Impact of topical oxygen therapy on diabetic foot ulcer healing rates: a systematic review

Objective: The aim of this systematic review was to determine the impact of topical oxygen therapy (TOT) on diabetic foot ulcer (DFU) healing.

Method: Using systematic review methodology, we considered randomised controlled trials (RCTs), controlled trials, pilot studies and observational studies. The search was conducted in January 2019, using PubMed, CINAHL, Ovid, Cochrane, Web of Science and EMBASE databases. Data analysis was undertaken using RevMan and a narrative synthesis. The article titles were assessed by two authors independently, and the abstracts (when available) of the studies identified by the search strategy were screened for their eligibility, according to the inclusion and exclusion criteria. The full-text version of potentially relevant studies was obtained and two authors independently screened this against the inclusion criteria. Data were extracted using a predesigned extraction tool and all included studies were quality appraised using the Evidence-Based Librarianship checklist.

Results: The search returned 565 records of which eight met the inclusion criteria. Of the included studies, three were set in single centre outpatient wound clinics, two studies were set in an outpatient wound care research clinic and three studies were multisite. Meta-analysis of four studies was undertaken. DFUs are >2 times more likely to heal with TOT than with standard care alone. The odds ratio (OR)=2.49 (95% confidence interval (CI): 1.59–3.90, p=0.00001). The remaining four studies also showed that using TOT increased healing rates. An included study reported that time to 50% DFU closure was significantly shorter in participants who received the TOT, mean 18.4 days versus 28.9 days in the sham therapy group (p=0.001). However, the validity of 65.5% of the eight studies was assessed as low.

Conclusion: The findings suggest that TOT enhances healing for patients with hard-to-heal DFUs when used with standard care. The results from the trials reviewed also indicate a benefit for patients over standard care alone. However, the sample sizes in the studies were generally small, thus, more RCTs are warranted to further validate these findings.

Declaration of interest: The authors have no conflicts of interest to declare.

evidence-based librarianship checklist ● diabetes ● diabetic foot ulcer ● randomised controlled trial ● standard care ● systematic review ● topical oxygen therapy ● treatment ● wound ● wound care ● wound healing ● wounds

The International Working Group on the Diabetic Foot defines a foot ulcer as a full thickness wound involving the foot or the ankle. As a common complication of diabetes, diabetic foot ulcers (DFUs) can lead to a significant psychological, social and economic burden on both the health system and the patient.

A study in 2005 by Boulton et al. estimated that, globally, every 30 seconds a limb was lost as a result of diabetes and that a person with diabetes had a lifetime risk of developing a foot ulcer of 25%. A further study carried out in 2011 by Bakker et al. showed that this figure had increased to a limb lost every 20 seconds from complications of diabetes. A study carried out over a five-year period from 2005 and 2009 showed that in Ireland lower extremity amputations related to diabetes were between 145–176 per 100,000 persons, and a person with diabetes was 22.3 times more likely to have a lower limb amputation than those without diabetes.

DFUs are a substantial and mounting problem. It has been estimated that one in every four people with diabetes is at risk of developing a DFU. In 2017 it was estimated that 451 million adults worldwide had diabetes, with this figure expected to increase to 693 million by 2045. In Europe, the figure was estimated to be 59.8 million, which equated to 9.1% of the population aged between 20 and 79 years. In the UK, diabetes has been estimated to affect approximately 3.8 million people.

An Irish study in 2014 found that wound care accounts for 5% of the active caseload for community
nurses, with 1% of patients being treated for a DFU. A study carried out to estimate the cost of treating a DFU in an Irish hospital setting estimated it to be €23,489 per hospital admission and the authors stated this was an underestimation as it did not include costs for blood testing or antibiotic therapy.

Many DFUs occur secondary to peripheral vascular disease, leading the tissue to be in a chronic state of hypoxia; restoring oxygen to the wound bed would therefore seem like a logical step in wound treatment. This can be done through revascularisation surgery; however, many patients with DFUs have comorbidities making them unsuitable candidates for surgery, thus, an alternative treatment of topical oxygen delivery systems may need to be used.

