City Research Online

City, University of London Institutional Repository

Citation: Lopez-Briz, E., Ruiz Garcia, V., Cabello, J. B., Bort-Marti, S., Carbonell Sanchis, R. & Burls, A. (2014). Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. Cochrane Database of Systematic Reviews, 2014(10), CD008462. doi: 10.1002/14651858.cd008462.pub2

This is the published version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/7384/

Link to published version: https://doi.org/10.1002/14651858.cd008462.pub2

Copyright: City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

Reuse: Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

City Research Online: http://openaccess.city.ac.uk/ publications@city.ac.uk

Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults (Review)

López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R, Burls A

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 10

http://www.thecochranelibrary.com

WILEY

Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults (Review)
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 3
BACKGROUND . . . 6
OBJECTIVES . . . 7
METHODS . . . 7
RESULTS . . . 9
Figure 1. . . . 10
Figure 2. . . . 12
Figure 3. . . . 13
Figure 4. . . . 15
Figure 5. . . . 16
Figure 6. . . . 16
DISCUSSION . . . 18
AUTHORS' CONCLUSIONS . . . 19
ACKNOWLEDGEMENTS . . . 20
REFERENCES . . . 20
CHARACTERISTICS OF STUDIES . . . 38
DATA AND ANALYSES . . . 61
Analysis 1.1. Comparison 1 Occlusion of CVCs, Outcome 1 Occlusion of CVCs (unit of analysis participant). . . . 62
Analysis 1.2. Comparison 1 Occlusion of CVCs, Outcome 2 Occlusion of CVCs (unit of analysis catheter). . . . 62
Analysis 1.3. Comparison 1 Occlusion of CVCs, Outcome 3 Occlusion of CVCs (unit of analysis line access). . . . 63
Analysis 2.1. Comparison 2 Duration of catheter patency, Outcome 1 Duration of catheter patency (unit of analysis participant). . . . 64
Analysis 2.2. Comparison 2 Duration of catheter patency, Outcome 2 Duration of catheter patency (unit of analysis catheter). . . . 65
Analysis 3.1. Comparison 3 Safety, Outcome 1 CVC-related thrombosis. . . . 65
Analysis 3.2. Comparison 3 Safety, Outcome 2 CVC-related sepsis. . . . 66
Analysis 3.3. Comparison 3 Safety, Outcome 3 Mortality. . . . 67
Analysis 3.4. Comparison 3 Safety, Outcome 4 Haemorrhage from any site. . . . 67
Analysis 3.5. Comparison 3 Safety, Outcome 5 Heparin-induced thrombocytopaenia. . . . 68
ADDITIONAL TABLES . . . 68
APPENDICES . . . 69
CONTRIBUTIONS OF AUTHORS . . . 74
DECLARATIONS OF INTEREST . . . 74
SOURCES OF SUPPORT . . . 74
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 75
INDEX TERMS . . . 75

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Eduardo López-Briz[1], Vicente Ruiz Garcia[2], Juan B Cabello[3], Sylvia Bort-Marti[4], Rafael Carbonell Sanchis[5], Amanda Burls[6]

[1]Department of Pharmacy & CASP Spain, Hospital Universitario y Politécnico La Fe, Valencia, Spain. [2]Unidad de Hospitalización a Domicilio Torre C planta 1 Despacho nº 5 & CASP Spain, Hospital Universitari i Politècnic La Fe, Valencia, Spain. [3]Department of Cardiology & CASP Spain, Hospital General Universitario de Alicante, Alicante, Spain. [4]Intellectual Property Department, University of Valencia, Valencia, Spain. [5]Servicio de Otorrinolaringologia, Hospital de Sagunt, Sagunt, Spain. [6]School of Health Sciences, City University London, London, UK

Contact address: Eduardo López-Briz, Department of Pharmacy & CASP Spain, Hospital Universitario y Politécnico La Fe, Bulevar Sur s/n, Valencia, Valencia, 46026, Spain. lopez_edubri@gva.es.

Editorial group: Cochrane Peripheral Vascular Diseases Group.
Publication status and date: New, published in Issue 10, 2014.
Review content assessed as up-to-date: 19 December 2013.

Citation: López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 10. Art. No.: CD008462. DOI: 10.1002/14651858.CD008462.pub2.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Heparin intermittent flushing is a standard practice in the maintenance of patency in central venous catheters. However, we could find no systematic review examining its effectiveness and safety.

Objectives

To assess the effectiveness of intermittent flushing with heparin versus 0.9% sodium chloride (normal saline) solution in adults with central venous catheters in terms of prevention of occlusion and overall benefits versus harms.

Search methods

The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (last searched December 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 11). Searches were also carried out in MEDLINE, EMBASE, CINAHL and clinical trials databases (December 2013).

Selection criteria

Randomised controlled trials (RCTs) in adults 18 years of age and older with a central venous catheter (CVC) in which intermittent flushing with heparin (any dose with or without other drugs) was compared with 0.9% normal saline were included. No restriction on language was applied.

Data collection and analysis

Two review authors independently selected trials, assessed trial quality and extracted data. Trial authors were contacted to retrieve additional information, when necessary.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Main results

Six eligible studies with a total of 1433 participants were included. The heparin concentrations used in these studies were very different (10-5000 IU/mL), and follow-up varied from 20 days to 180 days. The overall risk of bias in the studies was low. The quality of the evidence ranged from very low to moderate for the main outcomes (occlusion of CVC, duration of catheter patency, CVC-related sepsis, mortality and haemorrhage at any site).

Combined findings from three trials in which the unit of analysis was the catheter suggest that heparin was associated with reduced CVC occlusion rates (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.29 to 0.94). However, no clear evidence of a similar effect was found when the results of two studies in which the unit of analysis was the participant were combined (RR 0.21, 95% CI 0.03 to 1.70), nor when findings were derived from one study, which considered total line accesses (RR 1.08, 95% CI 0.84 to 1.40). Furthermore, results for other estimated effects were found to be imprecise and compatible with benefit and harm: catheter duration in days (mean difference (MD) 0.41, 95% CI -1.29 to 2.12), CVC-related thrombosis (RR 1.22, 95% CI 0.74 to 1.99), CVC-related sepsis (RR 1.02, 95% CI 0.34 to 3.03), mortality (RR 0.77, 95% CI 0.45 to 1.32) and haemorrhage at any site (RR 1.37, 95% CI 0.49 to 3.85).

Authors' conclusions

We found no conclusive evidence of important differences when heparin intermittent flushing was compared with 0.9% normal saline flushing for central venous catheter maintenance in terms of efficacy or safety. As heparin is more expensive than normal saline, our findings challenge its continued use in CVC flushing outside the context of clinical trials.

PLAIN LANGUAGE SUMMARY

Heparin versus saline solution flushing for prevention of occlusion in central venous catheters in adults

Central venous catheters (CVCs) are temporary devices implanted into patients when easy or frequent intravenous access is needed. Doctors often use them. A Hickman line is an example of a CVC. A CVC is used, for instance, for monitoring patients in intensive care, or for giving chemotherapy or intravenous nutrition. However, such catheters can cause blood clots, which can block the line, increase the risk of infection and travel elsewhere in the body such as to the lung (this is called thromboembolism). Heparin is a drug that helps to prevent blood clots and may help prevent these unwanted consequences. But heparin can also cause serious adverse effects (bleeding, allergic reactions, fall in platelet count, etc.). Normal saline solution, a sterile solution of salt in water at a concentration suitable for the blood, is typically used for intravenous infusions. We wanted to know whether heparin helps prevent the unwanted effects of blood clots in CVCs, and if this benefit outweighs its risk of harms.

Six studies with a combined total of 1433 participants were included. The quality of the evidence ranged from very low to moderate for the main outcomes.

Our review found no compelling evidence of a decrease in the rate of blocking of CVCs flushed with heparin compared with CVCs flushed with sterile saline solution, nor of differences in the number of days the catheter lasted, the rate of thrombosis, rate of infection, mortality, bleeding rates or heparin-induced fall in platelet count.

We conclude there is no good evidence that heparin flushing of CVCs is better than flushing with sterile saline solution. As heparin is more expensive, the findings of this review do not support its use except in future clinical trials.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Heparin for central venous catheters

Patient or population: patients with central venous catheters
Settings: adults
Intervention: heparin
Comparison: normal saline (0.9% NaCl)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Heparin				
Occlusion of CVC (unit of analysis-participant) Blood withdrawing Follow-up: not reported	**Study population**		**RR 0.21** (0.03-1.7)	150 (2 studies)	⊕◯◯◯ **very low**[a,b,c]	
	53 per 1000	**11 per 1000** (2-89)				
	Moderate					
	49 per 1000	**10 per 1000** (1-83)				
Duration of catheter patency (unit of analysis-participants) Blood withdrawing Follow-up: until 180 days		Mean catheter survival (unit of analysis participants) in the intervention groups was **0.41 higher** (1.29 lower-2.12 higher)		952 (3 studies)	⊕⊕◯◯ **low**[d,e]	
CVC-related sepsis Positive microbiological culture[f] Follow-up: 1-180 days	**Study population**		**RR 1.02** (0.34-3.03)	1097 (2 studies)	⊕⊕⊕◯ **moderate**[f]	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

	11 per 1000	**11 per 1000** (4-33)			
	Moderate				
	16 per 1000	**16 per 1000** (5-48)			
Mortality Follow-up: 180 days	**Study population**		**RR 0.77** (0.45-1.32)	1100 (3 studies)	⊕⊕⊕○ **moderate**[g]
	55 per 1000	**42 per 1000** (25-72)			
	Moderate				
	14 per 1000	**11 per 1000** (6-8)			
Haemorrhage at any site Oozing blood from catheter[h] Follow-up: 1-22 days[i]	**Study population**		**RR 1.37** (0.49-3.85)	1145 (3 studies)	⊕⊕○○ **low**[j,k]
	28 per 1000	**39 per 1000** (14-109)			
	Moderate				
	96 per 1000	**132 per 1000** (47-370)			

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Two trials (Bowers 2008; Kaneko 2004) were rated as unclear risk of bias for insufficient information to permit judgement of allocation concealment (selection bias).
[b] Heparin concentration for flushing was different: 100 IU/mL in Bowers 2008 and 1000 IU/mL in Kaneko 2004.
[c] Confidence intervals in trials were very wide.
[d] The 3 trials (Bowers 2008; Goosens 2013; Kaneko 2004) were rated as unclear risk of bias for insufficient information to permit judgement of allocation concealment (selection bias).
[e] Confidence intervals were very wide.
[f] Only Goosens 2013 stated diagnostic procedures for bloodstream infection.
[g] Follow-up of 1 trial (Pumarola 2007) was very short for assessment of mortality.
[h] In Schallom 2012 bleeding is mentioned, but no data about it were reported.
[i] Reported only in Schallom 2012.
[j] Trial of Kaneko 2004 was rated as unclear risk of bias for random sequence generation and allocation concealment (selection bias).
[k] Wide confidence intervals in both studies.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Vascular access devices (VADs) are commonly used in health care. They encompass a wide range of devices that include, among others, central venous catheters (CVCs). A CVC is a catheter with a tip that lies within the proximal third of the superior vena cava, the right atrium or the inferior vena cava. Catheters can be inserted through a peripheral vein or a proximal central vein, most commonly the internal jugular, subclavian or femoral vein. Four types of CVCs are available: non-tunnelled, tunnelled (e.g. Hickman catheters, tunnelled dialysis catheters) and peripherally inserted catheters and totally implantable ports (port-a-cath) (Smith 2013).

In the United States, more than five million CVCs are inserted every year (Merrer 2001), leading to approximately 15 million central line days per year in intensive care units (ICUs) (Mermel 2000). CVCs allow measurement of haemodynamic variables that cannot be measured accurately by non-invasive methods (although some minimally invasive methods are now available), and they allow delivery of blood, medication and nutritional support that cannot be given safely through peripheral venous catheters. Unfortunately, the use of CVCs is associated with adverse events, among them mechanical complications during insertion (arterial puncture, haematoma and pneumothorax are the most common mechanical complications), infectious complications in 5% to 26% (Merrer 2001; Raad 1997; Veenstra 1999) and thrombosis in 2% to 26% (Lee 2007).

To some extent, thrombi are formed on CVCs during the first few hours in the form of fibrin tail, fibrin sheath, intraluminal occlusion or mural thrombus (Jonker 2010), and thrombosis of large vessels occurs after long-term catheterisation (Valerio 1981). The incidence of CVC-related thrombosis varies depending, among others factors, on the patient's condition, catheter tip position and diameter, side and technique of insertion and the chemical structure and nature of the infusate (Verso 2003). CVC-related thrombosis represents an important source of morbidity and mortality among affected patients, not only for its inherent risks but also because thrombus creates a medium for bacterial proliferation that promotes infection (Mermel 2000). Pulmonary embolism, a severe medical condition, occurs in approximately 15% of patients with CVC-related upper extremity deep venous thrombosis (Burns 2008).

To avoid thrombus formation in CVCs, several measures are currently being applied with different levels of success. Among others, heparin flushing (Bishop 2009), heparin-bonded catheters (Shah 2008), systemic heparinisation with unfractionated heparin or with low molecular weight heparin (Randolph 1998b), anticoagulation with warfarin (Bern 1990) or administration of alteplase (Hemmelgarn 2011) or urokinase (Ray 1999) may be used. Heparin flushing is the most commonly used procedure. According to some authors, the use of heparin may be justified with some types of VADs when they are not used frequently (Bishop 2009); but the efficacy of this practice is unproven (López-Briz 2005).

Description of the intervention

Heparin flushing essentially consists of filling the lumens of CVCs between uses using solutions of unfractionated heparin of varying strength.

