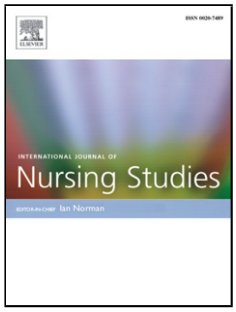

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Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children: a systematic review*

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Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants, children and adolescents: A systematic review*

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Abstract

Background

Around the world, guidelines and clinical practice for the prevention of complications associated with central venous catheters (CVC) vary greatly. To prevent occlusion, most institutions recommend the use of heparin when the CVC is not in use. However, there is debate regarding the need for heparin and evidence to suggest normal saline may be as effective. The use of heparin is not without risk, may be unnecessary and is also associated with increased costs.

Objectives

To assess the clinical effects (benefits and harms) of heparin versus normal saline to prevent occlusion in long-term central venous catheters in infants, children and adolescents.

Design

A Cochrane systematic review of randomised controlled trials was undertaken.

Data sources

The Cochrane Vascular Group Specialised Register (including MEDLINE, CINAHL, EMBASE and AMED) and the Cochrane Register of Studies were searched. Hand searching of relevant journals and reference lists of retrieved articles was also undertaken.

Review Methods

Data were extracted and appraisal undertaken. We included studies that compared the efficacy of normal saline with heparin to prevent occlusion. We excluded temporary CVCs and peripherally inserted central catheters. Rate ratios

per 1000 catheter days were calculated for two outcomes, occlusion of the CVC, and CVC-associated blood stream infection.

Results

Three trials with a total of 245 participants were included in this review. The three trials directly compared the use of normal saline and heparin. However, between studies, all used different protocols with various concentrations of heparin and frequency of flushes. The quality of the evidence ranged from low to very low. The estimated rate ratio for CVC occlusion per 1000 catheter days between the normal saline and heparin group was 0.75 (95% CI 0.10 to 5.51, two studies, 229 participants, very low quality evidence). The estimated rate ratio for CVC-associated blood stream infection was 1.48 (95% CI 0.24 to 9.37, two studies, 231 participants; low quality evidence).

Conclusions

It remains unclear whether heparin is necessary for CVC maintenance. More well-designed studies are required to understand this relatively simple, but clinically important question. Ultimately, if this evidence were available, the development of evidenced-based clinical practice guidelines and consistency of practice would be facilitated.

What is already known about this topic?

- Central venous catheters maintenance practices vary around the world
- Variations include the quantity of flush and lock solutions, the proportional volume of heparin lock solution, and the frequency of flushes and locks.
- The use of heparin may be unnecessary, is costly and is not risk free

What this paper adds?

- There was not enough evidence to determine which solution, heparin or normal saline, was superior to prevent occlusion in long-term central venous catheters in infants and children.
- There is a need for healthcare organisations to consider undertaking further research in this area to contribute to the evidence base.
- Nurses are ideally placed to contribute to such research and ultimately this would facilitate the development of evidence-based clinical practice guidelines and consistency of practice

Introduction

Central venous catheters (CVCs) are commonly used in hospital-based care to enable the administration of medications and fluids, as well as for the collection

of blood specimens. Long term CVCs are typically inserted when the administration of intravenous medication or nutritional support is required over a considerable time period. The use of long term CVCs for the management of complex or chronic medical conditions, such as cancer, in infants, children and adolescents, has greatly improved the quality and safety of care provision. (Gonzalez et al., 2012)

Adverse events associated with CVCs, such as mechanical failure or central line associated-blood stream infection (CLABSI) may cause complications in up to 46% of children (Athale et al., 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. The fibrin sheath may prevent aspiration of blood from the catheter and cause resistance when infusing fluids. An intraluminal clot can also occur, which can totally occlude 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 et al., 2007).

To prevent occlusion, it is common to regularly flush the CVC with 0.9% sodium chloride, and to use a heparin lock when the CVC is not in use. However, there is debate regarding the effectiveness of heparin to prevent occlusion over long 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 (normal saline) to lock CVCs, particularly in the paediatric population (Bertoglio et al., 2012, Lee and Johnston, 2005). Normal saline, when used with pulsatile (push-pause rather than continuous) 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.

