Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children

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TABLE OF CONTENTS

[Intervention Protocol]

Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children

Natalie K Bradford[1,2], Rachel M Edwards[2], Raymond J Chan[3,4]

[1]Centre for Online Health, University of Queensland, Brisbane, Australia. [2]Queensland Children's Cancer Centre, Royal Children's Hospital, Brisbane, Australia. [3]Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane, Australia. [4]School of Nursing and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Contact address: Natalie K Bradford, Centre for Online Health, University of Queensland, Herston Road, Brisbane, Queensland, 4012, Australia. n.bradford@uq.edu.au, natalie_bradford@health.qld.gov.au.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the clinical effects (benefits and harms) of intermittent flushing of heparin versus 0.9% sodium chloride to prevent occlusion in long term central venous catheters (CVCs) in infants and children.

BACKGROUND

Description of the condition

A central venous catheter (CVC) is a catheter which is inserted into a large central vein, with the tip of the catheter ideally placed within the superior vena cava (Schuster 2000). This enables the administration of medications and fluids, as well as the collection of blood specimens to avoid unnecessary venipunctures. The use of long term CVCs for the management of chronic medical conditions in infants and children has greatly improved the quality and safety of care provision. Long term CVCs are typically inserted when the administration of intravenous medication or nutritional support is required over a considerable time period. Hypertonic medications such as vesicant chemotherapy drugs, certain antibiotics, other supportive drugs and parenteral nutrition are not able to be safely administered through peripheral venous catheters. For children with cancer and other chronic medical conditions who require such medications, this safety issue is overcome by the insertion of a CVC which commonly remains in place for the duration of treatment (Gonzalez 2012). There are three types of long term CVCs: tunnelled catheters; implanted ports; and peripherally inserted central catheters (PICC). A tunnelled CVC is surgically inserted under the skin, with the catheter lumen(s) typically exiting from the chest or neck. An implanted port is also surgically implanted, but is placed entirely under the skin. The port reservoir is accessed with a needle through the skin. A PICC line is inserted into a central vein through the arm and thus is a narrower catheter.

Adverse events associated with CVCs may cause complications in up to 46% of children (Athale 2012). Adverse events include mechanical failure, infections and thrombotic complications, all of which can effect patient morbidity and mortality (Baskin 2009; Fratino 2005; Stocco 2012; Wong 2012). Mechanical failure is often attributed to catheter occlusion. Over time, it is common for a fibrin sheath to develop at the tip of the catheter. This may prevent aspiration of blood from the catheter and cause resistance when infusing fluids. An intraluminal clot can also occur, totally occluding the catheter. Occlusion can result in the need for the catheter to be removed (and replaced), interrupting and delaying treatment of the underlying disease (Shah 2007). Occlusions of CVCs are estimated to occur in 14% to 36% of patients within one to two years of catheter insertion (Fratino 2005) or at an incidence rate of 1.35 per 1000 catheter days (95% confidence interval (CI) 1.1 to 1.63) (Revel-Rilk 2010). Incidence rates of blood stream infection associated with CVCs differ depending upon the type of catheter, with rates reported between 1.40 per 1000 catheter days (95% CI 1.06 to 1.82) and 0.46 per 1000 catheter days (95% CI 0.29 to 0.69). Thrombotic complications are the rarest adverse events reported in children, with a lower incidence rate of 0.08 per 1000 catheter days (95% CI 0.04 to 0.16) (Fratino 2005).

Description of the intervention

A flush refers to solution being injected to clean the catheter of blood or fibrin buildup. This is commonly used when the catheter is accessed, between administration of medications, or before and after collection of blood specimens. A positive pressure lock is used when the catheter will not be accessed for a period of time, and refers to the technique used to ensure blood does not flow back into the catheter after it is flushed, which may otherwise clot and cause occlusion. Tunnelled CVCs and PICC lines are typically flushed and locked weekly, while implanted ports are flushed and locked every 4 to 6 weeks. A typical intervention for tunnelled catheters in children is to use between 1 ml to 3 ml (depending on the volume of the catheter) of 10 units/ml of heparin for a 24 hour to 7 day lock. For implanted ports, 5 mls of 100 units/ml is typically used for a 30 day lock (Davis 2013). However, there is debate regarding the effectiveness of heparin to prevent occlusion over such time periods, given its short half life (Young 2008). The evidence to support the use of heparin to prevent occlusion in adult CVCs is inconclusive and there is growing evidence to support the use of 0.9% sodium chloride to lock CVCs, particularly in the paediatric population (Bertoglio 2012; Lee 2005).

How the intervention might work

Heparin is used to prevent occlusion because of its anti-coagulant properties which are believed to prevent thrombus forming in the catheter. Alternatively 0.9% sodium chloride, when used with pulsatile flushing techniques and a positive pressure lock or positive displacement device, may be as effective in preventing thrombus formation in catheters - eliminating the need for heparin to be used.

