower leg venous leg ulcer (VLU), presented to the nurse practitioner’s wound clinic for assessment and implementation of a wound management plan. She was well known to health professionals and was receiving care from a vascular surgeon, neurologist, rheumatologist, general medical practitioner, and community nursing service. She had a history of hypertension, previous intravenous drug use, vasculitic neuropathy developed on the background of hepatitis C, an elevated rheumatoid factor, Raynaud’s phenomenon, venous disease and smoking.

The patient presented to the clinic walking on the metatarsal heads of her right foot. During clinical examination, she described the increasing difficulty she was having with daily activities, such as mobilisation, shopping, socialising, working and household tasks, owing to the pain associated with her VLU. She described her pain as sharp, shooting and burning with a pain rating, using the NRS, of 9/10. This resulted in very poor sleep over the previous 9 months. During the clinic visit, the patient appeared debilitated, exhausted and emotional.

The wound surface area was 18.54 cm². The wound had a low level of exudate, thin, soft yellow-to-brown adhered non-viable tissue covering most of the wound bed, and the wound margins were dry and crusty (Fig 1a). The intact surrounding tissues were highly sensitive to tactile stimuli. There was minimal lower leg oedema and no signs of spreading infection. Several primary dressings had been used previously, including 0.9% iodine in a starch polymer base ointment, silver Hydrofiber, hydrogel, and silver alginate; however, these dressings did not appear to reduce WRP nor aid wound healing. An absorbent pad initially, followed by silicone foam, had previously been used as the secondary dressings.

The patient continued to experience excruciating, unresolved WRP over a 9-month period. Various analgesic agents were prescribed but had little effect. These included oral ibuprofen, paracetamol/codeine and oxycodone hydrochloride, plus topical lignocaine gel to the wound bed. Ineffective pain relief resulted in a painful wound that failed to heal and an inability to tolerate optimum wound management strategies, such as compression therapy. Her WRP and the prescribed opiate analgesic medication dulled her ability to function adequately. This was evidenced by her inability to work and socialise. With most treatment options exhausted, an alternative treatment was considered. The topical application of EMLA (EMLA Cream; AstraZeneca Inc.) to the wound bed was trialed as a primary dressing in an effort to provide the patient with effective pain relief.

Her wound was cleansed with normal saline 0.9%. A measured dose of 1gm of EMLA per 10cm² was applied to the right medial lower leg VLU as the primary dressing, with silicone foam continuing as the secondary dressing. Within the first 24 hours, she experienced a marked reduction in WRP from NRS 9/10 to 5/10, and reported having her first full night of sleep in 9 months. The applications of EMLA continued daily. Within 1 week, extra doses of oxycodone hydrochloride necessary before dressing changes were reduced. Within 2 weeks, regular doses of slow-release oxycodone hydrochloride were eliminated altogether and, by week 3, her WRP level was further reduced (NRS 3/10). The patient also reported a significant improvement in her quality of life following this reduction in WRP and analgesia. She was able to walk with normal action, and shop and socialise more frequently compared with the weeks before commencing EMLA. After 4 weeks, the patient was able to tolerate compression therapy.

Throughout the 13 weeks of EMLA application, there was no evidence of wound or peri-wound maceration. Furthermore, there was no increase in exudate level, bacterial load or non-viable tissue on the wound bed. This, together with compression therapy, resulted in a significant improvement in wound healing time compared with the previous 9 months. Within 1 week after the initial application of EMLA, the wound had decreased in surface area from 18.54 cm² to 11.44 cm² (Fig 1b). By week 12, it had reduced to 0.97 cm² (Fig 1c). After
13 weeks of daily application of EMLA as the primary dressing, the wound had completely healed. Six months after complete wound closure there has been no recurrence of the wound.

Discussion

Unresolved pain can negatively impact wound healing in acute and chronic wounds. The causes of leg ulcer pain can be diverse. Pain can be a normal reaction to the inflammatory response to wounding and to damaged nerves. Oedema, thrombosis, skin changes, ischaemia and inflammation can also result in leg ulcer pain, with increased non-viable tissue, bacterial burden, wound infection, cellullites, maceration, wound desiccation, and poor wound management and product selection also contributing factors. Comprehensive assessment of the patient and the wound are crucial to the identification of pain type and intensity, resulting in timely effective management. It is paramount that the underlying causes are identified and treated and the local factors described above are addressed as soon as possible. If not, WRP reduction strategies may be ineffective.

This novel strategy to reduce WRP in a chronic VLU was initiated following review of the literature to determine the safety of repeated applications of EMLA to a VLU over an extended period of time, and following informed consent by the patient.

Although the literature has reported the use of topical medications, including EMLA, as primary dressings for reducing VLU pain, in this case EMLA was chosen as it is readily available in our health service and the patient had responded well to applications of EMLA before debridement. Morphine gel was not considered as there were no compounding facilities for morphine gel available at the time and access required medical prescribing owing to morphine’s opiate status, as this drug was not on the nurse practitioner’s approved formulary. Lignocaine gel 2% was available but was not considered as it had previously had little effect on reducing WRP, and an ibuprofen foam dressing was not available in Australia at the time.

EMLA 5% cream is a eutectic mixture of 1:1 oil/water emulsion of lignocaine 2.5% and prilocaine 2.5% that is non-sterile and preservative free. When mixed, they form an oil at temperatures above 16°C, hence a eutectic mixture. The overall 5% concentration of EMLA was maintained to reduce systemic toxicity that is linked to higher concentrations.

Lignocaine and prilocaine are both amide-type local anaesthetic agents that stabilise the neuronal membrane, preventing the initiation and conduction of nerve impulses and thereby effecting local anaesthetic action and providing dermal anaesthesia. EMLA applied to intact skin has direct effects on smooth muscle cells, resulting in vasoconstriction, which reaches its peak after 90min. During prolonged application, there is pure vasodilatation and increased perfusion in the deeper underlying vessels after 2–3 hours, hence no negative effect on skin blood flow. EMLA on a leg ulcer over a 24-hour period has been found to be systemically safe. Furthermore, it has been reported that, even after 24 hours of continuous exposure with up to 10g of EMLA on a leg ulcer, there was no evidence of neurotoxicity.

One study determined that the peri-operative application of EMLA in the breast and axilla area reduced analgesic requirements, as well as the acute and chronic pain after breast surgery. EMLA was also found to have rapid acting and powerful antibacterial effects in vitro on typical wound pathogens, such as Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Streptococcus pyogenes, suggesting some benefit in bacteria minimisation is possible. Furthermore, EMLA has also been found to significantly increase cell multiplication; however, the effect EMLA has on wound healing is unknown.

The principle use of EMLA is to provide dermal anaesthesia. EMLA cream is currently used before IV catheter insertion, blood sampling, vaccination, superficial surgical procedures, as well as for topical anaesthesia of leg ulcers during cleansing and wound debridement. The current dose recommendations for the use of EMLA before debridement is 1–2g/10cm², up to a total of 10g, with an application time of 30–60min. The depth and quality of the anaesthesia depends on the characteristics of the ulcer, application time and the dose applied.

For this patient who had a VLU, the use of EMLA was effective in significantly reducing WRP. It was evident that this rapid, effective reduction of WRP was also accompanied by a reduction in oral opiate analgesic intake, thus minimising any side effects of these medications. Furthermore, optimum wound management strategies, such as compression therapy, were instigated 1 month after the commencement of the daily application of EMLA to the wound bed, which had been previously not possible. Wound healing was evident within the first week of the daily application of EMLA, even before the application of compression therapy, suggesting no detriment to wound healing following repeated daily applications of this anaesthetic cream. For this patient, EMLA was well tolerated with no adverse reactions to the medication detected.