Catheter maintenance practices vary among institutions because of the lack of evidence regarding best practice to prevent occlusion of CVCs (Lee and Johnston, 2005, Conway et al., 2014).Variations include the quantity of flush and lock solutions, the proportional volume of heparin lock solution, and the frequency of flushes and locks. The use of heparin is not risk free and in certain instances may actually cause harm, including infection (Shanks et al., 2005) and heparin-induced thrombocytopenia (HIT) (Barclay et al., 2012). Additionally, treatments for diseases such as cancer involve the use of medications that can affect coagulation. For these reasons 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.

In the adult population, there have been several trials (Goossens et al., 2013, Schallom et al., 2012) a systematic review (Mitchell et al., 2009), and a Cochrane Review of the use of heparin versus normal saline to prevent occlusions in CVCs (Lopez-Briz et al., 2014). As evidence from adult studies is not directly transferable to paediatrics, a systematic review focused on infants and children is required. A review published in 2014 that did relate specifically to paediatrics,

(Conway et al., 2014) did not identify all relevant studies and made recommendations based on the current practice of several institutions. These recommendations were not evidence-based, and are contrary to the practice of many other institutions. Therefore, it is important to systematically appraise the evidence for the use of heparin compared with normal saline to prevent occlusion of central venous catheters.

Aims

To compare the clinical effects (benefits and harms) of heparin versus normal saline to prevent occlusion in long-term central venous catheters in infants, children and adolescents.

Methods

Criteria for inclusion in this review

We undertook a Cochrane systematic review (Bradford et al., 2015). We included all randomised controlled trials (RCTs) that compared the efficacy of heparin with normal saline for the prevention of occlusion of CVCs. The participants were infants, children and adolescents aged 0 to 18 years of age, who had a CVC (tunnelled catheter or totally implanted catheter), inserted for long-term venous access. Because midline catheters are not placed in the same position as a CVC (superior or inferior vena cava), and PICC have narrow lumens that require specific care, they were excluded. Where studies had a mixed population that included infants, children and adults, we included data from infants and children only. If information was not presented in the article, we contacted the study authors to attempt to obtain age-stratified results.

The interventions were the intermittent (any time frequency) flushing of heparin (any dose or concentration) compared with intermittent flushing with normal saline (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.
The outcomes included:

- Occlusion of the CVC, determined by the inability to infuse fluids through the catheter.
- CVC-associated blood stream infection or colonisation of the catheter.
- Duration in days of catheter placement.
- Inability to withdraw blood from the CVC.
- Any use of urokinase or recombinant tissue plasminogen such as alteplase.
- Incidence of removal/re-insertion of the catheter.
- Other CVC-related complication (e.g. dislocation of CVCs, thrombosis, tunnel or site infection, allergic reaction, haemorrhage, heparin-induced thrombocytopaenia, elevated hepatic enzymes.

Identification of studies

The Cochrane Vascular Trials Search Co-ordinator (TSC) searched the Specialised Register and the Cochrane Register of Studies (CRS) http://www.metaxis.com/CRSWeb/Index.asp (2015, Issue 3). The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through hand-searching relevant journals. Trial databases were searched by the TSC in April 2015 for details of ongoing and unpublished studies using the terms heparin and sodium and (catheter or cannula or CVC or PICC). No restriction was placed on language.

Study screening

Two review authors (NB, RE) independently reviewed all titles and abstracts of retrieved articles to assess eligibility against inclusion criteria. Discrepancies were resolved by consensus.

Data extraction

Two review authors (NB, RC) extracted the data independently using the Cochrane Vascular Group forms for dichotomous and continuous data. Data were collected regarding the: lead author and year of study; country where the study was undertaken; participant inclusion criteria; participant age and gender; study design; description of interventions; setting of study; number of participants in each arm; attrition or losses to follow-up; catheter days at risk; outcome measures. We resolved any disagreement regarding data extraction by discussion between all review authors (NB, RE, RC).

Study quality assessment

We assessed bias within studies using the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011) reporting the following domains: sequence generation; allocation concealment; blinding; incomplete data; selective outcome reporting, and other biases. This led to an overall assessment of bias of each of the included studies. Two review authors (NB, RC) independently undertook the risk of bias assessment. Disagreement regarding the assessment of bias was resolved by discussion between review authors (NB, RC).