How the intervention might work

Use of CVCs predisposes to vascular thrombosis by means of vessel wall injury (during catheter placement), hypercoagulability and alterations in normal blood flow. Balance between haemostatic systems producing thrombi and the fibrinolytic systems dissolving them regulates blood vessel lumen patency, but placement of a CVC can alter this fine-tuned process, leading to a persistent thrombotic state. Catheter composition also plays a role in this thrombotic situation, allowing adsorption of fibrin and fibrinogen on its surface and thereby worsening the problem (Jacobs 2003). The anticoagulant properties of heparin have led clinicians to use heparin flushes in an attempt to prevent thrombus formation and to prolong the duration of catheter patency between uses. This physiopathological rationale, however, may be wrong when applied to peripheral venous catheters, for which no benefit in using heparin flushing versus 0.9% NaCl (normal saline) flushing has been demonstrated, as two published systematic reviews have independently shown (Goode 1991; Randolph 1998a).

Why it is important to do this review

Heparin flushing is a standard practice in the maintenance of CVCs (Bishop 2009), but the effectiveness of this practice has not been established in a systematic review so far. Moreover, variation in nursing practice is considerable because current guidelines provide conflicting recommendations about flushing frequency and heparin concentration and volume (Mitchell 2009). A recent survey conducted in ICUs in the United States (Sona 2012) showed that 64.6% of respondents used normal saline solution and 31% used heparin. The most frequent concentrations of heparin used were 100 IU/mL (37.5%) and 10 IU/mL (29.7%), and the most frequent intervals for flushing were every eight hours and after each use (74.4%). No information is available on CVC maintenance practices in other countries, so could clinical expertise be the guiding principle on this topic?

There are reasons to think that heparin flushing might be helpful. It makes pathophysiological sense. The systematic review by Randolph et al. (Randolph 1998b) looking at the benefits of heparin in central venous and pulmonary artery catheters showed that prophylactic *systemic* heparin decreases catheter-related venous throm-

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

bosis (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.23 to 0.78) and bacterial colonisation of CVCs (RR 0.18, 95% CI 0.06 to 0.60), and may decrease catheter-related bacteraemia (RR 0.26, 95% CI 0.07 to 1.03). Said systematic review included combined data from trials using several doses of systemic prophylactic heparin, including unfractionated heparin (dose regimens of 1 IU/kg, 3 IU/kg, 50 IU q12h and 5000 IU intermittently), low molecular weight heparin (2500 IU given subcutaneously daily) or heparin-bonded catheters. It did not include trials using intermittent flushing of CVCs with heparin.

However, there are also potential harms associated with heparin use. Heparin-induced thrombocytopenia (HIT), a severe immunological drug reaction known to cause arterial and venous thromboembolism without haemorrhage, raises serious concerns regarding the use of heparin (Warkentin 2007). Exposure of surgical patients to unfractionated heparin for longer than four days implies an overall risk of HIT of 2.6% (Martel 2005). This adverse effect of heparin treatment is a typical late-onset complication that can develop five or more days after initiation of the drug.

From an economic point of view, avoiding heparin flushing would represent very important cost savings (Sona 2012). In the above mentioned systematic review by Goode et al (Goode 1991), yearly savings of $109 million to $218 million were estimated when peripheral venous lines were flushed with 0.9% NaCl instead of heparin.

In summary, the effectiveness of heparin flushing of CVCs has not yet been demonstrated, and wide systematic variations in both guideline recommendations and practice have surrounded its use. Moreover, use of heparin is not free of risk and has a considerable economic impact. A systematic review is urgently needed.

OBJECTIVES

To assess the effectiveness of intermittent flushing with heparin versus 0.9% sodium chloride (normal saline) solution in adults with central venous catheters in terms of prevention of occlusion and overall benefits versus harms.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials of heparin flushing versus flushing of normal saline solution in adults. Studies were excluded when alternative methods of randomisation (quasi-randomised), such as alternate days of the week, odd and even numbers, dates of birth, hospital numbers or historical controls, were used.

Types of participants

Adults 18 years of age or older with a CVC.

Studies on infants and children were excluded from this review, as they are the topic of another Cochrane review (Bradford 2014).

Types of interventions

Intermittent flushing with heparin (any dose with or without other drugs) compared with 0.9% normal saline solution. All flushing protocols were acceptable for inclusion.

Types of outcome measures

Primary outcomes

- Occlusion of CVCs (defined as inability to infuse fluids through the catheter due to a blockage).
- Duration (in days) of catheter patency.

Secondary outcomes

- CVC-related thrombosis (determined by colour-coded Doppler ultrasonography, venography, computerised tomography or magnetic resonance venography).
- Episodes of CVC-related sepsis and CVC-related colonisation. CVC-related sepsis is defined as the presence of symptoms and signs suggestive of sepsis, accompanied by positive blood cultures obtained from a normally sterile site different from the CVC and from the CVC or CVC tip, each growing the same micro-organism; CVC-related colonisation is defined as the presence of micro-organisms in the CVC only and not from another sterile site.
- Number of additional CVC insertions.
- Mortality.
- Abnormality of coagulation profile.
- Allergic reactions to heparin.
- Heparin-induced thrombocytopaenia (HIT) (development of thrombocytopaenia after heparin flushing of a CVC in an adult with a previously normal platelet count after exclusion of all other causes of thrombocytopaenia, along with a positive antibody test).
- Haemorrhage from any site in the body.

Search methods for identification of studies

No restriction on language of publication was applied.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Electronic searches

The Cochrane Peripheral Vascular Diseases (PVD) Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched December 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 11) (www.thecochranelibrary.com). See Appendix 1 for details of the search strategy used to search CENTRAL. The Specialised Register is maintained by the TSC and is constructed through weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and by handsearching of relevant journals. The full list of databases, journals and conference proceedings that have been searched and the search strategies used are presented in the Specialised Register section of the Cochrane PVD Group module within *The Cochrane Library* (www.thecochranelibrary.com).

The following trial databases were searched by the TSC (December 2013) for details of ongoing and unpublished studies, using the terms 'heparin' and 'catheter.'

- 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/).

In addition MEDLINE, EMBASE and CINAHL were searched using the strategies shown in Appendix 2, Appendix 3 and Appendix 4.

Searching other resources

The reference lists of relevant studies identified through the electronic searches were searched. Authors of unpublished and ongoing trials were contacted to obtain additional data (Goosens 2013; Schallom 2012).

Data collection and analysis

Selection of studies

Two review authors independently read the abstracts and, if necessary, the full text of potentially relevant references, to identify studies that needed to be further examined. Letters, editorials, commentaries, reviews and lectures that did not contain original research data were excluded. When differences in opinion arose, a third review author was consulted.

Data extraction and management

For studies fulfilling inclusion criteria, three review authors independently extracted data regarding population, interventions and relevant outcomes, using the standard Cochrane PVD Group forms for dichotomous data and for continuous data.

Assessment of risk of bias in included studies

Risk of bias in included studies was assessed by using standardised criteria from The Cochrane Collaboration (Higgins 2011) on the following.

- Adequacy of random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective reporting.
- Other bias.

Measures of treatment effect

Odds ratio (OR), risk ratio (RR) with 95% confidence interval (CI) and number needed to treat for an additional beneficial outcome (NNTB) were used to analyse dichotomous variables (i.e. occlusion of CVCs, mortality, adverse events, etc.). NNTB values have been calculated from the RR according to the formula NNTB (or number needed to treat for an additional harmful outcome (NNTH)) = 1/ACR*(1-RR), where ACR is the assumed control risk (McQuay 1997).

Unit of analysis issues

Initially, when the present systematic review was planned, because of clinical considerations, the unit of analysis was assumed to be the participant. Once the literature search was performed, three studies were found wherein the unit of analysis was the catheter, and in only two studies the unit of analysis was the participant; in one study the unit of analysis was line access (each time that a line is used to provide drugs, blood, etc.). In view of this, all studies were included and analysed separately for each different unit of analysis.

Dealing with missing data

The principal investigators of two studies (Goosens 2013; Schallom 2012) were contacted to obtain additional data. They provided relevant data that were later published.

Assessment of heterogeneity

We attempted to explain relevant clinical, methodological or statistical heterogeneity using forest plots, and we quantified heterogeneity using the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We planned to assess reporting bias by using funnel plots if sufficient numbers of studies were identified.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Data synthesis

Data were statistically summarised if available. Statistical analysis was performed according to the statistical guidelines referenced in the current version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used Review Manager 5 for review production and data analysis. We used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

The incidence of CVC-related thrombosis varies depending on the clinical type of the participant (onco-haematological, critical, on dialysis, etc.), CVC implantation site, CVC type and infusate-related factors. Subgroup analyses were planned to take these factors into account, if available.

Sensitivity analysis

Sensitivity analyses were carried out to explore the influence of the following factors on effect size.

- Published or unpublished studies.
- Quality of studies.
- Weight of different studies.

Robustness of results was assessed using different measures of effect size (OR and RR).

RESULTS

Description of studies

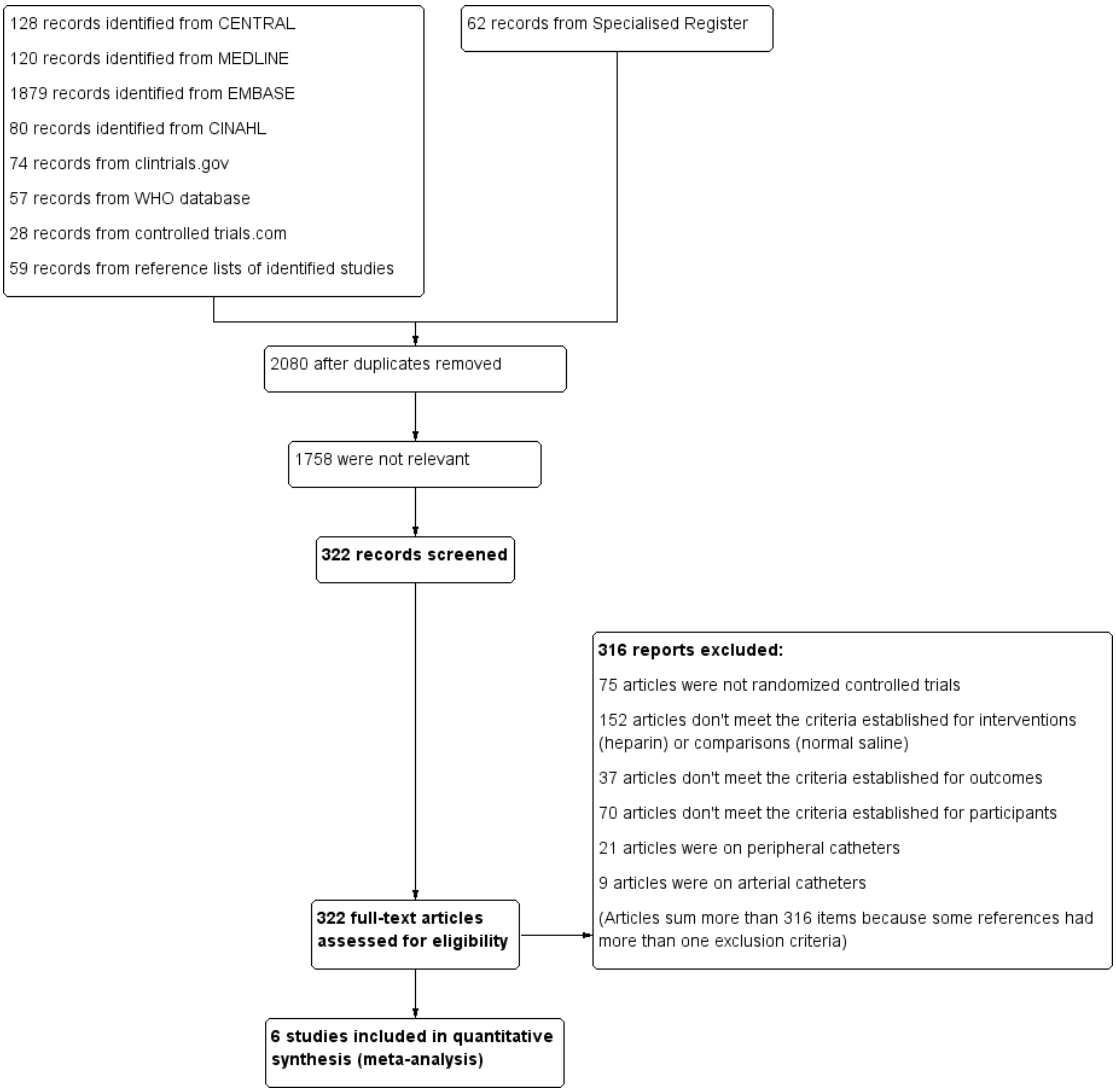
Only randomised controlled trials of heparin flushing versus flushing with 0.9% NaCl (normal saline) sterile solution in adults were included.

Results of the search

See Figure 1.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. Study flow diagram.



Included studies

Six studies met the predefined inclusion criteria (Bowers 2008; Goosens 2013; Kaneko 2004; Pumarola 2007; Rabe 2002; Schallom 2012). These studies included a combined total of 1433 participants. See Characteristics of included studies.

Bowers 2008 conducted a single-centre randomised study in 102 adult participants with single-lumen peripherally inserted central catheters (PICCs) with luer-activated devices. Participants were randomly assigned by means of a random block design with allocation concealment to receive 0.9% NaCl sterile solution (NS) or heparin lock flush (100 USP U/mL). All participants completed the study (50 in the NS group and 52 in the heparin group). The main outcome studied was occlusion rate, and the secondary outcome was duration of PICCs (in days).

Goosens 2013 conducted a randomised controlled open-label non-inferiority trial in 802 participants older than one year, scheduled for a first totally implantable venous access device (TIVAD) insertion through the superior vena cava (SVC) system, with an onco-haematological malignancy and with sufficient life expectancy to complete the planned follow-up of 180 days at the study centre. After randomisation by means of computerised random number generation, 398 were assigned to receive an NS lock and 404 were assigned to receive a heparin lock in a non-blinded

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

manner. Although participants were randomly assigned, the unit of analysis was the number of catheters accessed. Outcomes considered were withdrawal of obstruction, catheter-related bacteraemia and catheter duration within 180 days, as well as adverse events. Data on sepsis, thrombosis and mortality were also provided.