However, adverse reactions to EMLA have been reported in the literature, although these are usually transient and localised. The most frequently observed adverse reactions include blanching, erythema and oedema. Less frequently, pruritus, burning, purpura and contact hypersensitivity have been reported. Methemoglobinemia, although rare, is an important systemic concern regarding
EMLA, particularly in neonates and young children,1,2 thus EMLA is not recommended in patients under 3 months of age.23 One report highlighted a particular patient having seizures following the seventeenth application of EMLA for the debridement of a Martorelle’s ulcer; however, a causal link to the use of EMLA was not established.24 The authors recommend caution when applying EMLA to elderly compromised skin.

Conclusion
This case report demonstrates how a patient with a painful chronic venous lower leg ulcer, who had not responded favourably to conventional wound-related pain management strategies, responded very well to the daily application of EMLA 5% to the wound bed, with a significant and rapid reduction of WRP, oral analgesia and wound size to complete healing, coupled with improved health-related quality of life.

At time of publication, no studies have reported using EMLA on chronic leg ulcers as a primary dressing to control WRP. To the best of our knowledge, this is the only case reported in the literature. Further investigation of this novel strategy is warranted. A randomised control trial is currently in progress by the authors to test the hypotheses that the daily topical application of EMLA 5% cream to the wound bed of painful chronic leg ulcers, as the primary dressing, will reduce WRP and analgesia requirements. Secondary outcome measures will be improved health-related quality of life and decreased wound healing times for patients with painful chronic leg ulcers.

References
Appendix 2: Harbour, Northern Sydney Central Coast Health HREC letter of approval

11 March 2010

Ms A Purcell
13 The Basin
Umina NSW 2257

Dear Ms Purcell,

Re: LEAD HREC MULTI-CENTRE APPLICATION APPROVAL,
NSW HEALTH ACCREDITED HREC: HARBOUR
NORTHERN SYDNEY CENTRAL COAST HEALTH (NSCCH)
LOCAL REFERENCE: Protocol 0911-31BM (CTH) - A Purcell, J King, A Marshall
A randomised controlled trial of EMLA cream as a primary dressing for painful
chronic leg ulcers: A pilot study. (AU REO Ref. HREC/09/HARR/162)

Thank you for providing additional information as requested at the meeting on the 16
November 2006 by the HARBOUR Human Research Ethics Committee (HREC) of
Northern Sydney Central Coast Health (NSCCH). Please be advised that your study has
now been approved. The documentation included in the approval is as follows:

• Patient Consent to Clinical Photography Version 2.0266.
• EMLA Protocol 01 dated 14 October 2006.
• Leg Ulcer Management Tool (LUMT).
• Daily Pain Diary.
• Community Nursing Assessment Form.
• Community Nursing Wound Pathway.
• Community Nursing Wound Assessment Tool.
• Wound Related Pain at Dressing Change - Monitoring & Evaluation Tool.
• Cardiff Wound Impact Schedule.
• GP Notification letter.
• Vascular Surgeon Notification letter.

It is noted that the approval covers the following NSW Health sites:

• Central Coast Community Nursing Service, Community Nursing Procedure Clinics:
  Woy Woy, Long Jetty, Lakehaven & Erina.

It is noted that the study has been assessed by the HREC for ethical and scientific review
ONLY and that clearance on the Site Specific aspects of the trial (local sign-offs, legal
documentation etc) MUST be obtained from the above listed sites prior to commencement
of research. Each site has different requirements. NSW Area Health Service sites require
submission and approval of a Site Specific Assessment (SSA), which can be completed at
www.ethicsform.org.au. Please contact each site for advice on any local requirements.

*If you wish to add an additional site to the project within the area you will be required to
complete a Site Specific Assessment Form* that can be accessed from

Research Business Unit
Level 2, 1 Bayview St, Royal North Shore Hospital
St Leonards NSW 2065. Ph: (02) 9430 8134. Fax: (02) 9430 2479

CASS NUMBER: 000302

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The HREC recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purpose of conducting this clinical trial.

At this time, we also remind you that, in order to comply with the Guidelines for Good Clinical Research Practice (GCP) in Australia, and in line with NSCCH HREC policy, the Chief Investigator is responsible to ensure that:

1. The HREC is notified of anything that might warrant review of the ethical approval of the project, including unforeseen events that might affect the ethical acceptability of the project.
2. The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines. Please refer to the Research Office website.
3. Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer.
4. Proposed changes to the personnel involved in the study are submitted to the HREC on a Change in Personnel Form (accompanied by the investigator’s CV where applicable).
5. The HREC must be provided with an annual progress report for the study by the 31st October each year. For multi-centre studies the Chief Investigator should submit to the Lead HREC on behalf of all sites.
6. The HREC must also be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer.
7. The HREC must be notified, giving reasons if the project is discontinued at a site before the expected date of completion.

Please refer to the NSCCHS Research Office website to access forms such as the amendment form, Annual/Final Report Form, Change in Personnel Form and Serious Adverse Event Guidelines and Forms;

Intranet:

Internet:
HREC approval is valid for four (4) years from the date of the approval letter. Your approval will therefore expire on the 11 March 2014. Your first progress report is due on the 31st October 2010.

Yours sincerely,

Dr Liz Newton
Chairperson
HARBOUR HREC
NORTHERN SYDNEY
CENTRAL COAST HEALTH
Dear Anne

NSLHD reference: 0911-318M
Title: A randomised controlled trial of EMLA cream as a primary dressing on painful chronic leg ulcers: a pilot study
HREC reference: HREC/09/HARBR/162

Thank you for submitting a request for an extension of HREC approval dated 23 March 2015 for the above project. This was considered by the Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee (HREC) at its Executive Committee meeting held on 13 April 2016. This HREC has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National model for Harmonisation of Multicentre Ethical Review (HoMER). This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice. No HREC members with a conflict of interest were present for review of this project.

- I am pleased to advise that your request for an extension of HREC approval has been granted. HREC approval is extended for a period of two years from the 13 April 2015. HREC approval will expire on 13 April 2017.

Please note the conditions of the approval:
- HREC approval will expire on 13 April 2017. An annual report for this study is due on 30 August 2015, and will be due on 30 August every year.
- The Co-ordinating Investigator is required to notify the HREC 3 months prior to this date if the project is expected to extend beyond the extension approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will provide any outstanding annual reports to the HREC as well as a final study report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by study participants regarding the conduct of the study.
- Proposed changes to the research protocol, conduct of the research, or length of HREC approval will be provided to the HREC for review, in the specified format.
- The HREC will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a university course are advised to contact the relevant university HREC regarding any additional requirements for the project.

For multi-site projects reviewed by the HREC after 1 July 2007 a copy of this letter must be forwarded to all Principal Investigators at every site approved by NSLHD HREC for submission to the relevant Research Governance Officer along with a copy of the approved documents.

Should you have any queries about your project please contact the Research Office, Tel: 9928 4590, email NSLHD-Research@health.nsw.gov.au. The HREC Terms of Reference, Standard Operating Procedures, National Statement on Ethical Conduct in Human Research (2007) and the CPMP/ICH Note for Guidance on...
Good Clinical Practice and standard forms are available on the Research Office website:

Please quote NSLHD reference RESP/14/265 in all correspondence.

Yours sincerely

Ellie Pratt
Research Ethics Manager
NORTHERN SYDNEY LOCAL HEALTH DISTRICT

RESP/15/2692
Appendix 3: Griffith University HREC letter of approval

27-May-2012
Dear Prof Marshall

I write further to the additional information provided in relation to the conditional approval granted to your application for ethical clearance for your project "PRIOR REVIEW: A randomised controlled trial of EMLA cream as a primary dressing for painful chronic leg ulcers: A pilot study" (GU Ref No: NRS/16/12/HREC).