Why it is important to do this review

Practices vary among institutions because of the lack of evidence regarding best practice to prevent occlusion of CVCs. The use of heparin is not risk free and in certain instances may actually cause harm including heparin-induced thrombocytopenia (HIT) (Barclay 2012). The mechanism of haemostasis in children is different when compared to adults, particularly in infants and very young children (Monagle 2010). Additionally, treatments for diseases such as cancer involve the use of medications which can affect coagulation; thus the use of heparin to prevent CVC occlusion should be judicious and evidence-based. While the risks of adverse effects from the use of heparin may be regarded as less than the potential occlusion of a catheter and subsequent replacement, it is important to ensure interventions are based on evidence.

There have been several trials (Goosens 2013; Schallom 2012; Schilling 2006), a systematic review (Mitchell 2009), and a Cochrane review protocol to review the use of heparin versus 0.9% sodium chloride to prevent occlusions in CVCs in the adult population (Lopez-Briz 2010). As evidence from adult studies is not directly transferable to paediatrics, a systematic review focused on infants and children is required.

OBJECTIVES

To assess the clinical effects (benefits and harms) of intermittent flushing of heparin versus 0.9% sodium chloride to prevent occlusion in long term central venous catheters (CVCs) in infants and children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials. Due to potential bias, we will exclude studies that use alternative methods (quasi-randomised) to allocate participants to a control or intervention group.

Types of participants

The study population comprises infants and children aged 1 to 18 years who have a CVC (tunnelled catheter or implanted port), inserted for long term venous access. Studies of infants or children with Midline catheters or PICCs are beyond the scope of this review and will be excluded. There are no restrictions on the insertion site, or catheter tip placement site (superior or inferior vena cava). There will be no restrictions on the healthcare setting in which the study has been conducted, e.g. tertiary hospital or community setting. Where studies have a mixed population that includes infants, children and adults, we will include data from infants and children only. If this information is not presented in the article, we will contact the study authors to attempt to obtain age-stratified results. If we are unable to contact the study authors, and children and infants comprise a proportion greater than 20% of the study population, we will include the appropriate threshold proportion. If we are unable to obtain any information regarding the proportion of infants and children in the study population, we will exclude the study from the review.

Types of interventions

The intervention of interest is the intermittent (any time frequency) flushing of heparin (any dose or concentration) compared with intermittent flushing with 0.9% sodium chloride solution (alone, or in combination with pulsatile flushing techniques, positive displacement devices or positive pressure lock) delivered with the intention to prevent occlusion of the CVC.

Types of outcome measures

Primary outcomes

- Occlusion of the CVC, determined by the inability to infuse fluids through the catheter
- Duration in weeks of catheter placement
- Any adverse event associated with CVCs (catheter-related thrombosis, sepsis, central line associated blood stream infection (CLABSI) or colonisation of the catheter, allergic reaction, haemorrhage, heparin-induced thrombocytopaenia (HIT), elevated hepatic enzymes)

Outcomes will not be considered a part of eligibility criteria.

Secondary outcomes

- Ability to withdraw blood from the CVC
- Any use of urokinase or recombinant tissue plasminogen such as alteplase
- Incidence of removal and re-insertion of the catheter

Search methods for identification of studies

No restrictions will be placed on language.

Electronic searches

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) will search the Group's Specialised Register and the Cochrane Central Register of Controlled Trials (CENTRAL), part of *The Cochrane Library* (www.thecochranelibrary.com). See Appendix 1 for details of the search strategy which will be used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in *The Cochrane Library* (www.cochranelibrary.com).

The following trial databases will be searched by the TSC for details of ongoing and unpublished studies:

- World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/
- ClinicalTrials.gov http://clinicaltrials.gov/
- Current Controlled Trials http://www.controlled-trials.com/
- Nederlands Trials Register http://www.trialregister.nl/trialreg/admin/rctsearch.asp

Searching other resources

We will screen the reference lists of retrieved articles for additional studies. We will attempt to contact authors of any studies identified in unpublished literature to obtain further data.

Data collection and analysis

Selection of studies

Two review authors (NB, RE) will independently review all titles and abstracts retrieved to assess eligibility against inclusion criteria. Where disagreement exists regarding the inclusion of a study, the third author (RC) will be consulted. The full text of all potentially eligible studies will be obtained and authors of primary studies will be contacted to clarify data if necessary. A flowchart based upon the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher 2009) statement will be used to document results and will be presented in the review. Data will be recorded regarding the results of all searches undertaken including: database searched; date; limiters, and number of results.

Data extraction and management

Data extraction will be completed independently by NB and RE and documented on the PVD Group forms for dichotomous and continuous data. Data will be collected regarding the population, intervention(s) and relevant outcomes for each study. Any disagreement will be resolved by discussion between all review authors (NB, RE, RC).