Kaneko 2004 performed a single-centre, open-label, randomised controlled clinical trial in adult participants with an inserted double-lumen CVC. This study compared a flush of 20 mL NS versus a flush of 20 mL NS followed by locking with 2 mL heparin (1000 IU/mL). Low molecular weight heparin was used during each haemodialysis session at 8 IU/kg/h. Forty-eight participants were randomly allocated to the NS (26) or heparin group (22). Outcomes studied were days of catheter survival and thrombotic occlusion, as well as coagulation analytical parameters such as activated coagulation time, activated partial thromboplastin time and prothrombin time.

Pumarola 2007 carried out a two-phase clinical trial in a polyvalent ICU. Participants were adults with multiple pathological processes in whom a three-lumen CVC had been inserted. Randomisation was provided by means of a registered software (Aleator®). However, the study was not blinded. In a first phase, two concentrations of heparin (100 IU/5 mL and 500 IU/5 mL) were compared, establishing patency at 24 hours after catheter implantation and at discharge. In a second phase, heparin at a concentration of 100 IU/mL was compared with NS, and patency was assessed at 24 hours, at 72 hours and at discharge. Only this second phase fulfilled our inclusion criteria. Ninety-five CVCs were assessed in this phase-38 in the heparin group and 57 in the NS group-for occlusion rates and mean days of catheter duration.

Rabe 2002 studied 99 three-lumen CVCs inserted in 91 adult participants locked with one of the following solutions: NS, heparin (5000 IU/mL) or vitamin C (200 mg/mL). Catheters were assigned randomly (by means of a list of random numbers prepared by the study authors) to one of three groups. Patency was assessed every two days to a maximum of 20 days. Study outcomes included thrombotic obstruction and catheter survival.

Schallom 2012 conducted a single-centre study wherein patients in the ICU with a newly placed three- or four-lumen CVC were randomly assigned (simple randomisation, sequence concealed) to be flushed with NS or with heparin (10 IU/mL every 8 hours). Among the randomly assigned participants, 295 had at least one lumen with a minimum of two flushes, resulting in 326 catheters (170 pertaining to the NS group and 156 to the heparin group) with 709 lumens-395 in the NS group and 314 in the heparin group. The primary outcome was lack of lumen patency. Secondary outcomes included rates of loss of blood return, flush failure, heparin-induced thrombocytopaenia and catheter-related bloodstream infection.

Excluded studies

A total of 316 studies did not fulfil inclusion criteria and were excluded. Reasons for exclusion can be found in the Characteristics of excluded studies section.

Among 2080 studies identified after duplicates and ongoing clinical trials were removed, 1757 were found not relevant. A total of 316 full-text articles were excluded for the following reasons.

- 75 studies were not randomised controlled trials.
- 152 studies did not meet the criteria established for intervention (heparin) or comparison (0.9% NaCl sterile solution).
- 37 studies did not meet the criteria established for outcomes reported.
- 70 studies did not meet the criteria established for participants.
- 21 studies focused on peripheral catheters.
- 9 studies focused on arterial catheters.

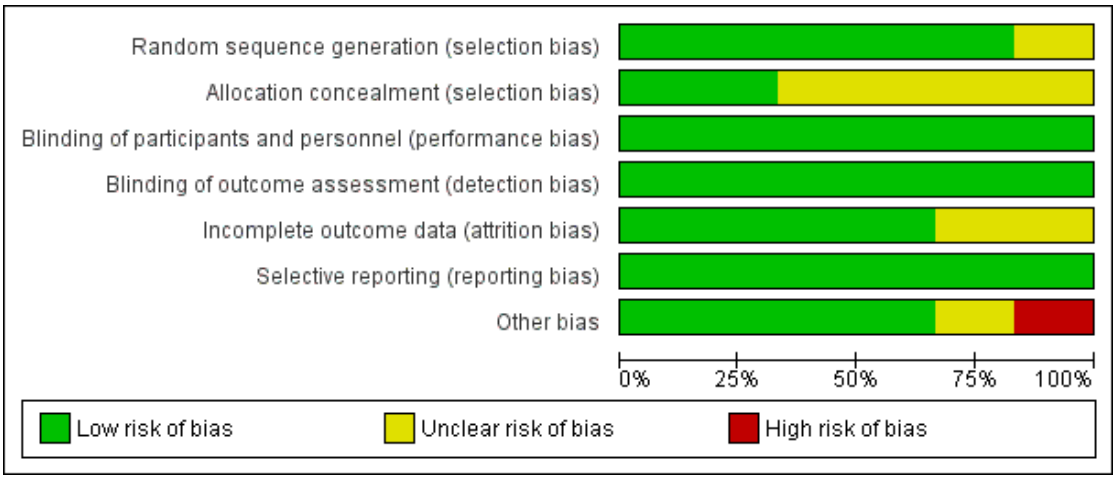
Some articles were excluded for more than one reason.

Risk of bias in included studies

Figure 2 and Figure 3 show risk of bias according to the quality of included trials.

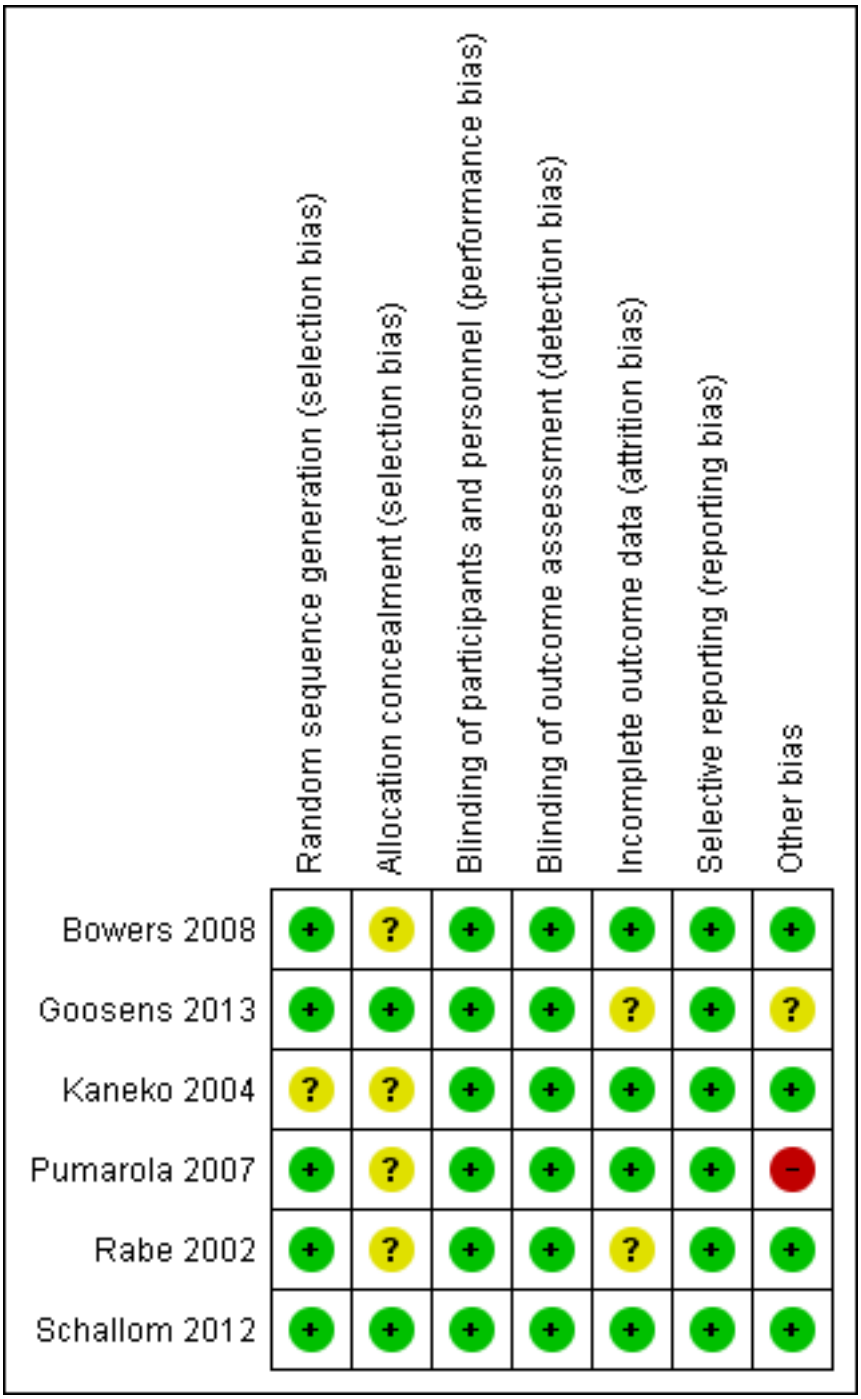
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

We did not create funnel plots for assessment of publication bias for primary outcomes because of the low number of included studies.

Summarising risk of bias for the outcomes: occlusion of CVCs, CVC-related thrombosis, CVC-related sepsis, mortality and haemorrhage across domains

Occlusion of CVCs

Unit of analysis: participant

Two trials (Bowers 2008; Kaneko 2004) assessed this outcome. Bowers 2008 was judged to be of low risk of bias for random sequence generation, but Kaneko 2004 was rated as unclear risk of bias for random sequence generation. Both were rated as unclear risk of bias for allocation concealment. Both studies were rated as low risk of bias in the domain of blinding and appear to be free of other bias. We believe that the risk of bias for this outcome is low.

Unit of analysis: catheter

The three trials that assessed this outcome (Pumarola 2007; Rabe 2002; Schallom 2012) were rated as low risk of bias for random sequence generation, but two studies (Pumarola 2007; Rabe 2002) were rated as unclear risk of bias for allocation concealment. All three studies were rated as low risk of bias in the domain of blinding and appear free of other bias. Despite the fact that Pumarola 2007 was stopped early, we judge that the risk of bias for this outcome is low.

Unit of analysis: line access

One trial (Goosens 2013) assessed this outcome. Goosens 2013 was judged to be at low risk of bias for all domains except attrition bias and other bias, as the study insufficiently reported exclusions. However, we believe this does not affect this outcome; therefore we judge that risk of bias for this outcome is low.

CVC-related thrombosis

The two trials assessing this outcome (Goosens 2013; Schallom 2012) were rated as low risk for random sequence generation, allocation concealment and blinding. Therefore, we judge the risk of bias for this outcome to be low.

CVC-related sepsis

The two trials assessing this outcome (Goosens 2013; Schallom 2012) were rated as low risk for random sequence generation, allocation concealment and blinding. Therefore, we judge the risk of bias for this outcome to be low.

Mortality

The three trials that assessed this outcome (Goosens 2013; Kaneko 2004; Pumarola 2007) were rated as having different risks of bias for the main domains. Goosens 2013 was at low risk of bias for all main domains, Pumarola 2007 was judged to be at unclear risk of bias for allocation concealment and Kaneko 2004 was judged to be at unclear risk of bias for random sequence generation and allocation concealment. However Kaneko 2004 reported no deaths; therefore we believe that the risk of bias for this outcome is low.

Haemorrhage across domains

Three trials (Goosens 2013; Kaneko 2004; Schallom 2012) assessed this outcome. Only Kaneko 2004 was rated as unclear risk of bias for the domains of random sequence generation and allocation concealment. Goosens 2013 and Schallom 2012 were rated as low risk of bias for the domains of random sequence generation, allocation concealment and blinding. Therefore we judge the risk of bias for this outcome to be low.

Allocation

All studies (Bowers 2008; Goosens 2013; Pumarola 2007; Rabe 2002; Schallom 2012) specified the procedure of random sequence generation, except for one (Kaneko 2004). Bowers 2008 used a permuted block sequence, whereas Goosens 2013, Rabe 2002 and Schallom 2012 used a list of random numbers, leading to a simple randomisation procedure. Pumarola 2007 randomly assigned participants by using a registered software (Aleator®).

Allocation concealment was not reported in three studies (Bowers 2008; Kaneko 2004; Rabe 2002), rendering the risk of selection bias unclear. Three studies specified allocation concealment: Pumarola 2007 used a method of closed envelopes, but it remains unclear whether the envelopes were opaque or sealed to conceal information; Goosens 2013 concealed the allocation sequence from researchers who enrolled participants by using sequentially numbered participant cards stored in a separate room; Schallom 2012 stated that the allocation sequence was concealed from the researcher enrolling participants.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Blinding

Although none of the included studies was blinded, neither occlusion nor time to occlusion was likely to be influenced by lack of blinding. Some secondary outcomes of the present systematic review may be influenced by lack of blinding, namely, CVC-related thrombosis, episodes of CVC-related sepsis and colonisation, but the secondary outcomes of number of additional CVC insertions, mortality, coagulation profile, HIT, allergic reactions to heparin and haemorrhage were not so influenced.

Incomplete outcome data

All (Bowers 2008; Kaneko 2004; Pumarola 2007; Schallom 2012) but two (Goosens 2013; Rabe 2002) included studies were considered to have low risk of attrition bias because missing outcome data were balanced in numbers across intervention groups, with similar reasons for missing data across groups. In the Rabe 2002 and Goosens 2013 studies, reporting of attrition or exclusions was insufficient to permit judgement, and information about the number of catheters losing patency in each treatment group was lacking in Rabe 2002. For this reason, a criterion of unclear risk of bias was assigned to Goosens 2013 and Rabe 2002.

Selective reporting

All studies that were considered were classified as having low risk of reporting bias. Although the study protocols were not available, it was clear that published reports included all expected outcomes, including those that were prespecified.

Other potential sources of bias

The study conducted by Pumarola 2007 may be underpowered. Only 38 and 57 catheters per group were analysed, but predetermined sample size was 185 catheters per group; the study was stopped early for 74 and 52 catheters in the heparin and NS groups, respectively. Risk of other bias was therefore high. In Goosens 2013, 3.5% of participants were children, but no separate analyses of children and adults were conducted; therefore the risk of other bias was unclear. The remaining studies were at low risk of other bias.