Topical oxygen therapy (TOT) is defined as the administration of oxygen applied topically over injured tissue by either continuous delivery or pressurised systems. Topical continuous oxygen is also known as continuous diffusion of oxygen (CDO) and provides a flow of oxygen to the wound bed, usually at a rate of 3–12ml/hour. The oxygen is delivered through a portable device. Topical pressurised oxygen therapy was originally termed topical hyperbaric oxygen therapy and has been in use since the 1960s. It works by placing a bag, boot or extremity chamber around the affected area. It is sealed tightly to prevent leaks and oxygen is delivered, usually from an outside tank, at a rate of 5–60l/minute to pressures just above that of atmospheric pressure. It is not continuous and sessions usually last 90 minutes/day, for 3–5 days/week but sometimes more. Gotttrup et al. have been able to draw on systematic research into wound healing. The authors also focused on topical and hyperbaric oxygen treatment in their search.

There is, at the time of writing, no systematic review that evaluates the use of TOT for DFUs. Therefore, this systematic review aimed to synthesise the published literature to determine the impact of TOT on healing rates among patients with DFUs.

Methods
Research question
The research question was as follows: ‘What is the impact of TOT on healing rates among patients with DFUs?’

Criteria for considering studies for this review
Types of studies: the systematic review included published and unpublished randomised controlled trials (RCTs), controlled trials, pilot studies and observational studies. Case series papers were excluded. There were no restrictions with respect to date of publication or trial setting. The only restriction to the search was that studies were published in the English language.

Types of participants: any adult only with DFUs.

Types of interventions: studies describing the following comparison were eligible for the review: TOT compared with no TOT.

Types of outcome measures
Primary outcome: wound healing, which could have been reported as the proportion of patients with DFUs that have reduced wound circumference or complete wound closure following the intervention.

Secondary outcomes: rate of healing, recurrence rates, pain and adverse reactions.

Electronic searches
The following electronic databases were searched to identify relevant literature:
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- The Cochrane library (latest issue)
- Ovid
- Cumulative CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature).
- PubMed
- Web of Science
- EMBASE.

Assistance from an expert librarian was sought to help develop and identify appropriate keywords to use.

Searching other resources
The bibliographies of all retrieved publications were searched to identify any further studies. The author of a study that had only produced interim results was contacted for clarification on some issues. Dressing manufacturers were contacted to enquire about current trials or recently completed trials. Ongoing clinical trials registers were also searched:
- Clinicaltrials.gov (www.clinicaltrials.gov)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).

For studies that met the inclusion criteria, the listed contact person was emailed to seek any available results of the study.

Study selection
The article titles were assessed by two authors independent of each other, and the abstracts (when available) identified by the search strategy were screened for their eligibility, according to the inclusion and exclusion criteria. The full-text version of potentially relevant studies was obtained and two authors independently screened this against the inclusion criteria. Consensus between the two authors in relation to the studies and the data to be included was obtained through a discussion when discrepancies were identified.
Data extraction
Data from the retrieved articles were extracted and inserted into a table using the following headings: study name, author, date of study, setting, unit, sample size, design, intervention, comparison and outcomes.

Quality appraisal and data analysis
The quality of studies was assessed independently by two authors, without blinding to journal or authorship, using The evidence-based librarianship (EBL) quality appraisal. This quality appraisal tool assesses the validity, the applicability and appropriateness of a study, based on four main steps of the research process:
- Population
- Data collection
- Study design
- Results.

According to this checklist, if the overall validity of the study (Yes/Total) is ≥75% or ((No+Unclear)/Total) is ≤25%, then the study is valid.

In this review, following the extraction of the main findings from the papers, meta-analysis statistical synthesis was undertaken using RevMan. Relative risks (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. Results of comparable trials were pooled using the fixed-effect model and 95% CI for the meta-analysis. Heterogeneity was investigated by calculating the I² statistic.

Results
Overview of all included studies
Fig 1 outlines the flow of articles through this review. After the initial search, a total of 563 hits were achieved, and following assessment, 16 articles were excluded as they did not meet the eligibility criteria (Fig 1).

The authors of two papers were contacted; one was a retrospective chart review of hard-to-heal wound patients treated with TOT carried out in the US. The author was contacted to see if data extracted on wound location had specified if any of the wounds were DFUs. The author responded that they had not collected this data, and so this paper was excluded. Another author of a multicentre RCT which had only published interim results was contacted to clarify some issues. Following correspondence from the author, it was decided to include this trial as it had produced results from the 12-week mark.