Data analysis

As dichotomous outcomes such as CVC occlusion or CVC-associated blood stream infection could occur more than once for individual participants, we calculated count data per time at risk of outcome (per 1000 catheter days) and reported rate ratios with 95% confidence intervals (CI). Using section 9.4.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins and Green, 2011) we also calculated the formula for the log of the standard error for each rate ratio. We pooled data statistically using meta-analysis Review Manager software (Cochrane Collaboration, 2011). Where substantial heterogeneity existed, we pooled data using the random-effects model. The decision to carry out meta-analysis was made after discussion with the Cochrane biostatistician

and with consensus from all authors. Where it was not appropriate to combine results, we presented a narrative review descriptively summarising the results

Table 1 Characteristics of included studies

Study, country, setting, participants and Catheter days at risk	Description of intervention, controls	Outcomes	Notes
Cesaro et al (2009) Country: Italy Clinical setting: single tertiary referral centre Participants: 203 paediatric (age 0-17 years) haematology or oncology patient with tunnelled Brioviac CVC inserted for chemotherapy. Catheter days at risk: 75,249	Experimental treatment group: flushing with normal saline at least weekly via a positive pressure cap Standard treatment group: flushing with 3 mL of normal saline with 200 units heparin twice weekly via a standard CVC cap	• Incidence of CVC complications: occlusion, dislocation of CVC, CVC-related infection, exit site infection, thrombosis • CVC survival (weeks) • Organisms isolated from blood cultures	Potential confounding of results due to outcomes being attributable to positive pressure cap or frequency between flushes rather than the flushing solution used ✓ Random sequence generation ✓ Allocation concealment ✗ Blinding of participants and personnel ✗ Blinding of outcomes assessment ✓ Complete data (attrition) ? Selective reporting ✗ Other bias
Goossens et al (2013) Country: Belgium Clinical setting: single tertiary referral centre Participants: 802 individuals (0-71 years old) with an oncology or haematology condition, who had a totally implantable intravenous catheter inserted. A subset of unpublished data was obtained from the investigators for 28 (3.5%) participants, aged one to 18 years of age Catheter days at risk: 115,991 (The assumption was made that the mean catheter days was equivalent in the paediatric population)	Experimental treatment group: pulsatile flushing with 10 mL of normal saline and then locking with positive pressure Standard treatment group: pulsatile flushing with 10 mL of normal saline, followed by 3 mL heparin (100 units/mL) and locking with positive pressure	• Rate of inability to aspirate blood while injection was easy (assessed at every access) • Incidence of CVC-associated blood stream infection • Incidence of functional problems associated with CVC	Subset of paediatric data (unpublished) was obtained to assess outcomes for children only: 26 out of 28 children contributed data. Not all variables available, there may be some systematic differences in the characteristics of children in the subset of data, the study was not powered to analyse this subset of data separately ✓ Random sequence generation ✓ Allocation concealment ✗ Blinding of participants and personnel ✗ Blinding of outcomes assessment ? Complete data (attrition) ? Selective reporting ✗ Other bias

Smith et al (1991) Country: Canada Clinical Setting: single tertiary referral centre Participants 14 participants (21 months-20 years of age) with a tunnelled Broviac CVC As a cross-over design, the same participants were in both the experimental treatment group and the standard treatment group Catheter days at risk: 3029	Experimental treatment group: once per week flush with 9 mL normal saline Standard treatment group: twice daily flushes with 5 mL heparinised normal saline (10 units/mL heparin)	• Thrombosis formation at baseline, cross over point (14 weeks) and end of study (28 weeks) as measured by echocardiogram or inability to infuse or withdraw from CVC (occlusion) • Incidence of CVC mechanical issues (leak, migration) • Incidence of CVC-associated infection	Older study, not reported using contemporary standards. Potential for confounding of results due to outcomes being attributable to frequency between flushes rather than solution used. No information available for first cross-over period results ? Random sequence generation ? Allocation concealment × Blinding of participants and personnel × Blinding of outcomes assessment ✓ Complete data (attrition) × Selective reporting × Other bias

✓ - Low risk of bias
? – Unclear risk of bias
× - Risk of bias
CVC – Central Venous Catheter

Results

Search Results

Study screening of 137 citations identified 10 studies that were potentially relevant and the full text were reviewed. We contacted three individual study authors for further study details and were able to find further information for two studies (Goossens et al., 2013, Smith et al., 1991). Of the 10 studies, three met the inclusion criteria (Cesaro et al., 2009, Goossens et al., 2013, Smith et al., 1991) and were included in this review. Details of data extraction are summarised in Table 1. A flow chart detailing the identification of studies can be found in Figure 1.