Effects of interventions

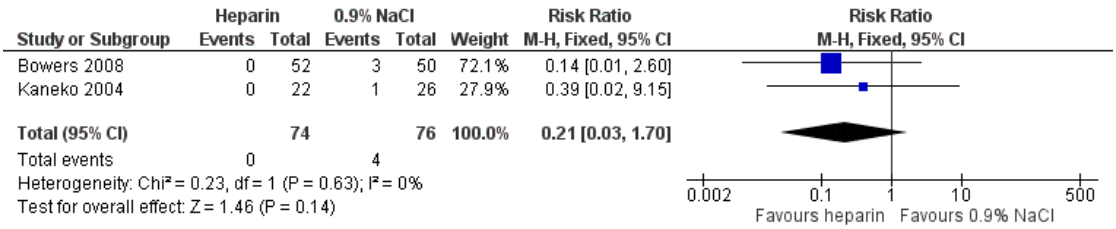
See: **Summary of findings for the main comparison** Heparin for central venous catheters

Primary outcomes

Occlusion of CVCs

- Two studies were focused on *participant as unit of analysis* (Bowers 2008; Kaneko 2004), including 76 participants. Findings are pooled in Figure 4. Analysis performed using a Mantel-Haenszel (M-H) fixed-effect model yielded an RR of 0.21 (95% CI 0.03 to 1.70) (i.e. a non-significant effect), with heterogeneity of $I^2 = 0$.

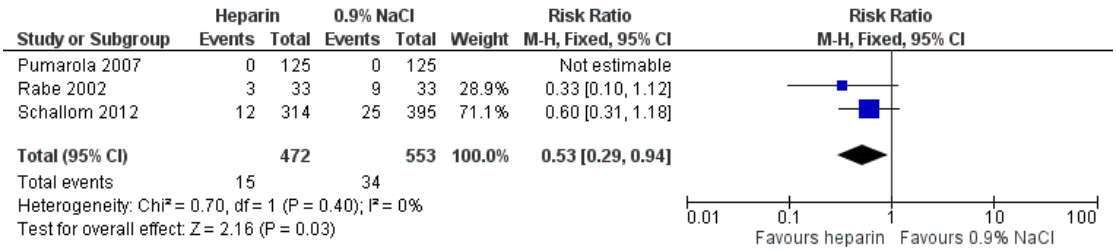
Figure 4. Forest plot of comparison: 1 Occlusion of CVCs, outcome: 1.1 Occlusion of CVCs (unit of analysis participant).



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

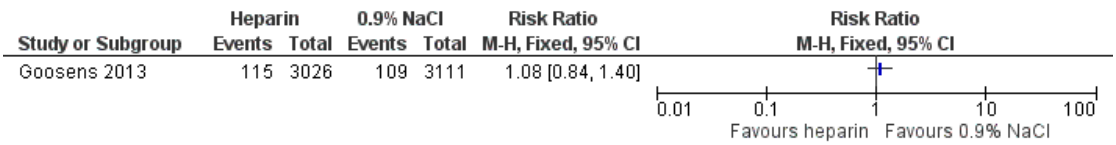
- Three studies were focused on *catheter as unit of analysis* (Pumarola 2007; Rabe 2002; Schallom 2012), totaling 1025 observations. Findings are pooled in Figure 5, demonstrating a favourable effect of heparin when results were analysed by means of an M-H fixed-effect model (RR 0.53, 95% CI 0.29 to 0.94, P value 0.03). No heterogeneity among studies was noted (I^2 = 0%), speaking well for statistical comparability of studies. The NNTB calculated according to the McQuay method (McQuay 1997) was 35 (95% CI 23 to 273).

Figure 5. Forest plot of comparison: 1 Occlusion of CVCs, outcome: 1.2 Occlusion of CVCs (unit of analysis catheter).



- Only one study was focused on *line access as unit of analysis* (Goosens 2013). This study included 6137 observations and showed no differences between heparin and NS (RR 1.08, 95% CI 0.84 to 1.40) (Figure 6).

Figure 6. Forest plot of comparison: 1 Occlusion of CVCs, outcome: 1.3 Occlusion of CVCs (unit of analysis line access).



Duration (in days) of catheter patency

- Three studies (Bowers 2008; Goosens 2013; Kaneko 2004) in whom *unit of analysis* was *the participant* were analysed and pooled for catheter patency duration. Mean difference analysis revealed no significant differences between heparin and NS (MD 0.41, 95% CI -1.29 to 2.12). Heterogeneity was found to be very low (I^2 = 0%).
- Two studies (Pumarola 2007; Schallom 2012) analysed

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

catheter patency using *catheter as unit of analysis*. The mean difference plot shows no statistical differences between heparin and NS groups (MD 0.40, 95% CI -0.20 to 0.99). Heterogeneity was found to be very low (I^2 = 0%).

Secondary outcomes

See additional Table 1.

CVC-related thrombosis

Only Schallom 2012 and Goosens 2013 reported incidences of CVC-related thrombosis. Schallom 2012 found 10.7% venous thromboembolisms in the NS group (16 participants) and 13.1% (19 participants) in the heparin group (X^2 = 0.419, P value 0.518), showing no statistical differences between groups. Goosens 2013 found retrospectively a confirmed diagnosis of central venous thrombosis in 13 participants (3.3%) in the heparin group and in 11 participants (2.8%) in the NS group (X^2 = 0.060, P value 0.807). Pooled results showed non-significant differences between heparin and NS groups through an M-H fixed-effect model (RR 1.22; 95% CI 0.74 to 1.99; Analysis 3.1). Low heterogeneity was noted among studies (I^2 = 0%).

Episodes of CVC-related sepsis and CVC-related colonisation

Two studies were focused on sepsis (Goosens 2013; Schallom 2012) and showed a non-significant effect by using an M-H fixed-effect model (RR 1.02, 95% CI 0.34 to 3.03; Analysis 3.2). Heterogeneity among studies was high (I^2 = 75%).
In Schallom 2012, four participants in the saline group experienced episodes of CVC-related sepsis or colonisation compared with none in the heparin group. All four participants were given non-antibiotic-impregnated catheters. This difference was not statistically significant (X^2 = 2.180, P value 0.140, Yates correction applied). In Goosens 2013, catheter-related bacteraemia was found in two out of 404 cases (0.5%) in the NS group and in six out of 398 cases (1.5%) in the heparin group (P value 0.18).

Number of additional CVC insertions

No data were provided.

Mortality

Three studies were focused on mortality (Goosens 2013; Kaneko 2004; Pumarola 2007), showing a non-significant effect by using an M-H fixed-effect model (RR 0.77, 95% CI 0.45 to 1.32; Analysis 3.3). Heterogeneity among studies was low (I^2 = 0%). No deaths were reported in the study of Kaneko 2004, three were reported in Pumarola 2007 (two in the heparin group and one in the NS group, without significant differences) and 48 in Goosens 2013 (28 in the NS group and 20 in the heparin group; P value 0.255). No other included studies reported mortality.

Abnormality of coagulation profile

Only Kaneko 2004 reported alterations in coagulation parameters. These investigators studied activated coagulation time (ACT), activated partial thromboplastin time (APTT) and prothrombin time (PT). Kaneko 2004 found differences between the two groups for both ACT (P value < 0.001) and APTT (P value 0.001). In particular, said parameters, except PT (P value 0.187), were higher in the heparin group. Differences observed in the PT parameter, which was elevated in the heparin group, did not reach statistical significance.

Allergic reactions to heparin

No data were provided.

Heparin-induced thrombocytopaenia

Only Kaneko 2004 and Schallom 2012 reported HIT, but whereas Kaneko 2004 found no cases of HIT, Schallom 2012 detected two cases, both in the NS group (Analysis 3.5; RR 0.21, CI 95% 0.01 to 4.27). These latter cases may be due, in our opinion, to systemic anticoagulation with heparin.

Haemorrhage from any site in the body

Goosens 2013, Kaneko 2004 and Schallom 2012 studied bleeding likely associated with heparin, using an M-H fixed-effect model (RR 1.37, 95% CI 0.49 to 3.85; Analysis 3.4). Heterogeneity among studies was low (I^2 = 0%). Goosens 2013 reported no haemorrhages in any group. Kaneko 2004 reported oozing from the exit site of the dialysis catheter in five participants in the heparin group and in five in the NS group with no statistically significant differences (X^2 = 0.088, P value 0.799). In Schallom 2012, one participant presented with bleeding in the heparin group versus none in the NS group (X^2 = 0, P value 0.984, Yates correction).

Subgroup analysis

We planned to do subgroup analyses but were unable to do so because of lack of data.

Sensitivity analysis

We planned to carry out sensitivity analyses for published versus unpublished studies, quality of studies and weight of studies, as well as for OR versus RR.
The only study initially identified as an unpublished study was Goosens 2013, but this study was later published, and no other unpublished studies were identified.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The quality of the included studies was found to be very similar, and sensitivity analyses were deemed not relevant.

All outcomes (both primary and secondary) were explored to analyse the effect of each particular study on the aggregated results. Not one outcome (occlusion of CVCs with unit of analysis the participant, occlusion of CVCs with unit of analysis line access, duration of catheter patency, CVC-related thrombosis, CVC-related sepsis, mortality, haemorrhage from any site, HIT) was sensitive to removal of any of the included studies, except for occlusion of CVCs when the unit of analysis was the catheter. In this case, when the trial with the greatest weight (Schallom 2012) was removed, the RR changed substantially (RR 0.33, 95% CI 0.10 to 1.12), making the difference between heparin and normal saline no longer significant.

Differences between OR and RR were explored and calculated, but these were found to be not significant.

DISCUSSION

Summary of main results

The aim of the present review was to assess the effectiveness of intermittent flushing with heparin versus 0.9% sodium chloride (normal saline) solution in adults with central venous catheters in terms of prevention of occlusion and overall benefits versus harms. Central venous catheters are frequently used in patients to provide blood derivatives, medication or nutritional support, as well as for diagnostic monitoring, cardiac pacing or other procedures. However, their use could result in thrombosis and infection and may prolong hospital stay.

We found no conclusive evidence of important differences when intermittent flushing with heparin versus 0.9% normal saline for central venous catheter maintenance was compared, in terms of efficacy or safety. The quality of the evidence was very low to moderate. As heparin is more expensive than normal saline, our findings challenge its continued use in CVC flushing outside the context of clinical trials.

Overall completeness and applicability of evidence

All of the addressed outcomes have been analysed. Statistical heterogeneity was low (I^2 = 0) for the main outcomes of efficacy (obstruction, patency) and safety (bleeding, thrombosis and mortality), despite inclusion of participants with very different conditions (critical, with onco-haematological malignancies or under haemodialysis), who were treated with a very wide range of heparin concentrations ranging from 30 IU/mL to 2500 IU/mL. Only sepsis showed significant statistical heterogeneity (I^2 = 75%), which could be explained by the different clinical conditions of included participants.

None of the studies showed statistically significant differences in any of the focused outcomes. It must be noted, in this respect, that CVC occlusion showed a statistically significant difference when the unit of analysis was the catheter; notwithstanding this observation, the fact that no differences were observed when the unit of analysis was the participant or lines accessed, together with lack of effect in survival catheter time when the unit of analysis was the catheter or the participant, suggests that no real differences were noted between groups. Our results disagree with those of a retrospective cohort study by Jonker 2010, which detected increased use of alteplase to clean catheters flushed with NS compared with catheters locked with heparin. However these results may be biased by the indirectness of outcomes.

It is interesting to consider also the use of systemic anticoagulants in the different studies. In Pumarola 2007 and Goosens 2013, the use of any anticoagulation was a criterion of exclusion; although no data were stated in Bowers 2008. Kaneko 2004, Rabe 2002 and Schallom 2012 on permitted use of systemic anticoagulation in every participant (Kaneko 2004) or in only some participants (Rabe 2002, Schallom 2012), differences were found to be not significant.

The length of follow-up for safety in this review could be too short to reveal relevant adverse events. Only Goosens 2013 provided long-term follow-up (180 days), whereas Pumarola 2007, Rabe 2002 and Schallom 2012 studied participants only for a short time, and Bowers 2008 and Kaneko 2004 studied participants for a period ranging from 40 to 50 days. Consequently, the potential for higher incidence with long-term follow-up cannot be discarded. Given that CVCs could be placed for several months according to the needs of patients, adverse events may be more relevant than those described in the present systematic review. None of the six included trials was planned to study adverse events. Moreover, two arms in all trials were too few. In summary, it cannot be ruled out that adverse events may occur with longer exposure or higher numbers of participants.

Despite results suggesting no differences, it is probable that a high proportion of patients could be at increased risk with heparin use. This increased risk of adverse events due to heparin flushing may be especially relevant among patients with liver or kidney failure and those with recent surgery (especially of the brain, eye or spine), spinal anaesthesia or recent injury. Also patients who have a history of heart problems, high blood pressure, menstrual problems, bleeding problems, a history of ulcers or other stomach problems, or who are taking drugs such as non-steroidal anti-inflammatory drugs or antiplatelet agents, may have increased risk of bleeding. Adverse events may be reduced by flushes with NS.

Heparin-induced thrombocytopaenia (HIT) is an adverse event that may be life threatening. It is more common after intraoperative or perioperative administration of heparin. Its incidence is reported at between 0.1% and 5%. Risk factors for HIT include

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

type of heparin (greater risk with unfractionated heparin), duration of exposure, patient setting and patient gender (1.5 to 2 times higher in women) (Battistelli 2010). In general, higher doses of heparin result in greater risk of HIT. However, lower heparin doses used to flush catheters have occasionally been associated with HIT (McNulty 2005). In the present systematic review, HIT was not reported in the heparin groups, and only two cases were reported in the NS groups (Schallom 2012), suggesting an altogether undiagnosed adverse event. Nevertheless, routine use of NS instead of heparin may reduce HIT.