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

Chris Rose'Meyer

Policy Officer, Research Ethics and Governance

Office for Research

G39 3.56 Gold Coast Campus

Griffith University

ph: +61 (0)7 5552 7227
fax: +61 (0)7 5552 9058
email: c.rosemeyer@griffith.edu.au
Appendix 4: Participant Information Sheet and Consent Form

Central Coast Community Nursing Service

PARTICIPANT INFORMATION SHEET AND CONSENT FORM

CLINICAL TRIAL

A randomised controlled trial of EMLA cream as a primary dressing

for painful chronic leg ulcers: A pilot study.

Invitation

You are invited to participate in a research study into the effectiveness of the daily topical application of EMLA cream to the wound bed of painful chronic leg ulcers.

The study is being conducted by Anne Purcell, Nurse Practitioner Wound Care, Department of Community Nursing, Central Coast Local Health District as part of a Doctor of Philosophy (Research) at the School of Nursing and Midwifery, Griffith University. The study is under the supervision of Professor Andrea Marshall, Professor of Acute and Complex Nursing, Griffith University; Dr Tom Buckley, Senior Lecturer, Sydney Nursing School, University of Sydney; Jennie King, Clinical Nurse Consultant Research, Nursing and Midwifery Directorate, Central Coast Health Local Health District; and Professor Wendy Moyle, Director - Research Centre for Clinical and Community Practice Innovation, Griffith University.

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. **What is the purpose of this study?**
The purpose is to investigate whether the daily application of EMLA 5% cream as a dressing to the wound bed of painful chronic leg ulcers is more effective than the standard dressing treatment in reducing wound-related pain and analgesia (pain relief) requirements, improving wound healing times, and improving the quality of life for patients with painful chronic leg ulcers.

2. **Why have I been invited to participate in this study?**
You are eligible to participate in this study because:
   i) you have one or more chronic lower leg ulcer(s) of at least 6 weeks duration and up to 100cm² in size;
   ii) you currently require oral pain relief due to previously reported wound-related pain;
   iii) your wound pain score on the Numerical Rating Scale is ≥ 4.

3. **What if I don't want to take part in this study, or if I want to withdraw later?**
Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.
New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your
willingness to continue in the study. If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason.

4. **What are the alternatives to participating in this study?**

If you decide not to participate in this study, and you wish to continue treatment, you will still receive the standard treatment available for your condition.

5. **What does this study involve?**

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. Your participation in this study will last for approximately 12 weeks. The treatment being investigated in this study is the use of EMLA cream applied as a dressing to the leg ulcer. This treatment uses EMLA in a different way to that for which it is approved. EMLA cream is a local anaesthetic cream frequently used to reduce pain when leg ulcers need extensive cleaning. However, EMLA may also have properties that may be useful in treating general wound-related pain. This treatment differs from the standard treatment offered in this institution which includes non-stick dressings and oral pain relief medication.

This study will use a ‘randomised trial’ design. Sometimes health professionals don’t know the best way of treating patients with a particular condition, so comparisons need to be made between different treatments. To do this, study participants are put into groups and given different treatments, and the results are compared to see whether one treatment is better. To ensure the groups are similar to start with, a computer allocates each study participant into a group randomly, like the flip of a coin. Neither the researchers nor the study participant can decide which treatment the participant receives. One group will receive the EMLA treatment and the other group will receive the standard treatment.

If you agree to participate in this study, you will then be asked to undergo the following procedures:

- **A comprehensive health assessment** will be undertaken which includes demographic information and medical and surgical history (such as allergies, vascular studies, nutrition assessment, blood pressure, blood glucose level, mobility, medications, cognitive status, body mass index, smoking and alcohol intake).

- **Arterial Brachial Pressure Index** (ABPI): This is a measurement to assist in determining what type of ulcer you have. This involves putting a gel on your feet and arms and the nurse will listen to your arteries using a hand-held Doppler (ultrasound) machine. This will take up to one hour and will only be performed once only.

- **Leg ulcer measurement**: Digital photographs will be taken of your wound(s) at the start of the study, so that the size of your leg ulcer(s) can be calculated. This takes approximately 5 minutes. You will be required to sign an additional ‘Patient Consent to Clinical Photography’ form in accordance with the Northern Sydney Central Coast Health Wound Photography Consent policy. The clinic nurse will also complete the **Leg Ulcer Measurement Tool** which is designed to detect changes in appearance of leg ulcers. This takes approximately 3 minutes. Both measures will be repeated at 2, 4, 8 and 12 weeks.

- You will be asked to complete a questionnaire called the **Cardiff Wound Impact Schedule** which is designed to assess health-related quality of life in people with chronic lower leg ulcers. This will take approximately 10 minutes to complete. You will be asked to complete this at the start of the study and again at 2, 4 and 12 weeks.

- You will be asked to complete a **Daily Pain Diary** for the duration of the study to record your wound-related pain and the measures taken to treat it. This diary includes the **Numerical Rating Scale** which allows you to describe the intensity of your discomfort in numbers ranging from 0 to 10 (where 0 = no pain and 10 = worst possible pain). The Pain Diary is completed daily, when pain is at its best, when pain is at its worst, and when pain relief is taken. Details of pain relief requirements include the type of medication, dose, frequency and your pain rating one hour after.

- At each dressing change, the clinic nurse will also assess your pain using the **Wound-related Pain at Dressing Change Assessment Tool**. This tool takes approximately one minute to complete.

Participating in the study may require some restrictions on your lifestyle during the study. This includes the need to attend the Community Nursing Procedure Clinic to have your dressing
changed. Participants allocated to the EMLA group will be required to attend daily (Monday to Friday).

6. How is this study being paid for?
The study is being paid for by the Department of Community Nursing, Central Coast Local Health District using funding received from research grants.

7. Are there risks to me in taking part in this study?
All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study. The known risks of this study are: adverse reaction to EMLA, for example, skin irritation occurs in < 1% of people; local reaction at the application site (eg. paleness, redness and oedema) occurs in < 10%. In rare cases (< 0.1%) local anaesthetic preparations have been associated with allergic reaction, in the most severe instances anaphylactic shock.

8. Will participating in this study affect my plans to start a family?
The effect of the study of EMLA cream on an unborn baby is unknown. It is possible that the treatment regime under this study could have serious effects of the development of a foetus. If at any time you think you, or your sexual partner may be pregnant, it is important to let researchers or your medical team know immediately.

Female participants
It is important that women participating in this study are not pregnant and do not become pregnant during this study as the study drugs may damage an unborn baby.

If you are a woman of childbearing age and there is any possibility that you are pregnant, the researchers will need to perform a urine pregnancy test before you start in the study. If necessary, you must use reliable contraception (such as oral or implanted contraception, an IUD or have had a tubal ligation if you are female, or condoms if you are male) during the course of this study.

Male participants
Because of the possible risk to an unborn child, you must use reliable contraception during the course of this study. You should also inform your sexual partner/s of the need to avoid the possibility of pregnancy.

9. What happens if I suffer injury or complications as a result of the study?
If you suffer any injuries or complications as a result of this study, you should contact the study researcher, Anne Purcell, as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. If you are not eligible for compensation for your injury or complicaion under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

10. Will I benefit from the study?
This study aims to further nursing knowledge and may improve future treatment of pain associated with chronic leg ulcers, however it may not directly benefit you.

11. Will taking part in this study cost me anything, and will I be paid?
Participation in this study will not cost you anything. You will not be paid to take part in this study.