Finally, eight papers met the inclusion criteria and these papers formed the basis of this review.

Study design
Of the eight studies, five were RCTs, one was a prospective controlled study, one was a pilot study, and one was a retrospective, non-comparative observational study.

Geographical location
The geographical location of the studies varied between Canada, the US, and a multinational study conducted in the UK, US, France, Germany and Luxembourg.

Study settings
A single centre outpatient wound clinic was the setting for three studies, two studies were set in an outpatient wound care research clinic, and three studies were multisite.

Sample size
The mean sample size was 47 participants (standard deviation (SD)=41.9) varying between 10 participants and 124 participants.

Table 1. Quality appraisal results

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<th>Authors</th>
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<th>Study design category (%)</th>
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</table>
Primary outcomes

Wound healing: proportion of patients with DFUs that have reduced wound circumference or complete wound closure following the intervention.

A meta-analysis of five RCTs\(^1\),\(^10\),\(^13\),\(^18\),\(^21\),\(^23\) was undertaken. The results are presented in a forest plot (Fig 2). Of 177 participants with DFUs who received TOT, 53.6% (n=95) had full wound closure. In the group of 172 participants who received standard care, 31.3% (n=54) had full wound closure. Results of the analysis show an odds ratio of healing of 2.49 (95% CI: 1.59–3.90; p=0.00001). From this, we can see that DFUs are >2 times more likely to heal with TOT than with standard care alone. It should be noted for the purpose of this review that we did not differentiate the methods of TOT used while carrying out this analysis. Due to the small number of studies retrieved, it was decided to look at the intervention of topical oxygen as a whole group.

Secondary outcomes

Healing rates: rate of healing in the study by Blackman et al.\(^18\) was measured as median time to closure. In the therapy group this was 56 days (interquartile range (IQR): 39–81 days) in comparison with 93 days (IQR: 62–127 days) in the control group. The estimate of time to complete closure using Kaplan–Meier was: therapy group=94 days, control group=340 days (p=0.013).

Kemp and Hermans\(^19\) showed a median time to closure of 46 days (range: 13–119 days) for the 12 ulcers that healed in their study. Previously, the ulcers had an average duration of 134 days (range: 14–350 days). Niederauer et al.\(^21\) reported that time to 50% DFU closure was significantly shorter in participants who received the CDO therapy than in the sham therapy group (mean: 18.4 days versus 28.9 days, respectively; p=0.001).

In the study by Driver et al.\(^23\) wounds were measured weekly, wound tissue biopsies obtained and wound fluid collected. At week four, average wound size reduction was 87% (range: 55.7–100%) in the treatment group compared with 46% (range: 15–99%) in the control group (p<0.05). Changes in cytokine levels (IL-6, IL-8) and proteinases (MMP-1,-2,-9, TIMP-1) in
Our review focused on TOT and its effectiveness in patients with DFUs. It shows that TOT has the potential to positively impact on the effectiveness of wound healing with the potential to improve limb salvage and a patient’s quality of life.

Recurrence rates: Blackman et al. compared DFU recurrence rates after 24 months in both the therapy group and the control group. They found there were no recurrences at the healed ulcer site in either the therapy group or control group. Hayes et al., stated in their study that there was no recurrence of any ulcers at follow-up.

In the trial by Niederauer et al., recurrence rates were collected at follow-up at 12 weeks. No statistical difference in the results was observed, with 87.5% in the therapy group remaining closed and 90% remaining closed in the placebo group. Frykberg et al. did not, as at the time of writing, report reoccurrence rates or time to heal figures.

Adverse events, ease of use and pain: Blackman et al. stated that no treatment-related adverse events were documented in either group. Hayes et al. provided feedback from patients regarding ease of use. The device was well tolerated and patients enjoyed being involved in their treatment. Pain levels were reduced: from 39% of participants reporting pain at ≥5/10 at the start of the study to only 7% of participants with levels ≥5/10 at the end of the study.