Quality of the evidence

The main results are described in Summary of findings for the main comparison. The quality of the evidence ranged from very low to high.

The quality of the evidence for the main outcome (occlusion of CVC) ranged from very low to low to high, according to the unit of analysis. Differences were found only when the unit of analysis was the catheter. It must be noted that results were sensitive to removal of the trial with the greatest weight (Schallom 2012) (RR 0.33, 95% CI 0.10 to 1.12), so they must be interpreted with caution. When the study with the lowest quality was not taken into account (Pumarola 2007), the results remained unchanged because this trial reported no events in both arms.

Duration of catheter patency was the second main outcome, and its quality of evidence was rated as low when the unit of analysis was the catheter or the participant. This outcome did not show statistical differences in terms of means of days for patency. Results did not change when the largest trials in both analyses were taken into account (with unit of analysis being the catheter and unit of analysis being the participant) (Goosens 2013; Schallom 2012) (MD 0.32, 95% CI -2.37 to 3.01, and MD 0.62, 95% CI -1.17 to 2.42, respectively).

Potential biases in the review process

Study selection and data extraction were carried out in duplicate manner. A protocol was published for this systematic review (López-Briz 2010). All outcomes analysed were selected a priori. The unit of analysis initially selected was the participant. The other units of analysis used-catheter and lines accessed-were added a posteriori. Trial authors were contacted, and additional information was retrieved, hence the probability of publication bias of this systematic review is low. Although we could not absolutely discard bias from non-published studies, contact with authors of the latest published studies and continued search of clinical trials registers led us to believe that risk of publication bias was low.

Agreements and disagreements with other studies or reviews

Other systematic reviews have focused on heparin use in CVCs using different inclusion and/or exclusion criteria from those of this review. Randolph 1998b reviewed randomised controlled trials in adult and paediatric study participants in whom heparin was infused continuously through the catheter, administered subcutaneously (SC) or bonded to the catheter. They found only a trend toward reduction of catheter thrombus and a significant reduction (57%) in venous thrombosis. Statistical heterogeneity was not significant in both cases. Heparin dosage ranged from SC 5000 IU every 12 hours to 1 IU/mL in continuous perfusion added to total parenteral nutrition.

Klerk 2003 also reviewed adult and paediatric study participants with CVCs in whom heparin flushes or antithrombotic agents were administered in prophylactic or therapeutic doses. This study concluded that the addition of heparin to parenteral nutrition did not significantly decrease the risk of catheter-related thrombosis. However this review cannot be compared with the present one because it differs in the design of included studies (randomised controlled trials and prospective cohort studies) and in the intervention provided (systemic heparin).

In a previous systematic review (López-Briz 2005) by some of the authors of this Cochrane review, only two studies were included, one of which was conducted in paediatric participants. Results showed no differences between heparin and NS flush.

Mitchell 2009 conducted a systematic review focused on adult study participants with CVCs or PICCs comparing heparin flushing, heparin continuous perfusion, NS flushing, urokinase flushing and heparin-bonded catheter versus any other intervention. As a result of heterogeneity of interventions and comparisons, results of the review are difficult to understand.

In paediatric participants, Shah 2008 found that continuous heparin infusion reduced the risk of catheter occlusion with no statistically significant differences in the duration of catheter patency. However, recommendations for heparin use in neonates with PICCs could not be made. The review authors detected high clinical heterogeneity and high heterogeneity in treatment effect. Guidelines have led to a wide variety of flushing protocols, with many different types of flushing solution, volumes, flushing frequencies and heparin concentrations (Mitchell 2009; Sona 2012). This is due to the fact that they are based mainly on manufacturers' recommendations-not on published evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, heparin flushing of CVCs is a recommended practice in many guidelines and is standard practice in many clinical care

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

settings, notwithstanding the fact that it is not supported by any strong evidence. The present systematic review confirms that no conclusive evidence shows important differences when heparin intermittent flushing was compared with 0.9% normal saline flushing in central venous catheter maintenance, in terms of efficacy or safety. As heparin is more expensive than normal saline, our findings challenge its continued use in CVC flushing outside the context of clinical trials.

Implications for research

Better designed, large-scale randomised controlled trials are needed to definitively establish or rule out a net benefit of flushing with heparin versus 0.9% NaCl (normal saline). More trials may be needed to address whether this practice could be effective in selected patients, such as patients under haemodialysis or those with onco-haematological malignancies. Different units of analysis (catheters, accesses) could have diminished the impact of findings of the two large trials (Goosens 2013; Schallom 2012), making them not directly comparable. On the other hand, whether this practice causes harm requires trials or observational studies specifically designed for safety with sufficient duration of follow-up.

ACKNOWLEDGEMENTS

The need for the present systematic review was first pointed out by the Evidence Based Medicine Committee at "Hospital Universitario y Politécnico La Fe" (Valencia, Spain), to whom we are indebted. We would also like to thank Lynn Schallom and Godeliebe A. Goosens for providing us with raw data from their clinical trial before publication. We thank the Cochrane Peripheral Vascular Diseases Review Group, namely, Dr Karen Welch, for the literature search, for ongoing support and for constructive comments. We would like to thank Warren Anthony Stevens for checking English spelling.

REFERENCES

References to studies included in this review

Bowers 2008 *{published data only}*
Bowers L, Speroni KG, Jones L, Atherton M. Comparison of occlusion rates by flushing solutions for peripherally inserted central catheters with positive pressure Luer-activated devices. *Journal of Infusion Nursing* 2008;**31**(1): 22–7.

Goosens 2013 *{published and unpublished data}*
Goossens GA, Jérôme M, Janssens C, Peetermans WE, Fieuws S, Moons P, et al.Comparing normal saline versus diluted heparin to lock non-valved totally implantable venous access devices in cancer patients: a randomised, non-inferiority, open trial. *Annals of Oncology* 2013;**24**(7): 1892–9.

Kaneko 2004 *{published data only}*
Kaneko Y, Iwano M, Yoshida H, Kosuge M, Ito S, Narita I, et al.Natural saline-flush is sufficient to maintain patency of immobilized-urokinase double-lumen catheter used to provide temporary blood access for hemodialysis. *Blood Purification* 2004;**22**(5):473–9.

Pumarola 2007 *{published data only}*
Pumarola CF, Mercader RC, Plana MC, Bueno CC, Casellas SS, Vidal MF, et al.[Comparative study of maintenance of patency of triple lumen central venous catheter] [Estudio comparativo del mantenimiento de la permeabilidad de los cateteres venosos centrales de tres luces]. *Enfermeria Intensiva* 2007;**18**(1):25–35.

Rabe 2002 *{published data only}*
Rabe C, Gramann T, Sons X, Berna M, Gonzalez-Carmona MA, Klehr HU, et al.Keeping central venous lines open: a prospective comparison of heparin, vitamin C and sodium chloride sealing solutions in medical patients. *Intensive Care Medicine* 2002;**28**(8):1172–6.

Schallom 2012 *{published and unpublished data}*
Schallom ME, Prentice D, Sona C, Micek ST, Skrupky LP. Heparin or 0.9% sodium chloride flush to maintain central venous catheter patency: a randomized trial. *Critical Care Medicine* 2012;**40**(6):1820–6.

References to studies excluded from this review

AACCN 1993 *{published data only}*
American Association of Critical-Care Nurses. Evaluation of the effects of heparinized and nonheparinized flush solutions on the patency of arterial pressure monitoring lines: the AACN Thunder Project. By the American Association of Critical-Care Nurses. *American Journal of Critical Care* 1993;**2**(1):3–15.

Abbas 2009 *{published data only}*
Abbas SA, Haloob IA, Taylor SL, Curry EM, King BB, van der Merwe WM, et al.Effect of antimicrobial locks for tunnelled hemodialysis catheters on bloodstream infection and bacterial resistance: a quality improvement report. *American Journal of Kidney Diseases* 2009;**53**(3):492–502.

Abdelkefi 2004 *{published data only}*
Abdelkefi A, Othman TB, Kammoun L, Chelli M, Romdhane NB, Kriaa A, et al.Prevention of central venous line-related thrombosis by continuous infusion of low-dose unfractionated heparin, in patients with haemato-oncological disease. A randomized controlled trial. *Thrombosis and Haemostasis* 2004;**92**(3):654–61.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Abdelkefi 2005 *{published data only}*

Abdelkefi A, Torjman L, Ladeb S, Othman TB, Achour W, Lakhal A, et al.Randomized trial of prevention of catheter-related bloodstream infection by continuous infusion of low-dose unfractionated heparin in patients with hematologic and oncologic disease. *Journal of Clinical Oncology* 2005;**23**(31):7864–70.

Abdelkefi 2005a *{published data only}*

Abdelkefi A. Prevention of catheter-related bloodstream infection in patients with haemato-oncological disease. http://clinicaltrials.gov/ct2/show/NCT00207779?term=Prevention+of+Catheter-Related+Bloodstream+Infection+in+Patients+With+Haemato-Oncological+Disease&rank=2 (accessed 6 October 2014) 2005.

Abdelkefi 2007 *{published data only}*

Abdelkefi A, Achour W, Othman TB, Ladeb S, Torjman L, Lakhal A, et al.Use of heparin-coated central venous lines to prevent catheter-related bloodstream infection. *Journal of Supportive Oncology* 2007;**5**(6):273–8.

Abdelkefi 2008 *{published data only}*

Abdelkefi A, Chelli M, Achour W, Ben Romdhane N, Torjman L, Ladeb S, et al.Catheter related bloodstream infection in haematological patients: a prospective, randomized study comparing Heparin-coated with chlorhexidine and silver sulfadiazine impregnated central venous catheters. *Blood* 2008;**112**(11):Abstract 1174.

Agnelli 2009 *{published data only}*

Agnelli G. Prevention of venous and arterial thromboembolism in cancer patients undergoing chemotherapy, with a low molecular weight heparin (nadroparin calcium). A randomized, placebo-controlled, double-blind, multicenter phase III study. http://clinicaltrials.gov/ct2/show/NCT00951574?term=Prevention+of+Venous+and+Arterial+Thromboembolism%2C+in+Cancer+Patients+Undergoing+Chemotherapy%2C+With+a+Low+Molecular+Weight+Heparin+%28N rank=1 (accessed 6 October 2014) 2009.

Akyuz 2010 *{published data only}*

Akyuz C, Kupeli S, Yagci-Kupeli B, Buyukpamukcu M. Prophylactic taurolidine use in central venous catheters of pediatric cancer patients: a prospective randomized study from single center. *Pediatric Blood and Cancer* 2010;**55**(5):949.

Alexander 2010 *{published data only}*

Alexander H. Heparin versus normal saline as a flush solution. *International Journal for the Advancement of Science and Arts* 2010;**1**(1):63–75.

Alpan 1984 *{published data only}*

Alpan G, Eyal F, Springer C, Glick B, Goder K, Armon J. Heparinization of alimentation solutions administered through peripheral veins in premature infants: a controlled study. *Pediatrics* 1984;**74**(3):375–8.

Andersen 1992 *{published data only}*

Andersen KM, Holland JS. Maintaining the patency of peripherally inserted central catheters with 10 units/cc heparin. *Journal of Intravenous Nursing* 1992;**15**(2):84–8.

Ankola 1993 *{published data only}*

Ankola PA, Atakent YS. Effect of adding heparin in very low concentration to the infusate to prolong the patency of umbilical artery catheters. *American Journal of Perinatology* 1993;**10**(3):229–32.

Anton 2009 *{published data only}*

Anton N, Cox PN, Massicotte MP, Chait P, Yasui Y, Dinyari PM, et al.Heparin-bonded central venous catheters do not reduce thrombosis in infants with congenital heart disease: a blinded randomized, controlled trial. *Pediatrics* 2009;**123**(3):e453–8.

Appelgren 1995 *{published data only}*

Appelgren P, Ransjo U, Bindslev L, Larm O. Does surface heparinisation reduce bacterial colonisation of central venous catheters?. *The Lancet* 1995;**345**(8942):130.

Appelgren 1996 *{published data only}*

Appelgren P, Ransjo U, Bindslev L, Espersen F, Larm O. Surface heparinisation of central venous catheters reduces microbial colonization in vitro and in vivo: results from a prospective, randomized trial. *Critical Care Medicine* 1996;**24**(9):1482–9.

Aquino 2002 *{published data only}*

Aquino VM, Sandler ES, Mustafa MM, Steele JW, Buchanan GR. A prospective double-blind randomized trial of urokinase flushes to prevent bacteremia resulting from luminal colonization of subcutaneous central venous catheters. *Journal of Pediatric Hematology/Oncology* 2002;**24**(9):710–3.

Araujo 2008 *{published data only}*

Araujo C, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, et al.A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. *European Journal of Surgical Oncology* 2008;**34**(2):222–6.

Arnts 2011 *{published data only}*

Arnts IJ, Heijnen JA, Wilbers HT, van der Wilt GJ, Groenewoud JMM, Liem KD. Effectiveness of heparin solution versus normal saline in maintaining patency of intravenous locks in neonates: a double blind randomized controlled study. *Journal of Advanced Nursing* 2011;**67**(12):2677–85.

Arone 2012 *{published data only}*

Arone KMB, Garbin LM, Reis PED, Galvao CM, Silveira RCCP. Thrombotic obstruction related of central venous catheter in patients submitted to haematopoietic stem cell transplantation. *Bone Marrow Transplantation* 2012;**47**(Suppl 1):S489.

Arrants 1999 *{published data only}*

Arrants J, Willis ME, Stevens B, Gripkey L, Herman JA, Hernandez-Brooks L, et al.Reliability of an intravenous intermittent access port (saline lock) for obtaining blood samples for coagulation studies. *American Journal of Critical Care* 1999;**8**(5):344–8.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ashton 1990 *{published data only}*
Ashton J, Gibson V, Summers S. Effects of heparin versus saline solution on intermittent infusion device irrigation. *Heart and Lung* 1990;**19**(6):608–12.