12. How will my confidentiality be protected?
Of the people treating you, only those named above or necessary others (e.g. nursing staff involved in your care, your general practitioner, and vascular surgeon) will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your details and results that will be held securely at the Central Coast Community Nursing Service, Wyong.
It is possible that your personal health records and information may be disclosed to other agencies such as regulatory bodies (including the Therapeutic Goods Administration) and Ethics Committees. This will only occur when necessary and the provisions of Australian privacy law will be complied with.

13. **What happens with the results?**
If you give us your permission by signing the consent document, we plan to discuss/publish the results in peer-reviewed journals, conference presentations or other professional forums. A final report will be provided to the Human Research Ethics Committee for monitoring purposes. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

14. **What happens to my treatment when the study is finished?**
You may be able to continue EMLA cream following completion of this study if it is found to be of benefit to you. This decision will be made in consultation between you and your treating doctor about the most appropriate treatment for you at that time.

15. **What should I do if I want to discuss this study further before I decide?**
When you have read this information, the researcher Anne Purcell will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact her on 0414 192 868.

16. **Who should I contact if I have concerns about the conduct of this study?**
This study has been approved by the Harbour HREC of Northern Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 9926 4590 and quote HREC project number: 0911-318M(CTN).

Thank you for taking the time to consider this study. If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.
CONSENT FORM

A randomised controlled trial of EMLA cream as a primary dressing

for painful chronic leg ulcers: A pilot study.

1. I, ...........................................................................................................................................................................
   of ...........................................................................................................................................................................
   agree to participate as a subject in the study described in the participant information statement attached to this form.

2. I acknowledge that I have read the participant information statement, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the statement has been explained to me to my satisfaction.

3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.

4. I understand that I can withdraw from the study at any time without prejudice to my relationship to Central Coast Local Health District.

5. I agree for digital photographs to be taken of my leg ulcer.

6. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.

7. I understand that if I have any questions relating to my participation in this research, I may contact Ms Anne Purcell, Nurse Practitioner Wound Management on telephone 0414 192 868, who will be happy to answer them.

8. I acknowledge receipt of a copy of this Consent Form and the Participant Information Statement.

Complaints may be directed to the Research Office, NSLHD. Phone: 02 9926 4590

________________________________________
Signature of subject
Please PRINT name
Date

________________________________________
Signature of investigator
Please PRINT name
Date

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Central Coast Community Nursing Service

A randomised controlled trial of EMLA cream as a primary dressing for painful chronic leg ulcers: A pilot study.

REVOCATION OF CONSENT

I hereby wish to WITHDRAW my consent to participate in the study described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with Central Coast Local Health District.

Signature_________________________ Date_________________________

Please PRINT Name_________________________

The section for Revocation of Consent should be forwarded to Anne Purcell, Nurse Practitioner Wound Care, Central Coast Community Nursing Service, Wyong Community Health Centre, 38A Pacific Highway, Wyong, NSW 2259.
### Appendix 5: Site Accountability Log

**EMLA TRIAL**

<table>
<thead>
<tr>
<th>Study Title:</th>
<th>EMLA as a primary dressing for painful chronic leg ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator:</td>
<td>Anne Purcell</td>
</tr>
<tr>
<td>Site Number:</td>
<td>GOSFORD</td>
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<tr>
<td>Product:</td>
<td>EMLA cream</td>
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<td>Dosage Form:</td>
<td>Cream (36g)</td>
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<tr>
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<td>Storage:</td>
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</table>

<table>
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<th>Amount Received (no. of tubes)</th>
<th>Amount Dispensed (no. of tubes)</th>
<th>Batch</th>
<th>Expiry (mm-yy)</th>
<th>Dispensed/Received by (name)</th>
<th>Total Balance on Hand</th>
<th>Date returned (dd-mm-yyyy)</th>
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Appendix 6: Drug Supply Authority

EMLA CLINICAL TRIAL
DRUG SUPPLY AUTHORITY

STUDY DETAILS:

Attention: GOSFORD HOSPITAL PHARMACY DEPARTMENT
Fax: (02) 43202324

Pharmacy Contact: Claire McCormack (Clinical Trials Pharmacist)
Phone: (02) 43205548

Prescriber: ________________________________

Prescriber Contact Number: __________________

PATIENT DETAILS:

Patient Name: ________________________________

Patient DOB: ________________

Patient MRN: ________________

Patient Study Number: ________________

OR

Attach patient details sticker here

SUPPLY DETAILS:

1 x 30g tube of EMLA® (Lignocaine/prilocaine 5%) for use as per study protocol

NOTES FOR SUPPLY:

Prescriber signature: ________________________________ Date: ____________
## Appendix 7: Site Specific Log

### EMLA TRIAL

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<tr>
<th>Study Title:</th>
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<tbody>
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<td>Principal Investigator:</td>
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<tr>
<td>Site Number:</td>
<td>Gosford</td>
</tr>
<tr>
<td>Product:</td>
<td>EMLA cream</td>
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<tr>
<td>Dosage Form:</td>
<td>Cream (30g)</td>
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<tr>
<td>Strength:</td>
<td>Lignocaine, prilocaine 5% (1:1 oil in water emulsion)</td>
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<tr>
<td>Storage:</td>
<td>Room temperature (below 30°C)</td>
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| NAME:                  |                                                        |
| MRN:                   |                                                        |
| SUBJECT NUMBER:        |                                                        |

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Comments: ________________________________________________________________
______________________________________________________________
______________________________________________________________
______________________________________________________________
Appendix 8: Operational dispensing protocols of EMLA® and other primary/secondary dressings

When a participant was allocated to the intervention treatment group, the clinical trial pharmacist was contacted. The EMLA® Clinical Trial Drug Supply Authority (prescription) was faxed to the clinical trial pharmacist who dispensed the EMLA® 30gm tube. This tube was labelled with the patient’s medical record number, name and required dose rate, that is, 1gm = 1 ml/10 cm². The researcher collected the EMLA® from the pharmacy and delivered it to the appropriate participating community nursing clinic.

Other primary dressings such as hydrogel, hydrofibre, alginate, rapid capillary dressings, hydroactive colloidal polymer gel, and antimicrobial dressings were dispensed through the Wound Prescription System incorporated within the Integrated Clinical Information System (ICIS). All clinic community nurses involved in this study have access to ICIS. The primary dressing deemed appropriate for the study participant in the ‘standard care’ group can be prescribed and dispensed through the Wound Prescription System weekly. This system has the capacity to monitor all aspects of product management such as who has prescribed, which product was prescribed, where it was dispensed to, and why any product is required for the study participants as the Central Coast Community Nursing Service Wound Assessment Tool is also incorporated into the ICIS database.

Dispensing of secondary dressings for intervention and control groups. The Central Coast Local Health District Community Nursing Service Wound Prescription System was not used for the prescribing and dispensing of the secondary dressing, Zetuvit®. It was specifically purchased for the study and dispensed by the Chief Investigator.
Appendix 9a: Content of educational sessions to community nurses

- Initial explanation of the study and the required commitment by the clinic nurse. Involvement of the clinic nurse was voluntary. If the nurse agreed they were asked to sign a Clinician Agreement to highlight the importance of adhering to the study protocols (Appendix 9b);
- Processes for maintaining and securing study data;
- Instruction for completion of data collection instruments;
- Instruction regarding the preparation and application of EMLA® on the chronic leg ulcers;
- Even though wound photography was already standard practice in the community nursing service, wound photography instruction was provided for reinforcement and to ensure consistency and quality of images. It was expected that all photos be taken the same way at every time point and uploaded into the Integrated Community Information System (ICIS), the community nursing electronic medical record data base. Wound photography specifications are presented in Appendix 15;
- All clinics were provided with a study-specific document folder. The folder contained copies of the research protocol, the Participant Information and Consent form, all study instruments to be used, a study flow chart which included the Schedule of Events and the intervention and control group treatment protocols (Appendices 9c and 9d). All data collected was kept in this folder except for wound photographs which were uploaded into the community nursing electronic medical record data base. The CI visited the relevant clinics regularly to collect completed data collection forms.
Appendix 9b: Clinician Agreement

A randomised controlled trial of EMLA® cream as a primary dressing for painful chronic leg ulcers: A pilot study

Clinician Agreement

I agree to take part in this pilot study specified above. I have had the study explained to me by the Chief Investigator, Anne Purcell.