Driver et al. found that there were fewer infections in the TOT group (3.5%) compared with the control group (10.15%), but the differences were not statistically significant. In addition, the authors reported that cellulitis incidents were more frequent in the control group (6.9%) compared with the TOT group (1.2%), but again, these differences were not significant.

Quality appraisal

The EBL Appraisal checklist was used to assess the methodological quality of the included studies in this systematic review by focusing on the four main domains: population, data collection, study designs and results. The assessment of these domains is summarised in Table 1, where validity figures can be found as well as any not reported, or unclear issues identified in each domain.

The mean validity score for all studies was 65.5±26.9%. The minimum score was 0%, while the highest overall validity was 92%. As can be seen in Table 1, 37.5% of the studies scored ≥75%, indicating that these studies were considered valid.

Discussion

The main goal of this systematic review was to examine the effect of TOT on healing of DFUs. All of the studies included produced positive results in favour of using TOT in the treatment of people with DFUs. It should be noted that the TOT was delivered by different methods. However, analysis showed that by using TOT, a DFU was >2 times more likely to heal than with standard care alone.

Primary outcomes measured number of wounds that gained wound closure or reduced wound circumference. Secondary outcomes were healing rates, recurrence rates, pain and device satisfaction; one paper looked at changes in biological markers in tissue samples of patients receiving therapy. In most of the studies reviewed, all the wounds were treated with standard care, regular debridement and offloading along with the TOT. It was interesting that three of the studies removed the possibility of wounds healing with standard care alone—without TOT—by having a run-in treatment before commencing TOT.

In 2005, the Undersea and Hyperbaric Medical Society published a position statement on TOT for hard-to-heal wounds. The aim was to ensure that TOT was not called hyperbaric oxygen therapy and that studies referencing systematic hyperbaric oxygen therapy should not be used when discussing the physiology of TOT. The paper concluded by stating that TOT should be considered to have mixed results rather than better results than hyperbaric oxygen therapy.

There have been a number of reviews of TOT in wound care, all of which discussed the different delivery methods. Our review focused specifically on TOT and its effectiveness in patients with DFUs.

DFUs are complex wounds and markers of comorbidities and serious disease. A study by Mavrogenis et al. estimated that 50% of DFUs would become infected and of these infected DFUs 20% would require amputation.

Previous literature with regard to TOT was limited to case reviews, making clinicians wary about trying this new therapy. Our review of eight studies that incorporated 349 participants provides a meta-analysis from four trials and has given a narrative analysis of the remaining three studies. Based on our findings, TOT—whether in the form of continuous delivery of oxygen or as topical pressurised oxygen—may, when used as an adjunct to standard care, improve healing rates in patients with DFUs. It shows that TOT has the potential to positively impact on the effectiveness of wound healing with the potential to improve limb salvage and a patient’s quality of life.

Limitations

In the search strategy of this systematic review the author focused on studies written in English only as there were no means to translate any studies in other languages. This may have resulted in language bias with perhaps important studies being missed that may have brought further evidence for or against the intervention.

There are also some limitations to the conclusions drawn. Only two of the eight studies included were deemed valid, and one study received a score of 0%; the main weakness of the papers being sample size. Too small a sample size will result in imprecise estimates in a descriptive study and will fail to achieve a statistical
significance in a comparative study. Also, recurrence rates were only measured in four of the eight papers. This would have been an important secondary outcome for all papers as a patient with a healed DFU has a 17–60% chance of another one occurring.

Recommendations for practice and research

This systematic review has shown that there are few RCTs conducted to show the benefit of TOT. Following a robust search, only five RCTs were found. Further studies need to address follow-up care, patient quality of life and cost. More robust research is needed to highlight its possible benefit in the adjunct treatment of DFUs.

Conclusion

DFUs are a challenging area of wound care practice. For the patient they can have an impact on their morbidity and mortality. The high rate of amputations following infection of DFUs is costly to the patient and the health service. This review found evidence that the adjunct therapy of TOT may lead to faster healing rates and wound closure for some patients if used alongside standard diabetic foot care.

References


Reflective questions

● What are the challenges to healing a diabetic wound, and why?
● What is the role of topical oxygen therapy on diabetic foot ulcer healing rates?
● What is the role of topical oxygen therapy on diabetic foot ulcer recurrence rates?