Aslam 2008 *{published data only}*
Aslam S, Trautner BW, Ramanathan V, Darouiche RO. Pilot trial of N-acetylcysteine and tigecycline as a catheter-lock solution for treatment of hemodialysis catheter-associated bacteremia. *Infection Control and Hospital Epidemiology* 2008;**29**(9):894–7.

Aslam 2010 *{published data only}*
Aslam S, Darouiche RO. Mechanical integrity of haemodialysis catheters after exposure to a novel catheter lock solution. *Infection Control and Hospital Epidemiology* 2010;**31**(11):1124–9.

Aslam 2011 *{published data only}*
Aslam S. Phase II trial of a novel catheter lock solution for adjunctive treatment of hemodialysis catheter-associated bacteremia. http://clinicaltrials.gov/ct2/show/NCT01483872?term=Use+of+a+Novel+Catheter+Lock+Solution+For+Treatment+of+Hemodialysis+Catheter+Infections&rank=1 (accessed 6 October 2014) 2011.

Bailey 1979 *{published data only}*
Bailey MJ. Reduction of catheter-associated sepsis in parenteral nutrition using low-dose intravenous heparin. *British Medical Journal* 1979;**1**(6179):1671–3.

Balduini 2010 *{published data only}*
Balduini C. Heparin in prophylaxis of peripheral venous catheters thrombosis: randomized clinical trial [Studio clinico randomizzato sull'utilizzo di eparina per la profilassi della tromboflebite da catetere venoso periferico]. http://clinicaltrials.gov/ct2/show/NCT01131754?term=Heparin+100U%2FL+for+Prevention+of+PVC+Complications&rank=1 (accessed 6 October 2014) 2010.

Baltrons 2008 *{published data only}*
Baltrons Bosch A, Coll Vinyoles S, Font Senen C, Jubany López M, Plana Illa C, Sunyer García A. Estudio comparativo del sellado de catéteres con citrato trisódico o heparina sódica más gentamicina. *Revista de la Sociedad Española de Enfermeria Nefrologica* 2008;**11**(2):95–100.

Barrett 1990 *{published data only}*
Barrett PJ, Lester RL. Heparin versus saline flushing solutions in a small community hospital. *Hospital Pharmacy* 1990;**25**(2):115–8.

Barriga 1997 *{published data only}*
Barriga FJ, Varas M, Potin M, Sapunar F, Rojo H, Martinez A, et al.Efficacy of a vancomycin solution to prevent bacteremia associated with an indwelling central venous catheter in neutropenic and non-neutropenic cancer patients. *Medical and Pediatric Oncology* 1997;**28**(3):196–200.

Bayes 1999 *{published data only}*
Bayes B, Bonal J, Romero R. Sodium citrate for filling haemodialysis catheters. *Nephrology Dialysis Transplantation* 1999;**14**(10):2532–3.

Beecroft 1997 *{published data only}*
Beecroft PC. Intravenous lock patency in children: dilute heparin versus saline. *Journal of Paediatric Pharmacological Practice* 1997;**2**(4):211–23.

Bennegard 1982 *{published data only}*
Bennegard K, Curelaru I, Gustavsson B, Linder LE, Zachrisson BF. Material thrombogenicity in central venous catheterization. I. A comparison between uncoated and heparin-coated, long antebrachial, polyethylene catheters. *Acta Anaesthesiologica Scandinavica* 1982;**26**(2):112–20.

Bertoglio 2012 *{published data only}*
Bertoglio S, Solari N, Meszaros P, Vassallo F, Bonvento M, Pastorino S, et al.Efficacy of normal saline versus heparinized saline solution for locking catheters of totally implantable long-term central vascular access devices in adult cancer patients. *Cancer Nursing* 2012;**35**(4):E35–E42.

Bertolino 2012 *{published data only}*
Bertolino G, Pitassi A, Tinelli C, Staniscia A, Guglielmana B, Scudeller L, et al.Intermittent flushing with heparin versus saline for maintenance of peripheral intravenous catheters in a medical department: a pragmatic cluster-randomized controlled study. *Worldviews on Evidence-Based Nursing* 2012;**9**(4):221–6.

Betjes 2004 *{published data only}*
Betjes MG, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. *Nephrology, Dialysis, Transplantation* 2004;**19**(6):1546–51.

Betremieux 1988 *{published data only}*
Betremieux P, Odent S, Prigent JY, Dabadie A, Roussey M, Lefrancois C. Study of continuous infusion of low doses of heparin in the prevention of complications of catheter during the neonatal period [Etude de l'infusion continue de bas doses de l'heparine pour la prevention de les complications du catheter pendant le periode neonatal]. *Revue de Pediatrie* 1988;**24**(7):311–5.

Birch 2010 *{published data only}*
Birch P, Ogden S, Hewson M. A randomised, controlled trial of heparin in total parenteral nutrition to prevent sepsis associated with neonatal long lines: the Heparin in Long Line Total Parenteral Nutrition (HILLTOP) trial. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2010;**95**(4):F252–7.

Bisseling 2010 *{published data only}*
Bisseling TM, Willems MC, Versleijen MW, Hendriks JC, Vissers RK, Wanten GJ. Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clinical Nutrition* 2010;**29**(4):464–8.

Bleyer 2005 *{published data only}*
Bleyer AJ, Mason L, Russell G, Raad II, Sherertz RJ. A randomized, controlled trial of a new vascular catheter flush solution (minocycline-EDTA) in temporary hemodialysis access. *Infection Control and Hospital Epidemiology* 2005;**26**(6):520–4.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Bolgiano 1990 *{published data only}*
Bolgiano CS, Subramaniam PT, Montanari JM, Minick L. The effect of two concentrations of heparin on arterial catheter patency. *Critical Care Nurse* 1990;**10**(5):47–57.

Bookstaver 2009 *{published data only}*
Bookstaver PB, Williamson JC, Tucker BK, Raad II, Sherertz RJ. Activity of novel antibiotic lock solutions in a model against isolates of catheter-related bloodstream infections. *Annals of Pharmacotherapy* 2009;**43**(2):210–9.

Bossert 1994 *{published data only}*
Bossert E, Beecroft PC. Peripheral intravenous lock irrigation in children: current practice. *Pediatric Nursing* 1994;**20**(4):346-9, 355.

Bracho-Blanchet 2010 *{published data only}*
Bracho-Blanchet E, Cortes-Sauza J, Davila-Perez R, Lezama-del Valle P, Villalobos-Alfaro C, Nieto-Zermeno J. Usefulness of intravenous heparin to prevent thrombosis of central venous catheter in children. *Cirugia y Cirujanos* 2010;**78**(5):423–9.

Branger 2011 *{published data only}*
Branger B, Reboul P, Prelipcean C, Noguera ME, Cariou S, Granolleras C, et al.Tunnelled internal jugular vein catheters with taurolidine lock: an acceptable challenge to arterio-venous fistula in 70 years old haemodialyzed patients: a prospective pilot study. *Nephrologie & Therapeutique* 2011; **7**(4):237–41.

Branson 1993 *{published data only}*
Branson PK, McCoy RA, Phillips BA, Clifton GD. Efficacy of 1.4 percent sodium citrate in maintaining arterial catheter patency in patients in a medical ICU. *Chest* 1993;**103**(3): 882–5.

Brismar 1982 *{published data only}*
Brismar B, Hardstedt C, Jacobson S, Kager L, Malmborg AS. Reduction of catheter-associated thrombosis in parenteral nutrition by intravenous heparin therapy. *Archives of Surgery* 1982;**117**(9):1196–9.

Broom 2009 *{published data only}*
Broom JK, O'Shea S, Govindarajulu S, Playford EG, Hawley CM, Isbel NM, et al.Rationale and design of the HEALTHY-CATH trial: a randomised controlled trial of Heparin versus EthAnol Lock THerapY for the prevention of Catheter Associated infecTion in Haemodialysis patients. *BMC Nephrology* 2009;**10**:23.

Broom 2012 *{published data only}*
Broom JK, Krishnasamy R, Hawley CM, Playford EG, Johnson DW. A randomised controlled trial of Heparin versus EthAnol Lock THerapy for the prevention of Catheter Associated infecTion in Haemodialysis patients - The HEALTHY-CATH trial. *BMC Nephrology* 2012;**13**: 146.

Brown-Smith 1990 *{published data only}*
Brown-Smith JK, Stoner MH, Barley ZA. Tunneled catheter thrombosis: factors related to incidence. *Oncology Nursing Forum* 1990;**17**(4):543–9.

Butt 1987 *{published data only}*
Butt W, Shann F, McDonnell G, Hudson I. Effect of heparin concentration and infusion rate on the patency of arterial catheters. *Critical Care Medicine* 1987;**15**(3):230–2.

Buturovic 1998 *{published data only}*
Buturovic J, Ponikvar R, Kandus A, Boh M, Klinkmann J, Ivanovich P. Filling hemodialysis catheters in the interdialytic period: heparin versus citrate versus polygeline: a prospective randomized study. *Artificial Organs* 1998;**22** (11):945–7.

Cabrita 2011 *{published data only}*
Cabrita J, Catorze N, Teixeira S, Carreto J, Vieira V, Goncalves S, et al.Maintenance of arterial catheters with heparin. It is time to stop!. *Intensive Care Medicine* 2011;**37 (Suppl 1)**:S168.

Calderero 2009 *{published data only}*
Calderero Aragon V, De Gregorio Ariza MA, Pazo Cid R, Puertolas Hernandez T, Lostale Latorre F, Artal Cortes A, et al.Role of low molecular weight heparins in prophylaxis of thromboembolic events on oncological patients with indwelling central venous catheter [Heparinas de bajo peso molecular en la profilaxis de episodios tromboembólicos en pacientes con cáncer portadores de catéter venoso central]. *Medicina Clinica* 2009;**133**(10):365–70.

Campbell 2011 *{published data only}*
Campbell MA. A randomized controlled crossover trial of two different central venous catheter flushing schemes in pediatric hematology and oncology patients in Alberta, Canada. http://clinicaltrials.gov/ct2/show/NCT01343680?term=Trial+of+Two+Central+Venous+Catheter+%28CVC%29+Flushing+Schemes+in+Pedia rank=1 (accessed 6 October 2014) 2011.

Campos 2011 *{published data only}*
Campos RP, do Nascimento MM, Chula DC, Riella MC. Minocycline-EDTA lock solution prevents catheter-related bacteremia in hemodialysis. *Journal of the American Society of Nephrology: JASN* 2011;**22**(10):1939–45.

Cardinal 2000 *{published data only}*
Cardinal P, Allan J, Pham B, Hindmarsh T, Jones G, Delisle S. The effect of sodium citrate in arterial catheters on acid-base and electrolyte measurements. *Critical Care Medicine* 2000;**28**(5):1388–92.

Carrasco 2004 *{published data only}*
Carrasco MN, Bueno A, De Las Cuevas C, Jimenez S, Salinas I, Sartorius A, et al.Evaluation of a triple-lumen central venous heparin-coated catheter versus a catheter coated with chlorhexidine and silver sulphadiazine in critically ill patients. *Intensive Care Medicine* 2004;**30**(4): 633–8.

Carratala 1999 *{published data only}*
Carratala J, Niubo J, Fernandez-Sevilla A, Juve E, Castellsague X, Berlanga J, et al.Randomized, double-blind trial of an antibiotic-lock technique for prevention of gram-positive central venous catheter-related infection in neutropenic patients with cancer. *Antimicrobial Agents and Chemotherapy* 1999;**43**(9):2200–4.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Carrero 2012 *{published data only}*
Carrero Caballero MC, Valbuena Esteban B. Maintenance and care of intravascular catheters. The significance of heparinization [Mantenimiento y cuidado de catéteres intravasculares]. *Revista Enfermeria* 2012;**35**(6):47–50.

Casale 2009 *{published data only}*
Casale KE, Horst MA, Anderson AS, Devereux RB. Lower concentration of heparinized flush solution is associated with a higher incidence of femoral sheath clot following diagnostic cardiac catheterization. *Journal of the American College of Cardiology* 2009;**53**(10 Suppl 1):A24.

Catorze 2011 *{published data only}*
Catorze N, Teixeira S, Cabrita J, Carreto J, Vieira V, Gonçalves S, et al.Maintenance of arterial catheters with heparin; should we continue?. *Critical Care* 2011;**15**(Suppl 1):P78.

Catton 2006 *{published data only}*
Catton JA, Davies J, Dobbins BM, Wood JM, McMahon MJ, Burke D. The effect of heparin in peripheral intravenous nutrition via a fine-bore midline: a randomised double-blind controlled trial. *Clinical Nutrition* 2006;**25**(3):394–9.

Cesaro 2009 *{published data only}*
Cesaro S, Tridello G, Cavaliere M, Magagna L, Gavin P, Cusinato R, et al.Prospective, randomized trial of two different modalities of flushing central venous catheters in pediatric patients with cancer. *Journal of Clinical Oncology* 2009;**27**(12):2059–65.

Chang 1997 *{published data only}*
Chang GY, Lueder FL, DiMichele DM, Radkowski MA, McWilliams LJ, Jansen RD. Heparin and the risk of intraventricular hemorrhage in premature infants. *Journal of Pediatrics* 1997;**131**(3):362–6.

Cheronis 2013 *{published data only}*
Cheronis JC. Multi-center, prospective, randomized, open-label, sponsor-blinded, active-control (heparin) clinical investigation to evaluate the safety and effectiveness of B-Lock™ as an antimicrobial catheter lock solution in dialysis patients with a central venous catheter. http://clinicaltrials.gov/ct2/show/NCT01989091?term=Antimicrobial+Lock+Solution+in+Dialysis+Patients+With+a+CVC&rank=1 (accessed 6 October 2014) 2013.

Chu 2009 *{published data only}*
Chu KH, Cheung W, Chan W, Fung KS, Tang HL, Yim KF, et al.A single centre experience of using gentamicin/heparin lock solution in preventing dialysis catheter-related infection. *Hemodialysis International* 2009;**13**(3):372.