The studies undertaken by Cesaro et al., (2009) and Goossens et al., (2013) were of medium duration (25 and 23 months respectively) and included follow-up periods of 14 and six months respectively. The Smith et al., (1991) study was a cross-over study of two, three-and-a-half month time periods (total duration seven months) and did not include a follow-up period. We were not able to ascertain if this study was analysed as paired data or not, and no information was available regarding the first cross-over period, therefore this study was not pooled with the others for meta-analysis. All studies had obtained ethical approval from their relevant institutions.

Population

The three included trials involved a total of 245 participants, with the majority of participants (203) coming from Cesaro et al., (2009). From the other two studies, Goossens et al., (2013) contributed 28 participants, and Smith et al., (1991) contributed 14. All participants had a long-term central venous catheter placed, and were undergoing treatment for haematology or oncology conditions. Participants in Cesaro et al., (2009) and Smith et al., (1991) had Broviac tunnelled CVCs inserted, whereas all participants in Goossens et al., (2013) had totally inserted catheters (ports) placed. All studies were undertaken in developed nations in tertiary referral centres. Both Cesaro et al., (2009) and Goossens et al., (2013) undertook power size calculations to obtain sample sizes, however it is important to note that children comprised only 3.5% of Goossens et al., (2013) study population, thus this study was not powered to analyse the results of children separately.

Interventions

Participants in all three included studies received standard care except where stated as follows. All studies involved an experimental arm where normal saline solution was used in place of standard solution (heparinised saline) when the CVC was not being used. As well as changing the type of solution used to flush the CVC, Smith et al., (1991) increased the time between flushes in the intervention arm from twice daily to weekly. Similarly, Cesaro et al., (2009) increased the duration between flushes in the intervention arm compared to standard care from twice per week to weekly. Cesaro et al., (2009) also introduced a positive

pressure cap into the intervention arm. These changes confound the interventions so it is not possible to associate outcomes with the use of the solution alone. Goossens et al., (2013) was the only study included in this review where the only difference between the intervention and standard arm was the use of normal saline (experimental) or heparin (standard) solution to flush the CVC.

Control

In all studies, participants randomised to the standard arm received various concentrations of heparinised saline to flush their CVC. Participants in Smith et al., (1991) study received 5 mL of 10 units/mL heparinised saline (i.e. 50 units of heparin) twice daily. Participants in Cesaro et al., (2009) study received 3 mL of 200 units/mL heparinised saline (i.e. 600 units of heparin) twice weekly. In Goossens et al., (2013) study, participants in the standard arm received 3 mL of 100 units/mL heparin (i.e. 300 units of heparin) under positive pressure at least every eight weeks when the CVC was not in use.

Outcomes

The primary outcome of interest, occlusion of CVC, was measured in all three studies. We were able to pool data related to occlusion and incidence of CVC – associated blood stream infection for two studies (Cesaro et al., 2009, Goossens et al., 2013). All studies reported the catheter-days participants were at risk of experiencing an outcome.

Methodological quality of studies

There was low risk of selection bias in the Cesaro et al., (2009) and Goossens et al., (2013) studies; these investigators reported using computerised random sequencing and concealing allocation until participants had been recruited and provided consent. Smith et al., (1991) study did not provide randomisation details. None of the three included studies blinded investigators, clinicians or participants regarding to which arm the participant had been allocated. All outcomes were objectively measured, but in all three studies there is the possibility clinicians may have modified their technique depending on the arm to which the participant had been allocated. All studies were therefore assessed as a high risk of both performance and detection bias. All three studies reported full results for primary and secondary outcomes for all participants. There were no study protocols available, therefore reporting bias for all studies is unclear. Smith et al., (1991) reported data in a basic format with no results from statistical tests.