Assessment of risk of bias in included studies

Bias will be assessed within studies using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The following domains will be reported: sequence generation; allocation concealment; blinding; incomplete data; selective outcome reporting, and other biases. If necessary, primary authors will be contacted to clarify any information. Disagreement regarding the assessment of bias will be resolved by discussion among all review authors (NB, RE, RC).

Measures of treatment effect

Odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI) will be calculated for dichotomous data (e.g. CVC occlusion, adverse event etc). Descriptive statistics including mean differences (MD) and standard deviations (SD) will be presented for continuous

data (e.g. duration of catheter placement). Time-to-event data (occlusion) will be reported as hazard ratios (HR) with 95% CI.

Unit of analysis issues

The unit of analysis for each trial will be identified. It is anticipated that outcomes for intervention or control groups will be reported as single effect measurements from each participant. Where results are reported from cluster randomised controlled trials, cross-over trials or repeated measurements of the same outcome, the appropriate design effect will be taken into consideration to avoid unit of analysis error.

Dealing with missing data

Primary authors of studies will be contacted to obtain any missing data. All data will be assessed for potential mislabelling and we will not make assumptions of missing data in order to include these in any analysis. Where data are missing and cannot be obtained, they will be excluded from the analysis.

Assessment of heterogeneity

If feasible, visual inspection of forest plots and the Chi^2 test (P value < 0.05) will be used to test for heterogeneity between effect sizes of included studies. Inconsistency between trials will be described by assessing the I^2 statistic and the variability between the effect estimates. A value of I^2 greater than 50% will be considered to represent substantial heterogeneity (Higgins 2011), and we will explore heterogeneity and possible reasons.

Assessment of reporting biases

If feasible, publication bias will be assessed using funnel plots and Egger's tests. Additionally reporting bias will be reduced by searching multiple electronic databases, proceedings of conferences and scientific meetings and trial registries. There will be no language restriction. Duplicates of the same trials will be excluded to avoid duplicate publication bias.

Data synthesis

We will enter data into RevMan (RevMan 2012) and undertake analysis according to recommended guidelines (Higgins 2011). Effect sizes across studies will be combined using a fixed-effect model. Where substantial heterogeneity exists, data will be pooled using the random-effects model. Confidence interval limits will be set at 95%. If we are not able to undertake a pooled analysis, results will be descriptively summarised.

Subgroup analysis and investigation of heterogeneity

Where sufficient studies are available for analysis, subgroup analysis will be performed regarding: type of CVC (tunnelled catheter or implanted port); insertion site and/or catheter tip placement site; age group, and diagnosis.

Sensitivity analysis

Sensitivity analysis will be undertaken to examine the effects of different trials and their methodology. The rigour of results will also be assessed by comparing different measures of effect sizes (OR, RR, MD) and random-effects or fixed-effect models.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Heparin] explode all trees
#2	(hep* or UH or UFH or LMWH):ti,ab,kw
#3	MeSH descriptor: [Sodium Chloride] this term only
#4	MeSH descriptor: [Saline Solution, Hypertonic] explode all trees
#5	saline*:ti,ab,kw
#6	sodium:ti,ab,kw
#7	NaCl:ti,ab,kw
#8	#1 or #2
#9	#3 or #4 or #5 or #6 or #7
#10	#8 and #9
#11	MeSH descriptor: [Catheterization, Central Venous] this term only
#12	MeSH descriptor: [Catheterization] this term only
#13	MeSH descriptor: [Catheters, Indwelling] explode all trees
#14	catheter*:ti,ab,kw
#15	cannula*:ti,ab,kw
#16	CVC* or PICC:ti,ab,kw
#17	port*:ti,ab,kw
#18	#11 or #12 or #13 or #14 or #15 or #16 or #17
#19	#10 and #18 in Trials

CONTRIBUTIONS OF AUTHORS

All authors contributed to the drafting and review of this protocol.

DECLARATIONS OF INTEREST

None declared

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital, Queensland, Australia.

  Royal Children's Hospital provides salary and facilities for NB and RE to conduct this systematic review.
- Royal Brisbane and Women's Hospital, Queensland, Australia.

  Royal Brisbane and Women's Hospital provides salary and facilities for RC to conduct this systematic review.
- The University of Queensland's Centre for Online Health, Australia.

  The Centre for Online Health provides salary and facilities for NB to conduct this systematic review.

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Catheter Obstruction; *Central Venous Catheters; Fibrinolytic Agents [*administration & dosage]; Heparin [*administration & dosage]; Randomized Controlled Trials as Topic; Sodium Chloride [*administration & dosage]

MeSH check words

Child; Child, Preschool; Humans; Infant