I understand that agreeing to take part in this study means I am willing to attend to the following:

Please read the following statements and indicate by circling the box provided:

I understand that my participation is voluntary, that I can choose not to participate in part or all of the project, and that I can withdraw at any stage of the project without being penalised or disadvantaged in any way.

I agree to adhere to the EMLA Study step by step instructions for Community Nurses.

I agree to collect evaluation data using the following tools:

- The Leg Ulcer Measurement Tool (LUMT) on weeks 2, 4, 8, 12.
- Digital Photography on weeks 2, 4, 8, 12.
- Insert wound photography into ICIS on weeks 2, 4, 8, 12.
- Wound-related Pain at Dressing Change Assessment Tool at each dressing change.
- Collect sealed envelopes from participating patients which will contain their pain and analgesia diaries and Numerical Rating Scale pain scores.
- To record type and date compression therapy commenced.
- And to record any adverse events on the ‘Adverse Events’ form.

I agree to store data safely then forward all data collected to the principle investigator or research assistant.

I agree to notify a principle investigator or the research assistant if there are any concerns expressed by the participating patient during their involvement in this study.

I agree to notify a principle investigator or the research assistant if I have any concerns or queries during my involvement in this study.

I agree to report any adverse event caused by the application of EMLA cream to the wound or periwound skin and also agree to complete the Adverse Event Form and send to a principle investigator or the research assistant as close as possible to the event.

Name…………………………………………………………… Date…………………………

Signature………………………………………………………………………..
Appendix 9c: The EMLA® Study - Instructions for Community Nurses

The EMLA Study - Instructions for Community Nurses

Pt identified as potential EMLA recruit

See BOX 2

Contact Chief Investigator
Anne Purcell 0414192868

See BOX 2

When Pt accepted into The EMLA Study they will be placed into either the EMLA GROUP or ‘USUAL CARE’ GROUP. You will be notified by Anne Purcell to which group the patient will be placed into. Please adhere to group protocols.

See BOX 3

BOX 1
- Painful chronic lower leg ulcer > 6/52
- Ability to have wound care in CN Clinic
- No EMLA used for debridement within previous 4/52

BOX 2
Anne Purcell will determine suitability of patient for The EMLA Study and attend to all baseline assessments and patient consents.

BOX 3 EMLA Group

Patients in the treatment group will have their wound cleansed with Normal Saline 0.9% and then EMLA cream applied to the wound bed of their chronic lower leg ulcer as the primary dressing.

How to measure EMLA dose:
To be drawn up in a 10 ml syringe by attaching the syringe to the top of the 30 g EMLA tube and drawing the required dose as per the formula below. Know the wound surface area before acquiring dose.

It is critical that the EMLA dose is measured accurately.
Dose: $1g/10cm^2$ Maximum dose 10gms/100cm²
NB: 1ml = 1gm

- Secondary dressing: absorbent pad (Zetwurt)
- Dressing frequency: daily for up to four weeks, unless the wound has healed prior to this. At week 4, patients will change to standard ‘usual care’ dressings.
- Compression therapy: can be instigated following comprehensive clinical assessment and if the ABPI result is within 0.8 – 1.2

‘Usual care’ Group

Patients in the usual care group will have their wound cleansed with Normal Saline 0.9% and then receive dressings deemed appropriate by the nurse at the time of each visit. The dressing choices will reflect usual care options and will include primary dressings such as: alginate, hydroFibre, hydrogel.

- Secondary dressing: absorbent pad (Zetwurt)
- Dressing frequency: ranging from daily to weekly according to exudate level and need, until the wound is healed.
- Compression therapy: can be instigated following comprehensive clinical assessment and if the ABPI result is within 0.8 – 1.2

It is imperative that all participating RNs follow all instructions exactly as written

THANK YOU

SCHEDULE OF EVENTS
Community nursing clinic RN is responsible for the following:

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPI</td>
<td>Anne Purcell</td>
<td></td>
<td></td>
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<tr>
<td>Leg Ulcer Measurement Tool (LUMT)</td>
<td>Anne Purcell</td>
<td>CN</td>
<td>CN</td>
<td>CN</td>
<td>CN</td>
</tr>
<tr>
<td>Photography (Data into ICIS)</td>
<td>Anne Purcell</td>
<td>CN</td>
<td>CN</td>
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<td>CN</td>
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<tr>
<td>Cardiff QOL</td>
<td>Anne Purcell</td>
<td>CN</td>
<td>CN</td>
<td>CN</td>
<td></td>
</tr>
<tr>
<td>Wound Pain Assessment Tool</td>
<td>Anne Purcell</td>
<td>CN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound Pain Scale &amp; Diary</td>
<td>Anne Purcell</td>
<td>CN</td>
<td></td>
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</tbody>
</table>

- Record type & date compression therapy commenced in ICIS.
- Adverse events to be recorded in ICIS & Notification of Adverse Event Form to be completed and given to Anne Purcell.
### Appendix 9d: Schedule of Events Check List

<table>
<thead>
<tr>
<th>Schedule of Events Check List</th>
<th>Patient ID:</th>
<th>Start Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive Assessment</td>
<td>Baseline</td>
<td>Week 2</td>
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<tr>
<td>Date:</td>
<td>AP</td>
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<td>ABPI</td>
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<tr>
<td>Input result into ICIS</td>
<td>AP</td>
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<tr>
<td>Leg Ulcer Measurement Tool</td>
<td></td>
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<tr>
<td><em>Keep completed tools in Blue EMLA Research folder</em></td>
<td></td>
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</tr>
<tr>
<td>Digital photography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Input data into ICIS</td>
<td></td>
<td></td>
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<tr>
<td>Cardiff Wound Impact Schedule</td>
<td></td>
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<tr>
<td><em>Keep completed tools in Blue EMLA Research folder</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound-related Pain at Dressing Change Assessment Tool</td>
<td>AP then DAILY by RN</td>
<td>1</td>
</tr>
<tr>
<td><em>Keep completed tools in Blue EMLA Research folder</em></td>
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<tr>
<td>Pain Diary &amp; Pain scale – NRS</td>
<td></td>
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<tr>
<td>Patient to place Pain Scales &amp; Diary into sealed envelope and give to Clinic RN/C1/or RA. NOT to be opened by RN/C1 or RA. Store in Blue EMLA Research folder. CI or RA will collect ASAP</td>
<td>DAILY By PT</td>
<td>1</td>
</tr>
<tr>
<td>Record date compression therapy commenced and type of compression in ICIS</td>
<td></td>
<td></td>
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<tr>
<td>Adverse events recorded in ICIS – Progress notes.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>The Chief Investigator, Anne Purcell, MUST be informed if there is any adverse event.</em></td>
<td></td>
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</tr>
</tbody>
</table>
# LOWER LIMB RISK ASSESSMENT

**Date:**

**Patient:**

**MRN:**

**Assessor:**

**Assessment location:**

**Wound Location:** (eg. foot, guitar, malleolus)

### POSSIBLE INDICATORS OF VENOUS HYPERTENSION

- Deep Venous Thrombosis
- Pulmonary Emboli
- Thrombophlebitis
- Leg/foot fracture
- Varicose veins surgery/sclerotherapy
- Family History
- Advanced Age