In both the Cesaro et al., (2009) and Smith et al., (1991) studies, there is a high concern for confounding of results. Both these studies altered the frequency between flushes for the experimental arm as well as the experimental solution. Additionally in Cesaro et al., (2009) the experimental arm included the use of a positive pressure cap. It is not possible therefore to attribute the outcome to the use of the solution alone, the outcome could plausibly also be attributed to the frequency of flushes or the use of a positive pressure cap. It may therefore be

more appropriate to view the intervention as a component of a bundle of care. Further bias may exist in the subset of unpublished data of paediatric participants provided by Goossens et al., (2013) . As a cross over study there may have been a carry-over effect of the intervention from one arm to the other in Smith et al., (1991). It is not clear if the study authors considered this. These other potential sources of bias across all three studies are substantial and reduce confidence in the results.

Effects of interventions

CVC occlusion

CVC occlusion was reported in all three included trials (243 participants; Goossens et al., (2013) provided data for 26 of 28 participants for CVC occlusion). In both Smith et al., (1991) and Cesaro et al., (2009) there were more CVC occlusions in the experimental (normal saline) arm. Rates were calculated for each study based upon 1000 catheter days and are presented as rate ratios of saline versus heparin (see Table 2). We pooled the results from the (Cesaro et al., 2009) and (Goossens et al., 2013) using random effects because of the clinical heterogeneity between studies (e.g. difference in frequency of flushing, implanted catheters and tunnelled catheters, use of positive pressure cap). The analysis suggested there was no statistical difference in the outcome of CVC occlusion between flushing with heparin or normal saline (rate ratio 0.75, 95% CI 0.10 to 5.51; participants = 229; studies = 2; Z = 0.29, P = 0.78). However the heterogeneity between studies indicates this result may be due to differences between the studies (See Figure 2). The results were imprecise and we graded this evidence as very low quality

Table 2. Rate ratio of outcome per 1000 catheter days – saline versus heparin

Outcome per 1000 catheter days	Smith et al., (1991)		Cesaro et al., (2009)		Goossens et al., (2013)	
	Rate ratio#	Variance*	Rate ratio#	Variance*	Rate ratio#	Variance*
CVC occlusion	2.0	1.22	1.95	0.19	0.25	0.54
CVC-associated blood stream infection rate	2.0	1.22	2.58	0.39	0.31	1.55
Inability to withdraw blood	Not reported	N/A	Not reported	N/A	0.32	0.47
CVC dislodgement	0.2	1.55	0.87	0.32	Not reported	N/A
CVC site infection	7.0	1.51	0.68	0.41	Not reported	N/A
CVC-related thrombosis	1.0	1.41	1.0	1.41	Not reported	N/A

CVC- Central venous Catheter
- incidence in saline group/incidence in heparin group
*- variance calculated as the standard error of the log rate ratio
N/A – not applicable

CVC-associated blood stream infection or colonisation

Incidence of CVC-associated blood stream infection was reported in all three included trials (245 participants). Rates were calculated as above (see table 2). There were more CVC-associated blood stream infections in the experimental (normal saline) arm in both Cesaro et al., (2009) and Smith et al., (1991) studies. We pooled the results of Cesaro et al., (2009) and Goossens et al., (2013) and found there was no significant association between the use of saline to flush CVC and the incidence of CVC-associated blood stream infection (rate ratio 1.48, 95% CI 0.24 to 9.37; participants = 231; studies = 2; Z = 0.42, P = 0.67). We graded this evidence as low quality as results were imprecise (See Figure 3).

Duration of CVC placement (days)

After a median follow-up of 360 days, Cesaro et al., (2009) reported that CVC survival was similar between the two study arms (203 participants): saline = 77% (95% CI 66% to 84%), heparin = 69% (95% CI 53% to 80%). Duration of CVC placement was not reported in the other two studies.

Inability to withdraw blood from the CVC

Goossens et al., (2013) reported on the inability to withdraw blood from the CVC (26 participants). Compared to normal saline group, there was a decreased inability to withdraw blood from the CVC in the heparin group, rate ratio 0.32 (95% CI 0.14 to 0.88). This outcome was not reported in the other studies.

Any use of urokinase or recombinant tissue plasminogen

Urokinase was used in 116 of 124 (94%) episodes of CVC occlusion in Cesaro et al., (2009) study of 203 patients, and patency was restored in 107 out of 116 (92%). Of note, 83 CVCs occluded in the normal saline group and 41 in the heparin group. Five of the CVCs were occluded in only one lumen and so were left in situ while the remaining four were unable to have patency restored in either lumen and were prematurely removed. There was no information regarding this outcome available in the other studies.