Clark 2009 *{published data only}*
Clark TWI, David Jacobs D, Charles HW, Kovacs S, Aquino T, Erinjeri J, Benstein JA. Comparison of heparin-coated and conventional split-tip hemodialysis catheters. *Cardiovascular and Interventional Radiology* 2009;**32**(4):703–6.

Clifton 1991 *{published data only}*
Clifton GD, Branson P, Kelly HJ, Dotson LR, Record KE, Phillips BA, et al.Comparison of normal saline and heparin solutions for maintenance of arterial catheter patency. *Heart and Lung* 1991;**20**(2):115–8.

Coli 2006 *{published data only}*
Coli L, Donati G, Cianciolo G, Raimondi C, Comai G, Panicali L, et al.Anticoagulation therapy for the prevention of hemodialysis tunneled cuffed catheters (TCC) thrombosis. *Journal of Vascular Access* 2006;**7**(3):118–22.

Conte 2003 *{published data only}*
Conte GF, Aravena PC, Fardella PD, Araos DM, Alfaro JI, Flores CA, et al.Prophylaxis of venous thrombosis (VT) associated with central venous catheter (CVC) with low molecular weight heparin (LMWH) in hematologic malignancies [abstract]. Blood 2003; Vol. 102, issue 11: 122b.

Coplon 2007 *{published data only}*
Coplon N. Prophylactic antimicrobial catheter lock in hemodialysis patients: a randomized controlled clinical trial. http://clinicaltrials.gov/ct2/show/NCT00571259?term=Prophylactic+Antimicrobial+Catheter+Lock&rank=1 (accessed 6 October 2014) 2007.

Corbett 2013 *{published data only}*
Corbett R, Ashby D, Edwards C, Prout V, Singh S, Bedi R, Duncan N. A randomised control trial of taurolidine-heparin-citrate line locks in prevention of recurrence of catheter related bacteraemia in haemodialysis patients. *Nephrology Dialysis Transplantation* 2013;**28**(Suppl 1):i19.

Cortes 2006 *{published data only}*
Cortes J. Prospective, randomized trial comparing heparin and minocycline-EDTA flush for the prevention of catheter-related infections and occlusions. http://clinicaltrials.gov/ct2/show/NCT00378781?term=Heparin+or+M-EDTA+in+Preventing+Catheter-Related+Infections+and+Blockages+in+Patients+at+High+Risk+for+a+Catheter-Related+Infection&rank=1 (accessed 6 October 2014) 2006.

Cottee 1995 *{published data only}*
Cottee S. Heparin lock practice in total parenteral nutrition. *Professional Nurse* 1995;**11**(1):25-6, 28-9.

Crews 1997 *{published data only}*
Crews BE, Gnann KK, Rice MH, Kee CC. Effects of varying intervals between heparin flushes on pediatric catheter longevity. *Pediatric Nursing* 1997;**23**(1):87–91.

Daghistani 1996 *{published data only}*
Daghistani D, Horn M, Rodriguez Z, Schoenike S, Toledano S. Prevention of indwelling central venous catheter sepsis. *Medical and Pediatric Oncology* 1996;**26**(6):405–8.

Danek 1992 *{published data only}*
Danek GD, Noris EM. Pediatric i.v. catheters: efficacy of saline flush. *Pediatric Nursing* 1992;**18**(2):111–3.

Daniell 1973 *{published data only}*
Daniell HW. Heparin in the prevention of infusion phlebitis. A double-blind controlled study. *JAMA* 1973;**226**(11):12317–21.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Davanipur 2011 *{published data only}*
Davanipur M, Pakfetrat M, Roozbeh J. Cloxacillin as an antibiotic lock solution for prevention of catheter-associated infection. *Iranian Journal of Kidney Diseases* 2011;**5**(5): 328–31.

David 1981 *{published data only}*
David RJ, Merten DF, Anderson JC, Gross S. Prevention of umbilical artery catheter clots with heparinized infusates. *Developmental Pharmacology and Therapeutics* 1981;**2**(2): 117–26.

De Cicco 2009 *{published data only}*
De Cicco M, Matovic M, Balestreri L, Steffan A, Pacenzia R, Malafronte M, et al.Early and short-term acenocumarine or dalteparin for the prevention of central vein catheter-related thrombosis in cancer patients: a randomized controlled study based on serial venographies. *Annals of Oncology* 2009;**20**(12):1936–42.

de la Torre 2012 *{published data only}*
de la Torre Montero JC, Montealegre Sanz M. Heparinization versus salinization in short peripheral catheters for blood draws in clinical trials [Heparinización versus salinización en catéteres periféricos cortos para extracciones de sangre en ensayos clínicos]. *Metas de Enfermeria* 2012;**15**(7):15–8.

del Cotillo 2008 *{published data only}*
del Cotillo M, Grane N, Llavore M, Quintana S. Heparinized solution vs. saline solution in the maintenance of arterial catheters: a double blind randomized clinical trial. *Intensive Care Medicine* 2008;**34**(2):339–43.

del Pozo 2012 *{published data only}*
del Pozo JL. Concentration and antibiotic activity in antibiotic lock solutions. http://clinicaltrials.gov/ct2/show/NCT01592032?term=Study+of+Concentration+and+Antimicrobial+Activity+of+Antibiotics+Used+for+Catheter-Related+Infections&rank=1 (accessed 6 October 2014) 2012.

de Neef 2002 *{published data only}*
de Neef M, Heijboer H, van Woensel JB, de Haan RJ. The efficacy of heparinization in prolonging patency of arterial and central venous catheters in children: a randomized double-blind trial. *Pediatric Hematology and Oncology* 2002; **19**(8):553–60.

Dias 2000 *{published data only}*
Dias EF, Viana ACN, Lourdes Andraus MS, Pereira MS. [Use of intermittent intravenous device in pediatrics]. *Revista Eletronica de Enfermagem* 2000;**2**(2):1–12.

Dillon 2004 *{published data only}*
Dillon PW, Jones GR, Bagnall-Reeb HA, Buckley JD, Wiener ES, Haase GM, Children's Oncology Group. Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. *Journal of Clinical Oncology* 2004;**22**(13): 2718–23.

Dogra 2002 *{published data only}*
Dogra GK, Herson H, Hutchison B, Irish AB, Heath CH, Golledge C, et al.Prevention of tunnelled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. *Journal of the American Society of Nephrology* 2002;**13**(8): 2133–9.

Donham 1987 *{published data only}*
Donham JA, Denning V. Heparin vs. saline in maintaining patency, intermittent infusion devices: pilot study. *Kansas Nurse* 1987;**62**(11):6–7.

Duemichen 2012 *{published data only}*
Dümichen MJ, Seeger K, Lode HN, Kühl JS, Ebell W, Degenhardt P. Randomized controlled trial of taurolidine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. *The Journal of Hospital Infection* 2012;**80**(4):304–9.

Duncan 2005 *{published data only}*
Duncan N, Singh S, Amao M, Brown W, Dalby E, Edwards C, et al.A single centre randomised control trial of sodium citrate versus Heparin line locks for cuffed central venous catheters [abstract no: F-PO539]. Journal of the American Society of Nephrology 2005; Vol. 16:451A.

Duncan 2010 *{published data only}*
Duncan N. A randomised controlled trial of taurolidine with heparin for prevention of recurrence of catheter related bacteraemia in haemodialysis patients. http://clinicaltrials.gov/ct2/show/NCT01243710?term=Taurolidine+in+Haemodialysis+Catheter+Related+Bacteraemia&rank=1 (accessed 6 October 2014).

Dunser 2005 *{published data only}*
Dünser MW, Mayr AJ, Hinterberger G, Flörl CL, Ulmer H, Schmid S, et al.Central venous catheter colonization in critically ill patients: a prospective, randomized, controlled study comparing standard with two antiseptic-impregnated catheters. *Anesthesia and Analgesia* 2005;**101**(6):1778–84.

Dupuis 2012 *{published data only}*
Dupuis E, Duval X, Domic Q, Bonnal C, Lucet JC, Cerceau O, et al.Trisodium citrate 46.7% versus heparin catheter locks for tunneled central venous catheters: a single-center study. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii253.

Edstrom 2002 *{published data only}*
Edstrom CS, McBride J, Theriaque D, Kao KJ, Christensen RD. Obtaining blood samples for anti-factor Xa quantification through umbilical artery catheters. *Journal of Perinatology* 2002;**22**(6):475–7.

Eloy 1987 *{published data only}*
Eloy R, Belleville J, Paul J, Pusineri C, Baguet J, Rissoan MC, et al.Thromboresistance of bulk heparinized catheters in human. *Thrombosis Research* 1987;**45**(3):223–33.

Epperson 1984 *{published data only}*
Epperson EL. Efficacy of 0.9% sodium chloride injection with and without heparin for maintaining indwelling intermittent injection sites. *Clinical Pharmacy* 1984;**3**(6): 626–9.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Everts 2004 *{published data only}*
Everts R, Harding H. Catheter-drawn blood cultures: is withdrawing the heparin lock beneficial?. *Pathology* 2004; **36**(2):170–3.

Ferreira 2011 *{published data only}*
Ferreira Chacon JM, Hato De Almeida E, De Lourdes Simoes R, Lazzarin C, Ozorio V, Alves BC, Mello De Andrea ML, et al.Randomized study of minocycline and edetic acid as a locking solution for central line (Port-A-Cath) in children with cancer. *Chemotherapy* 2011;**57**(4): 285–91.

Festini 2013 *{published data only}*
Festini F. Normal saline Versus heparinized solution flush for maintaining patency of peripheral venous catheters in children. http://clinicaltrials.gov/ct2/show/NCT01794767?term=Normal+Saline+Versus+Heparinized+Solution+Flush+for+Maintaining+Patency+of+Peripheral+Venous+Catheters+in+Children&rank=1 (accessed 6 October 2014) 2013.

Filippi 2007 *{published data only}*
Filippi L, Pezzati M, Di Amario S, Poggi C, Pecile P. Fusidic acid and heparin lock solution for the prevention of catheter-related bloodstream infections in critically ill neonates: a retrospective study and a prospective, randomized trial. *Pediatric Critical Care Medicine* 2007;**8**(6):556–62.

Fonseca 2010 *{published data only}*
Fonseca UNK, Nielsen SG, Hau J, Hansen AK. Permanent catheterization of the carotid artery induces kidney infection and inflammation in the rat. *Laboratory Animals* 2010;**44** (1):46–53.

Fort 2011 *{published data only}*
Fort AE, Cummings JJ. . Journal of Investigative Medicine Conference: American Federation for Medical Research Southern Regional Meeting, AFMR 2011. [A prospective, randomized, blinded, placebo–controlled trial of periodic, brief ethanol locks to prevent peripherally inserted central catheter (PICC) infections in preterm infants in the neonatal intensive care unit]. Journal of Investigative Medicine. 2011; Vol. 59, issue 2:175.

Fratino 2002 *{published data only}*
Fratino G, Molinari AC, Mazzola C, Giacchino M, Saracco P, Bertocchi E, et al.Prospective study of indwelling central venous catheter-related complications in children with broviac or clampless valved catheters. *Journal of Pediatric Hematology/Oncology* 2002;**24**(8):657–61.

Garay Rubio 2011 *{published data only}*
Garay Rubio T, Urruela Oliván M, Hernando Uzkudun A, Asensio Bermejo B, Cossío Díaz C. Efectivity [sic] of saline versus heparinized solution in flushing clogged peripheral catheter [Efectividad en la utilización de suero salino frente a suero salino heparinizado para el lavado de catéteres periféricos obturados]. *Enfermeria Clinica* 2011; **11**(6):283–8.

Garland 2005 *{published data only}*
Garland JS, Alex CP, Henrickson KJ, McAuliffe TL, Maki DG. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics* 2005;**116**(2): e198–205.

Garrelts 1989 *{published data only}*
Garrelts JC, LaRocca J, Ast D, Smith DF Jr, Sweet DE. Comparison of heparin and 0.9% sodium chloride injection in the maintenance of indwelling intermittent i.v. devices. *Clinical Pharmacy* 1989;**8**(1):34–9.

Gillies 1985 *{published data only}*
Gillies H, Rogers HJ, Johnston J, Harper PG, Rudge CJ. Is repeated flushing of Hickman catheters necessary?. *British Medical Journal (Clinical Research Edition)* 1985;**290**(6483): 1708.

Gittins 2007 *{published data only}*
Gittins NS, Hunter-Blair YL, Matthews JN, Coulthard MG. Comparison of alteplase and heparin in maintaining the patency of paediatric central venous haemodialysis lines: a randomised controlled trial. *Archives of Disease in Childhood* 2007;**92**(6):499–501.

Glaspy 2000 *{published data only}*
Glaspy JA. A phase III randomized, double-blind, placebo-controlled study to evaluate the effects of fragmin (5,000 IU subcutaneously) in preventing catheter-related complications when given daily to cancer patients with central venous catheters. http://clinicaltrials.gov/ct2/show/NCT00006083?term=Dalteparin+to+Prevent+Complications+in+Cancer+Patients+Receiving+Chemotherapy+T&rank=1 (accessed 6 October 2014) 2000.

Goh 2011 *{published data only}*
Goh LJ, Teo HS, Masagoes M. Heparinised saline versus normal saline in maintaining patency of arterial and central venous catheters. *Proceedings of Singapore Healthcare* 2011; **20**(3):190–6.

Golberg 1999 *{published data only}*
Golberg M, Sankaran R, Givelichian L, Sankaran K. Maintaining patency of peripheral intermittent infusion devices with heparinized saline and saline: a randomized double blind controlled trial in neonatal intensive care and a review of literature. *Neonatal Intensive Care* 1999;**12**(1): 18–22.

Gomez Palomar 2005 *{published data only}*
Gomez Palomar C, Gomez Palomar MJ. Comparison of the yield of arterial cannulas maintained with heparinized and nonheparinized fluids: a prospective study [Comparación en el rendimiento de cánulas arteriales mantenidas con fluidos heparinizados y no heparinizados: estudio prospectivo]. *Enfermeria Clinica* 2005;**15**(5):262–6.