### POSSIBLE INDICATORS OF ARTERIAL INSUFFICIENCY

- Angina/PVD
- Hypertension
- TIA/stroke
- CVA
- Diabetes
- Rheumatoid Arthritis
- Stroke
- Advanced age

### LIMB Clinical Signs / Symptoms

- Limb pain may be present (aching, tired)
- Pain relieved when leg elevated
- Prominent superficial veins
- Ankle flare (distension veins medical foot)
- Lipodermatosclerosis (hard woody skin/tissue)
- Haemosiderin staining (brown pigmentation golfers area)
- Swell Eczema
- Atrophic Blanche
- Oedema

### Ulcer

- Large, shallow
- May or may not be painful, NRS
- Poorly defined margins
- Slight progression
- Guitar, medial/lateral malleolus
- Other

**Pulses**

- Are the foot pulses palpable? **YES** **NO**
  - dorsalis pedis pulse (circle): Left: ++ +++, Right: ++ +++,
  - posterior tibial pulse (circle): Left: ++ +++, Right: ++ +++

### Assessors Signature

**Comments:**

---

**IMPORTANT**

See:

NSCCAHS Leg Ulcer Clinical Guidelines on Intranet
Appendix 11: Ankle brachial pressure index work sheet

ANKLE BRACHIAL PRESSURE INDEX WORK SHEET

Step 1. Rest patient 15 – 20 minutes prior to ABPI assessment.

☐ Laying Flat (most optimal)  ☐ Laying with head elevated  ☐ Reclining chair

Step 2.
• Record both left and right brachial readings.
• Circle and use the higher reading.

Right Brachial: ........................................ Left Brachial:...........................................

Step 3.
• Record both Dorsalis Pedis and Posterior Tibial readings.
• Circle and use the higher of the two in ABPI calculations.

Right Dorsalis Pedis..........................Right Posterior Tibial..........................
Left Dorsalis Pedis............................Left Posterior Tibial...........................

Step 4.
• Divide the higher lower limb reading (of a particular side) with the highest brachial reading to calculate the ABPI for both the right and left limb.

Right Resting ABPI..........................Left Resting ABPI...............................
• Resting ABPI > 1.2 = vessel wall calcification.
• Resting ABPI > 0.8 < 1.0 = mild arterial disease
• Resting ABPI > 0.5 < 0.8 = moderate arterial disease
• Resting ABPI < 0.5 = severe arterial disease

Step 5. Limb measurements:
Right Ankle.............................cm  Right Calf.............................cm
Left Ankle..............................cm  Left Calf.............................cm

Comments:..........................................................................................................

Compression Therapy

• Graduated compression therapy must be used by health professionals with care and close observation for the treatment of venous hypertension when the ABPI is > 0.8 and < 1.2 in the absence of contraindications.

• Contraindications can be acute heart failure; Rheumatoid arthritis; Vasculitis; Ischaemic pain with bandaging; Diabetes; Neuropathy; Renal disease.
Appendix 12: Wound-related pain at dressing change monitoring and evaluation tool

**WOUND-RELATED PAIN AT DRESSING CHANGE MONITORING & EVALUATION TOOL**

Surname: _______________________________ Initials: ___________ DOB: __________________

Date each dressing change and plot wound-related pain score on the graphs below. Record, monitor and evaluate interventions initiated to minimise wound-related pain at each dressing-related procedure.

<table>
<thead>
<tr>
<th>Date</th>
<th>Pain Score</th>
<th>Intervention</th>
<th>Sign</th>
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</table>

N.B. Once an appropriate pain scale tool is selected (self-reporting or observational), continue to use the same tool at each assessment.
Appendix 13: Wound-related pain at dressing change assessment tool

WOUND-RELATED PAIN AT DRESSING CHANGE ASSESSMENT TOOL

1. Indicate location of wound/s and number on the body map and leg/foot pictures

2. Do you experience pain or discomfort related to your wound/s?
   □ Yes   □ No   If yes, complete the questions on the next page.

Signature

This pain assessment tool has been adapted by the International Pain Advisory Panel.1

**WOUND-RELATED PAIN AT DRESSING CHANGE ASSESSMENT TOOL**

<table>
<thead>
<tr>
<th>Date: ____________________</th>
<th>Initials: ____________________</th>
<th>Signature: ____________________</th>
</tr>
</thead>
</table>

3. **When do you experience wound-related pain?** (May mark more than one box if applicable)
   - [ ] Pain at rest (Background)
   - [ ] Pain during day-to-day activities (Incident)
   - [ ] Pain during biopsy/derbrideement (Operative)
   - [ ] Pain after dressing change
   - [ ] Pain during dressing change (Procedural)

4. **Where is the wound-related pain?** (May mark more than one box if applicable)
   - [ ] In the wound
   - [ ] In the area surrounding the wound (skin)

   Does the pain go anywhere, if yes where does it go? ______________________________________________________

5. **What words would you use to describe your pain?** (May mark more than one box if applicable)
   - [ ] Burning
   - [ ] Aching
   - [ ] Throbbing
   - [ ] Tender
   - [ ] Sharp
   - [ ] Crawling
   - [ ] Stinging
   - [ ] Shooting
   - [ ] Stabbing
   - [ ] Tingling
   - [ ] Other*

   *Give details: ______________________________________________________

6. **At dressing change, what makes the wound-related pain worse (triggers)?** (May mark more than one box)
   - [ ] Removing dressing
   - [ ] Applying dressing
   - [ ] Some dressing types*
   - [ ] Cleansing
   - [ ] Touch
   - [ ] Other*

   *Give details: ______________________________________________________

7. **At dressing change, what makes the wound-related pain better (relievers)?** (May mark more than one box)
   - [ ] Removing dressing myself
   - [ ] Time-outs or brief rests
   - [ ] Certain types of dressings*
   - [ ] Warm cleansing solutions
   - [ ] Pain-relieving medication
   - [ ] Other*

   *Give details: ______________________________________________________

8. **Have you been prescribed or are you currently taking pain-relieving medications (tablets, injections, topical applications, patches) for your wound-related pain?**
   - [ ] Yes
   - [ ] No

   If yes, list name/dose and when last taken/applied/used: ______________________________________________________

9. **Are any of the following activities negatively affected because of the wound-related pain you experience?**
   - [ ] Sleeping
   - [ ] Activities of daily living
   - [ ] Other*
   - [ ] Leisure activities
   - [ ] Sport or exercise
   - [ ] Other*

   *Give details: ______________________________________________________

10. **If the wound-related pain was reduced, which activity would you look forward to the most?**

____________________________________________________
Appendix 14: Daily Pain Diary

Use this diary to record your pain and what you did to treat it. This will help your health care provider to understand your pain better. Fill in the information and bring the journal with you to your next appointment. If your pain is not relieved by your treatment, call your health care provider.