Incidence of removal/re-insertion of the catheter

Cesaro et al., (2009) reported premature removal of a CVC was required in 44 (22%) participants. Premature removal was comparable between the two study arms, and was generally indicated because of dislocation of the catheter or infection, rather than CVC occlusion. There was no information regarding this outcome from the other studies.

Other CVC-related complications

Dislodgment of the CVC occurred in 38/203 (19%) of the total study population in Cesaro et al., (2009) There were no statistical differences between study arms; rate ratio 0.87 (95% CI 0.46 to 1.63). In Smith et al., (1991) dislodgement

occurred in 2/14 (14%) of the study population. There was no statistically significant difference between study arms; rate ratio 0.2 (95% CI 0.01 to 4.81). There was no information regarding this outcome available from Goossens et al., (2013).
CVC site infection was reported in 24/203 (12%) in Cesaro et al., (2009) with no statistically significant differences between study arms; rate ratio 0.68 (95% CI 0.30 to 1.52). In Smith et al., (1991) CVC site infection was reported in 6/28 (21%) of the study population, again there was no difference between study arms and the results were imprecise; rate ratio 7.0 (95% CI 0.37 to 132.4).
CVC-related thrombosis was reported in 2/203 (1%) of the study population in Cesaro et al., (2009) with no differences between study arms; rate ratio 1.0 (95% CI 0.06 to 15.86). In Smith et al., (1991), CVC-related thrombosis was reported in 2/14 (14%) of the population, again there was no difference between study arms and results were imprecise; rate ratio 1.0 (95% CI 0.06 to 15.86).
There were no data available from Goossens et al., (2013) regarding other CVC complications in the paediatric population of 28 patients.

Discussion

This systematic review compared the use of heparin locks (standard care) with experimental use of normal saline locks. The quantity of the evidence was small; we were only able to include three studies and the results were inconsistent. We found that there is insufficient data to determine the effects of intermittent flushing of normal saline versus heparin to prevent CVC occlusion or CVC-associated blood stream infection in infants and children. The use of a positive pressure cap in Cesaro et al., (2009) may have biased the results of this study regarding the outcome of CVC-associated blood stream infection; there is evidence of an association between the use of a positive pressure cap and CVC-associated blood stream infection in other studies (Jacobs et al., 2004, Jarvis et al., 2009, Marschall et al., 2014).

The trials included in the review directly compared the use of normal saline and heparin in long-term central venous catheters in children in community and acute settings, and we were able to undertake two meta-analyses. All studies included participants representative of those usually found in the clinical setting. However, between studies, all used different protocols for the standard and experimental arms with different concentrations of heparin and different frequency of flushes reported. Additionally, within studies, Cesaro et al., (2009) and Smith et al., (1991) changed not only the solution being used, but also the frequency of flushes. Any difference seen could therefore be plausibly attributed to either the solution or the frequency of flushes; changing the frequency of flushes may actually confound the results towards the null hypothesis.

The three included studies employed a pragmatic approach to assess the effectiveness of saline in routine care. While this approach is desirable to inform policy and routine practice, greater emphasis is required to minimise bias and confounding in the study design to ensure generalisibility. As there are concerns with the internal validity of all three studies, the generalisibility (external validity) of results from the studies included in the review is poor.

The overall quality of the evidence was assessed as very low to low using the GRADE assessment tool; there was a high risk of performance and detection bias in all studies as well as a high risk of other bias related to differences in frequency of flushes between heparin and saline groups in Cesaro et al., (2009) and Smith et al., (1991). A high risk of other bias is also assumed for the subset of unpublished paediatric data provided for Goossens et al., (2013). In addition we identified heterogeneity, imprecision and inconsistency of the effect estimates. Consequently, the significance of the results of these meta-analyses should be interpreted with caution. Further research is likely to improve the confidence in the estimate of these effects if undertaken with greater attention to methodology.

The study undertaken by Smith et al., (1991) in particular is subject to high levels of uncertainty regarding its precision. This study was undertaken many years ago and is reported with minimal detail. Following this study, the institution where the study was conducted changed their practice, replacing heparin with normal saline locks. Recent communication with this institution confirmed that the facility continues to routinely use normal saline locks for long term CVCs in children over 12 months of age, providing strong support of the study's findings. Therefore despite the bias evident in this study, it is important to consider the clinical implications of the experience of the efficacy of normal saline locks in long term CVCs over two decades.