<table>
<thead>
<tr>
<th>Time</th>
<th>Where is the pain? Rate the pain (0-10), or list the word from the scale that describes your pain.</th>
<th>What were you doing when the pain started or increased?</th>
<th>Did you take medicine? What did you take? How much?</th>
<th>What other treatments did you use?</th>
<th>After an hour, what is your pain rating?</th>
<th>Other problems or side effects? Comments.</th>
</tr>
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</tbody>
</table>

Appendix 15: Wound Photography Specifications

- Camera type: Fujifilm FinePix S7000 digital camera – 19 x 6 x optical and 3.2 x Digital lens and with a macro facility. Identical cameras were used in all participating clinics;
- All images were taken in line with the wound, centrally framed and 20cms from the wound;
- Natural light was used where possible. Flash used only when necessary;
- All wound aspects were included in the image and included: wound bed, wound edge, peri-wound and surrounding tissues;
- A disposable wound ruler was used in all images taken. This allowed for calibration when measuring the wound within the ICIS database. Patient study number, date and wound location were the only means of image identification;
- Wound depth measured with Smith and Nephew Visitrak® Depth Indicator, a sterile disposable depth indicator;
- All wound images for this study were placed in Integrated Community Information System (ICIS) database
### Appendix 16: Leg Ulcer Measurement Tool (LUMT)

#### ITEM / DOMAIN
- **A1. Exudate type**
  - 0 None
  - 1 Serous
  - 2 Serosanguineous
  - 3 Seropurulent
  - 4 Purulent

- **A2. Exudate amount**
  - 0 None
  - 1 Scant
  - 2 Small
  - 3 Moderate
  - 4 Copious

- **A3. Size (from edge of advancing border of epithelium)**
  - 0 Healed
  - 1 <2.5 cm²
  - 2 2.5-5.0 cm²
  - 3 5.1-10.0 cm²
  - 4 >10.1 cm² or more

- **A4. Depth**
  - 0 Healed
  - 1 Partial thickness skin base
  - 2 Full thickness
  - 3 Tendon/joint capsule visible
  - 4 Probes to bone

- **A5. Undermining**
  - 0 None
  - 1 0 cm
  - 2 >0 - 0.4 cm
  - 3 >0.4 - 0.9 cm
  - 4 >0.9 - 1.4 cm
  - 5 >1.5 cm

- **A6. Necrotic tissue type**
  - 0 None
  - 1 Loose white to yellow slough
  - 2 Attached white to yellow slough or fibrin
  - 3 Soft grey to black eschar
  - 4 Hard dry black eschar

- **A7. Necrotic tissue amount**
  - 0 None visible
  - 1 1 to 25% of wound bed covered
  - 2 26 to 50% of wound bed covered
  - 3 51 to 75% of wound bed covered
  - 4 76 to 100% of wound bed covered

- **A8. Granulation tissue type**
  - 0 Healed
  - 1 Bright beefy red
  - 2 Dark pink
  - 3 Pale
  - 4 Absent

- **A9. Granulation tissue amount**
  - 0 Healed
  - 1 76 to 100% of wound bed covered
  - 2 51 to 75% of wound bed covered
  - 3 26 to 50% of wound bed covered
  - 4 1 to 25% of wound bed covered

- **A10. Edges**
  - 0 Healed
  - 1 >50% advancing border of epithelium or indistinct borders
  - 2 <50% advancing border of epithelium
  - 3 Attached, no advancing border of epithelium
  - 4 Unattached or undermined

© M. Gail Woodbury, PhD; Pamela E. Houghton, PhD; Karen E. Campbell, MSc(hons); and David H. Keast, MD
### ITEM / DOMAIN | RESPONSE CATEGORIES | SCORE
---|---|---
A11. Periulcer skin viability 0 None
- callus 1 One only
- dermabites (gape) 2 Two or three
- maceration 3 Four or five
- induration 4 Six or more factors
- erythema (bright red)
- purple blanchable
- purple non-blanchable
- skin dehydration

A12. Leg edema type
0 None
1 Non-pitting or firmness
2 Pitting
3 Fibrosis or lipodermatosclerosis
4 Indurated

A13. Leg edema location
0 None
1 Localized perulcer
2 Foot, including ankle
3 To mid calf
4 To knee

A14. Assessment of bieburden
0 Healed
1 Lightly colonized
2 Heavily colonized
3 Localized infection
4 Systemic infection

Total - (A) CLINICIAN RATED DOMAINS:

**B) PATIENT (PROXY) RATED DOMAINS**

B1. Pain amount (as it relates to the leg ulcer) 0 None
Numerical rating scale (0-10)
- <0 - 2
- >2 - 4
- >4 - 7
- >7

B2. Pain frequency (as it relates to the leg ulcer) 0 None
1 Occasional
2 Position dependent
3 Constant
4 Disturbs sleep

B3. Quality of life (as it relates to the leg ulcer) 0 Delighted
1 Satisfied
2 Mixed
3 Dissatisfied
4 Terrible

Total - (B) PATIENT (PROXY) RATED DOMAINS:

Proxy Completed by:

Total LUMT Score:
GENERAL INSTRUCTIONS

Section A CLINICIAN-RATED DOMAINS Assessments are to be done predribedment but after cleansing the wound. Evaluators should note the exudate type and amount on removal of dressings. Whenever possible, the time since the last dressing change should be consistent from one assessment to the next.

A1. Exudate type—Reminder: Some wound care products may change the appearance of the exudate, eg, silver sulfadiazine or hydrocolloids.
   Definitions:
   1. Serosanguineous—thin, watery, pale red to pink
   2. Serous—thin, watery, clear, pale yellowish
   3. Seropurulent—thin, opaque
   4. Purulent—thick, opaque, yellow to green with foul odour (distinct from body or foot odour)

A2. Exudate amount—Reminder: Consider time since last dressing change.
   0 None—ulcer healed or wound tissue dry (if wound dressings changes are not regular)
   1 Scant—wound bed moist with dressing dry
   2 Small—wound bed moist with some drainage on dressing
   3 Moderate—obvious fluid in wound bed and >50% of dressing soaked
   4 Copious—overwhelming the dressing system

A3. Size—Measure length as the longest diameter; width is perpendicular to length. Avoid diagonals. Calculate wound area as length by width. Write this in space provided and select appropriate response category.

A4. Depth—layers. Pick the most appropriate descriptor.

A5. Undereining—Place moistened rayon-tipped sterile applicator or wound probe under the edge of the wound. Advance it gently as far as it will go. Place gloved thumb on the applicator against the wound edge to mark the extent of undermining on the applicator. Holding the thumb in place, remove the applicator and measure the distance along the applicator in centimetres. Indicate the area of greatest undermining according to the face of a clock, with 12 0’clock at the top of the patient.

A6. Necrotic tissue type—Reminder: The wound should be thoroughly cleansed before evaluating.
   Pick the predominant type of necrotic tissue, eg, if most of the wound bed is attached fibrin with small amount of black eschar, choose attached fibrin as tissue type.

A7. Necrotic tissue amount of predominant type selected in A6. The sum of the percentages in A7 and A9 may be less than but should not exceed 100%.

A8. Granulation tissue type—Choose predominant type of granulation tissue.

A9. Granulation tissue amount—(The sum of the percentages in A7 and A9 may be less than but should not exceed 100%) The percentage of granulation tissue refers only to the nonepithelialized (open portion of the wound. The advancing border of epithelium is not considered part of the wound surface.

A10. Edges—Definition: Indistinct borders—where you would not be able to trace the wound edge.
   1 More than half of advancing borders may be indistinct because most of wound is epithelializing.
   2 Less than half of the wound edge is advancing (the process of epidermal resurfacing appears smooth and shiny).
   3 Attached, no advancing border—unable to probe. Looks like
   4 Unattached wound edge is undermined wound edge is

A11. Periulcer skin viability—Select the following items that are present; count the number selected; then use this total to determine appropriate response category.

Definitions:
   Callus—thick, dry epidermis
   Scaling dermatitis—scaling, red skin which may be weeping
   Maceration—wet, white, opaque skin
   Induration—feels firmer than surrounding skin when pressed
   Erythema—skin redness (bright red)
A12. Leg edema type—Indicate the worst edema type located anywhere on leg. 
Definition: lipodermatosclerosis—waxy; white, firm tissue.

A13. Leg edema location—Indicate the most proximal location of any type of edema. Clinical example: pitting edema ankles with nonpitting edema to mid calf: For A10, leg edema type = 2 > pitting =, A11, leg edema location = 3 > to mid calf =.