Comparison to other evidence

A recent systematic review (Conway et al., 2014) concurred with our findings that there is insufficient evidence to support the use of normal saline to prevent CVC occlusion. This review included studies related to the adult population and also peripherally inserted CVCs. Conway et al., (2014) concluded with recommendations for daily flushing with heparin based on the practices of selected facilities. However, there is insufficient evidence to make this recommendation and this recommendation may lead to higher amounts of heparin being used than is necessary, introducing avoidable costs and risks associated with the use of heparin in this patient group.

There are numerous observational studies that investigate this issue (Fratino et al., 2005). Many of these studies support the use of normal saline for routine flushing of long term CVCs (Abate et al., 2014, J Kelly, 2008) and institutions report the practice of using normal saline in their clinical practice guidelines (Nelson et al., 2008). Despite the literature suggesting that heparin may not be required to maintain patency of CVCs, more RCTs are required to determine the ideal flush solution, concentration, and the frequency of flushes (Baskin et al., 2009). Without strong evidence to support the use normal saline, debate will continue and inconsistencies in practice will prevail. In an area where patients are already vulnerable as a result of their disease state, there should be greater understanding of this relatively simple question and clinical practice should be standardised.

Implications for education practice and research

There is insufficient evidence to determine the effects of intermittent flushing of heparin versus normal saline to prevent occlusion in long-term central venous catheters in infants and children. It remains unclear whether heparin is necessary to prevent occlusion or CVC-associated blood stream infection. Controversy between institutions around the world regarding the appropriate care and maintenance of these devices remains. Given the results of this review, there is a need for healthcare organisations to consider undertaking further research in this area to contribute to the evidence base. Ultimately this would facilitate the development of evidence-based clinical practice guidelines and consistency of practice. Nurses are ideally placed to contribute to this research.

Careful attention to study design is required, including blinding and proper sample size calculations to detect clinically meaningful differences, and ensuring only one aspect of the intervention is changed in the experimental arm (flushing frequency, concentration of heparin or use of normal saline). Cost analysis would be a useful addition to future studies. Consistency of outcome reporting would aid interpretation of results. Such studies would generate evidence and ensure results could be appraised and generalised to address the current gaps in knowledge.

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Figures

Figure 1: Flow chart of search strategy

Figure 2: Forest plot comparison: normal saline versus heparin flush, outcome CVC occlusion rate per 1000 catheter days

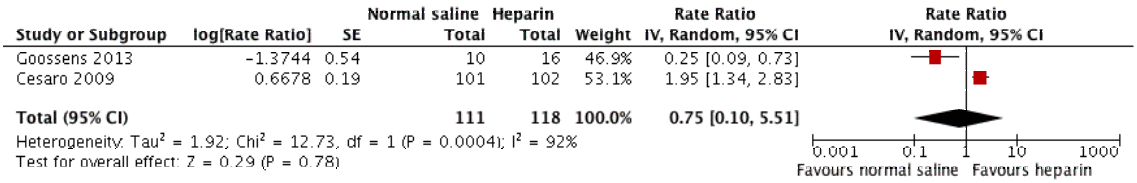
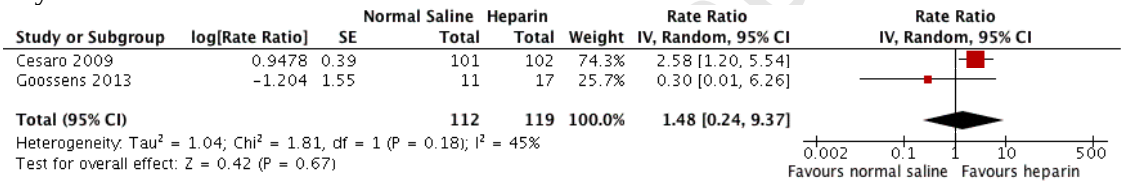


Figure 3: Forest plot comparison: normal saline versus heparin flush, outcome CVC associated blood stream infection rate per 1000 catheter days



CVC – Central Venous Catheter
SE – Standard Error
IV – Inverse Variance
CI- Confidence Interval