A14. Assessment of bioburden
1 Lightly colonized: small amount of serous-type exudate.
2 Heavily colonized: large amount of seropurulent drainage with foul odour and no other cardinal signs of inflammation.
3 Localized infection: large amount of seropurulent drainage with foul odour and either induration, erythema, warmth, or pain.
4 Systemic infection: advancing cellulitis or osteomyelitis.

Section B PATIENT- (PROXY) RATED DOMAINS Read the questions “as they are” to the patient. It is important to qualify that the questions refer to the last 24 hours. If the patient is unable to understand the questions due to cognition or language deficits, section B should not be completed or it may be completed by a proxy only if the proxy knows the patient well and has been with the patient for most of the last 24 hours. The same person should provide proxy information for each assessment; do not complete section B by proxy if the person providing proxy information is not the same.

B1. Pain amount as it relates to the leg ulcer in the last 24 hours. Determine the rating based on a numerical rating scale ranging from 0-10, then place response in appropriate category.
B2. Pain frequency as it relates to the leg ulcer in the last 24 hours. How often patient experienced pain in the last 24 hours.
B3. Quality of life as it relates to the leg ulcer in the last 24 hours.
Appendix 17: Cardiff Wound Impact Schedule Questionnaire

Overall Quality of Life
We would like you to rate your overall quality of life during the past 7 days.
Please circle a number below
How good is your quality of life?

<table>
<thead>
<tr>
<th>My quality of life is the worst possible</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>My quality of life is the best possible</th>
</tr>
</thead>
</table>

How satisfied are you with your overall quality of life?
Not at all satisfied

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Very satisfied</th>
</tr>
</thead>
</table>

Overall Comments

Cardiff Wound Impact Schedule, English version for the USA
The following questionnaire is concerned with the effects that your wound(s) have on your daily life. Please answer the questions carefully by placing a check mark in the box which most closely reflects how you feel; it should take about ten minutes to complete.

If you are unsure about how to answer a question, please mark the answer which is closest to how you feel. All answers are confidential.

**Personal Details**

**Patient Initials**

**Sex**

**Patient Number**

**Date of Birth**

**Assessment**

1st 2nd 3rd 4th 5th

**Assessment Date**

MMDDYYYY

**Next Assessment Due**

MMDDYYYY

**Wound(s) status**

Healed  Not Healed

**Do you live on your own?**

Yes  No

**How often do you see your family and friends?**

Daily  Once a month
### Social Life
**How stressful has this experience been for you during the past 7 days?**

<table>
<thead>
<tr>
<th>Difficulty getting out and around</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Very</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relying more on others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Your family/friends being overly protective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to enjoy your usual social life (e.g., hobbies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited contact with family/friends</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not going out for fear of bumping your wound site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wanting to withdraw from people</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Social Life
**Have you experienced any of the following during the past 7 days?**

<table>
<thead>
<tr>
<th>Difficulty getting out and around</th>
<th>Not at all</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relying more on others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Your family/friends being overly protective</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to enjoy your usual social life (e.g., hobbies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited contact with family/friends</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not going out for fear of bumping your wound site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wanting to withdraw from people</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Well-being

To what extent do you agree/disagree with the following statements?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Not Sure</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel anxious about my wound(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel frustrated with the time it is taking for the wound(s) to heal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am confident that the wound(s) I have will heal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I worry that I may get another wound in the future</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The appearance of the wound site is upsetting to me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I worry about bumping the wound site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I worry about the impact of the wound(s) on my family/friends</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Physical Symptoms and Daily Living

Have you *experienced* any of the following during the past 7 days?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Not at all/Not applicable</th>
<th>Seldom</th>
<th>Sometimes</th>
<th>Frequently</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty bathing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobility around the home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobility outside the home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leakage from the wound(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain from the wound site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discomfort from the bandaging/dressing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpleasant odor or smell from the wound(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems with everyday tasks (eg shopping)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty in finding appropriate footwear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems with the amount of time needed to care for the wound site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial difficulties as a result of the wound(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix 18: Description of SPSS Mixed Syntax (IBM SPSS Statistics)

<table>
<thead>
<tr>
<th>Descriptions</th>
<th>Syntax</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPSS</strong></td>
<td>Analyse &gt; Mixed models &gt; Linear &gt; Options &gt;</td>
</tr>
<tr>
<td><strong>Linear Mixed Models Specify Subjects/Repeated Variables</strong></td>
<td>Move Pt ID across to Subjects &gt;</td>
</tr>
<tr>
<td>Allows the selection of variables that define subjects and repeated</td>
<td>Move ‘time’ across to Repeated &gt;</td>
</tr>
<tr>
<td>observations plus a choice of covariance structure for the residuals.</td>
<td>Repeated Covariance Type: Heterogeneous AR(1) &gt; continue</td>
</tr>
<tr>
<td><strong>Linear Mixed Model – specifies the dependent and independent variables</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Linear Mixed Model Fixed Effects</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Linear Mixed Model Random Effects</strong></td>
<td></td>
</tr>
<tr>
<td>To specify the covariance structure for the random-effects model.</td>
<td></td>
</tr>
<tr>
<td><strong>Linear Mixed Model Statistics – Summary Statistics:</strong></td>
<td></td>
</tr>
<tr>
<td>Descriptive statistics – displays sample sizes, means, standard deviations</td>
<td></td>
</tr>
<tr>
<td>of dependent variables and covariates (if specified).</td>
<td></td>
</tr>
<tr>
<td>Model Statistics: Parameter estimates - displays fixed effects and</td>
<td></td>
</tr>
<tr>
<td>random-effects parameter estimates and their approximate standard errors.</td>
<td></td>
</tr>
<tr>
<td>Tests for covariance parameters – displays asymptotic standard errors and</td>
<td></td>
</tr>
<tr>
<td>Wald tests for covariance parameters. Confidence interval - a value greater</td>
<td></td>
</tr>
<tr>
<td>than or equal to 0 and less than 100 can be specified. The default value is</td>
<td></td>
</tr>
<tr>
<td>95.</td>
<td></td>
</tr>
<tr>
<td><strong>Linear Mixed Model EM Means</strong> (<em>Estimated Marginal Means of Fitted Models</em>)</td>
<td></td>
</tr>
<tr>
<td>Can request model-predicted marginal means of the dependent variable and</td>
<td></td>
</tr>
<tr>
<td>their standard errors for specified factors. Additionally, comparison of</td>
<td></td>
</tr>
<tr>
<td>factor levels of main effects can be requested.</td>
<td></td>
</tr>
</tbody>
</table>

Dependent Variable: e.g. pain, QOL subgroup > Factor(s): group + time >
Fixed > ‘Build Terms’ > Model > move across to Model, group + time together > continue >
Random > Covariate Type > Heterogeneous AR1 > move Pt ID across to ‘Combination’ > continue >
Statistics > Summary Statistics: Descriptive statistics > Model Statistics: Parameter estimates > Tests for covariance parameters > Confidence interval: 95% > continue >
EM Means > move across group, time and group x time > continue > OK
Appendix 19: Permissions for the inclusion of publications in the thesis

Impetus for study- case report:
Thursday, 26 July 2018 3:07 AM

To: Anne Purcell

Dear Anne,

Thank you for your email. You can republish this report as part of your thesis.

Kind regards,
Rachel

Dr Rachel Webb
Editor, Journal of Wound Care
Rachel Webb [rachel.webb@markallengroup.com]

Publication 1:
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With kind regards,
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Global Open Research Support Executive
Global Open Research Support
Springer Nature
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www.springernature.com

Publication 2:
License Not Required - 1 December 2018

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