Goode 1993 *{published data only}*
Goode CJ, Kleiber C, Titler M, Small S, Rakel B, Steelman VM, et al.Improving practice through research: the case of heparin vs. saline for peripheral intermittent infusion devices. *MEDSURG Nursing* 1993;**2**(1):23–7.

Griffin 2005 *{published data only}*
Griffin MP, Siadaty MS. Papaverine prolongs patency of peripheral arterial catheters in neonates. *Journal of Pediatrics* 2005;**146**(1):62–5.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Grosso 1989 *{published data only}*
Grosso P, Martello L, Petrini PL, Massei R. Prevention of vena cava thrombosis during catheterization. Comparison of calciheparin and defibrotide. *Minerva Anestesiologica* 1989;**55**(6):273–6.

Guillet 1997 *{published data only}*
Guillet P, La Scola B, Bagarry-Liegey D, Lorvellec K, Martin N, Nicoara A, et al.Clinical pilot study on repeated use of heparin, vancomycin, colimycine locked flush solution for central intravenous implanted catheter in oncology [Etude clinique pilote de l'utilisation repétée dune solution héparine, vancomycine, colimycine en verrouillage systématique des chambres implantables avec cathéter centeral en cancérologie]. *Pathologie-Biologie* 1997;**45**(6): 506–13.

Gyr 1995 *{published data only}*
Gyr P, Burroughs T, Smith K, Mahl C, Pontious S, Swerczek L. Double blind comparison of heparin and saline flush solutions in maintenance of peripheral infusion devices. *Pediatric Nursing* 1995;**21**(4):383-9. 366.

Hall 2006 *{published data only}*
Hall KF, Bennetts TM, Whitta RK, Welman L, Rawlins P. Effect of heparin in arterial line flushing solutions on platelet count: a randomised double-blind study. *Critical Care and Resuscitation* 2006;**8**(4):294–6.

Hamilton 1988 *{published data only}*
Hamilton RA, Plis JM, Clay C, Sylvan L. Heparin sodium versus 0.9% sodium chloride injection for maintaining patency of indwelling intermittent infusion devices. *Clinical Pharmacy* 1988;**7**(6):439–43.

Handrup 2012 *{published data only}*
Handrup MM, Fuursted K, Funch P, Møller JK, Schrøder H. Biofilm formation in long-term central venous catheters in children with cancer: a randomized controlled open-labelled trial of taurolidine versus heparin. *Acta Pathologica Microbiologica Immunologica Scandinavica* 2012;**120**(10): 794–801.

Handrup 2013 *{published data only}*
Handrup MM, Moller JK, Schroder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of taurolidine versus heparin. *Pediatric Blood & Cancer* 2013;**60**(8):1292–8.

Hanrahan 1994 *{published data only}*
Hanrahan KS, Kleiber C, Fagan CL. Evaluation of saline for IV locks in children. *Pediatric Nursing* 1994;**20**(6):549–52.

Harlev 2010 *{published data only}*
Harlev D, Zaidman I, Sarig G, Ben Arush MW, Brenner B, Elhasid R. Prophylactic therapy with enoxaparin in children with acute lymphoblastic leukemia and inherited thrombophilia during L-asparaginase treatment. *Thrombosis Research* 2010;**126**(2):93–7.

Harter 2002 *{published data only}*
Harter C, Salwender HJ, Bach A, Egerer G, Goldschmidt H, Ho AD. Catheter-related infection and thrombosis of the internal jugular vein in hematologic-oncologic patients undergoing chemotherapy: a prospective comparison of silver-coated and uncoated catheters. *Cancer* 2002;**94**(1): 245–51.

Haynes 2002 *{published data only}*
Haynes BJ, Quarles AW, Vavrinchik J, White J, Pedan A. The LifeSite hemodialysis access system: implications for the nephrology nurse. *Nephrology Nursing Journal* 2002;**29** (1):27-33, 72.

Heilskov 1998 *{published data only}*
Heilskov J, Kleiber C, Johnson K, Miller J. A randomized trial of heparin and saline for maintaining intravenous locks in neonates. *Journal of the Society of Pediatric Nurses* 1998;**3** (3):111–6.

Hemmelgarn 2006 *{published data only}*
Hemmelgarn BR, Moist L, Pilkey RM, Lok C, Dorval M, Tam PYW, et al.and the Canadian Hemodialysis Catheter Working Group. Prevention of catheter lumen occlusion with rT-PA versus heparin (Pre-CLOT): Study protocol of a randomized trial [ISRCTN35253449]. *BMC Nephrology* 2006;**7**:8.

Hemmelgarn 2011 *{published data only}*
Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, et al.for the Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin (PreCLOT) Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *New England Journal of Medicine* 2011;**364**(4):303–12.

Hendrickx 2001 *{published data only}*
Hendrickx L, Kuypers D, Evenepoel P, Maes B, Messiaen T, Vanrenterghem Y. A comparative prospective study on the use of low concentrate citrate lock versus heparin lock in permanent dialysis catheters. *International Journal of Artificial Organs* 2001;**24**(4):208–11.

Heng 2011 *{published data only}*
Heng A-E, Abdelkader MH, Diaconita M, Nony A, Guerraoui A, Caillot N, et al.Impact of short term use of interdialytic 60% ethanol lock solution on tunneled silicone catheter dysfunction. *Clinical Nephrology* 2011;**75**(6): 534–41.

Henrickson 2000 *{published data only}*
Henrickson KJ, Axtell RA, Hoover SM, Kuhn SM, Pritchett J, Kehl SC, et al.Prevention of central venous catheter-related infections and thrombotic events in immunocompromised children by the use of vancomycin/ciprofloxacin/heparin flush solution: A randomized, multicenter, double-blind trial. *Journal of Clinical Oncology* 2000;**18**(6):1269–78.

HGU Gregorio Marañón 2010 *{published data only}*
HGU Gregorio Marañón. Clinical study of ethanol lock-therapy in the prevention of non-tunnelled, short term central venous catheter associated infections. http://clinicaltrials.gov/ct2/show/NCT01229592 (accessed 6 October 2014) 2010.

Hill 2011 *{published data only}*
Hill SM, Chu H-P, Koeglmeier J, Brind J, Turner S, Penfold-Forbes D, et al.Significant reduction in catheter-related bloodstream infections with taurolidine lock in

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

children treated with intravenous nutrition for 16,000 catheter days. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**52(Suppl 1)**:E64.

Hoffer 1999 *{published data only}*
Hoffer EK, Borsa J, Santulli P, Bloch R, Fontaine AB. Prospective randomized comparison of valved versus nonvalved peripherally inserted central vein catheters. *AJR. American Journal of Roentgenology* 1999;**173**(5):1393–8.

Hook 1987 *{published data only}*
Hook ML, Reuling J, Luettgen ML, Norris SO, Elsesser CC, Leonard MK. Comparison of the patency of arterial lines maintained with heparinized and nonheparinized infusions. The Cardiovascular Intensive Care Unit Nursing Research Committee of St. Luke's Hospital. *Heart and Lung* 1987;**16**(6 Pt 1):693–9.

Horgan 1987 *{published data only}*
Horgan MJ, Bartoletti A, Polansky S, Peters JC, Manning TJ, Lamont BM. Effect of heparin infusates in umbilical arterial catheters on frequency of thrombotic complications. *Journal of Pediatrics* 1987;**111**(5):774–8.

Horne 1995 *{published data only}*
Horne MK III, May DJ, Alexander HR, Steinhaus EP, Whitman ED, Chang RC, et al.Venographic surveillance of tunneled venous access devices in adult oncology patients. *Annals of Surgical Oncology* 1995;**2**(2):174–8.

Horne 2006 *{published data only}*
Horne MK, McCloskey DJ, Calis K, Wesley R, Childs R, Kasten-Sportes C. Use of heparin versus lepirudin flushes to prevent withdrawal occlusion of central venous access devices. *Pharmacotherapy* 2006;**26**(9):1262–7.

Hryszko 2013 *{published data only}*
Hryszko T, Brzosko S, Mysliwiec M. Low concentration of heparin used for permanent catheters canal locking is effective and diminishes the risk of bleeding. *International Urology and Nephrology* 2013;**45**(3):825–9.

Hu 2011 *{published data only}*
Hu HH, Hsu CY, Fang HC, Lee PT, Chen CL, Chang TY, et al.Low-dose heparin retention in temporary hemodialysis double-lumen catheter does not increase catheter occlusion and might reduce risk of bleeding. *Blood Purification* 2011; **32**(3):232–7.

Imamovic 2009 *{published data only}*
Imamovic G. Randomized control trial on citrate as the central venous catheter lock solution. http: //clinicaltrials.gov/ct2/show/NCT00862966?term= Central+Venous+Catheter+Lock+Solution&rank=1 (accessed 6 October 2014) 2009.

Ishii 2013 *{published data only}*
Ishii Y, Mishima S, Yukioka T. Comparison of normal saline and heparinized solutions for maintenance of arterial catheter pressure waves. *Academic Emergency Medicine* 2013;**20**(5 Suppl 1):s248.

Israel Ministry of Health *{published data only}*
Israel Ministry of Health. Addition of heparin to taurolock-TM CLS in HD patients with TCC does it improve catheter patency problems ?. http://clinicaltrials.gov/ct2/show/NCT00749619? term=Addition+of+Heparin+to+Taurolock-TM+CLS+in+HD+Patients+With+TCC+Dose+it+Improve+Catheter+Patency+Proble rank=1 (accessed 6 October 2014) 2008.

Jaksic 2010 *{published data only}*
Jaksic T. Trial of 70% ethanol versus heparin to reduce the rate of central line infections in children with short bowel syndrome. http:// clinicaltrials.gov/ct2/show/NCT01263574?term= Trial+of+70%25+Ethanol+Versus+Heparin+to+Reduce+the+Rate+of+Central+Line+In rank=1 (accessed 6 October 2014) 2010.

James 1994 *{published data only}*
James C. Commentary on changing from heparin to saline flush solutions: a research utilization model for implementation. *ENA'S Nursing Scan in Emergency Care* 1994;**4**(1):22.

Jasinsky 2007 *{published data only}*
Jasinsky L, Wurster J. Occlusion reduction and heparin elimination trial using an anti-reflux device on central intravenous lines. *Journal of the Association for Vascular Access* 2007;**12**(4):205.

Jeppesen 2013 *{published data only}*
Jeppesen PB. A double blinded, randomized, controlled investigation of taurolidine-citrate/eparin catheter lock solution versus heparin in patients on home parenteral nutrition with previously proven high risk of catheter related blood stream infections. http:// clinicaltrials.gov/ct2/show/NCT01948245?term=Clini-cal+Trial+Comparing+Catheter+Lock+Solutions+TaurolockTMHep+100+and+Hepari rank=1 (accessed 6 October 2014) 2013.

Johnson 2002 *{published data only}*
Johnson DW, MacGinley R, Kay TD, Hawley CM, Campbell SB, Isbel NM, et al.A randomized controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. *Nephrology Dialysis Transplantation* 2002;**17**(10):1802–7.

Jonker 2010 *{published data only}*
Jonker MA, Osterby KR, Vermeulen LC, Kleppin SM, Kudsk KA. Does low-dose heparin maintain central venous access device patency?: a comparison of heparin versus saline during a period of heparin shortage. *JPEN Journal of Parenteral and Enteral Nutrition* 2010;**34**(4):444–9.

Jonkers 2012 *{published data only}*
Jonkers C, Looman KI, Tabbers MM, Tas TA, Serlie MJ. Incidence of central venous catheter related bloodstream infections in adults and children on home parenteral nutrition: Heparin versus taurolidine catheter lock. *Clinical Nutrition Supplements* 2012;**7**(1):203–4.

Jowett 1986 *{published data only}*
Jowett NI, Stephens JM, Thompson DR, Sutton TW. Do indwelling cannulae on coronary care units need a heparin flush?. *Intensive Care Nursing* 1986;**2**(1):16–9.

Kalmanti 2002 *{published data only}*
Kalmanti M, Germanakis J, Stiakaki E, Syfridaki C, Christidou A, Tsetis D, et al.Prophylaxis with urokinase in

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

pediatric oncology patients with central venous catheters. *Pediatric Hematology and Oncology* 2002;**19**(3):173–9.

Kamala 2002 ***{published data only}***
Kamala F, Boo NY, Cheah FC, Birinder K. Randomized controlled trial of heparin for prevention of blockage of peripherally inserted central catheters in neonates. *Acta Paediatrica* 2002;**91**(12):1350–6.

Kankanala 2012 ***{published data only}***
Kankanala S, Smith K, Henner DE. Efficacy and safety of a 4% sodium citrate locking solution in cuffed tunneled hemodialysis catheters compared with heparin. *American Journal of Kidney Diseases* 2012;**59**(4):A45.

Karthaus 2006 ***{published data only}***
Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al.Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. *Annals of Oncology* 2006;**17**(2):289–96.

Kleiber 1993 ***{published data only}***
Kleiber C, Hanrahan K, Fagan CL, Zittergruen MA. Heparin vs. saline for peripheral IV locks in children. *Pediatric Nursing* 1993;**19**(4):405-9, 376.

Klenner 2003 ***{published data only}***
Klenner AF, Fusch C, Rakow A, Kadow I, Beyersdorff E, Eichler P, et al.Benefit and risk of heparin for maintaining peripheral venous catheters in neonates: a placebo-controlled trial. *Journal of Pediatrics* 2003;**143**(6):741–5.

Knofler 1999 ***{published data only}***
Knofler R, Siegert E, Lauterbach I, Taut-Sack H, Siegert G, Gehrisch S, et al.Clinical importance of prothrombotic risk factors in pediatric patients with malignancy-impact of central venous lines. *European Journal of Pediatrics* 1999; **158**(Suppl 3):S147–S150.

Kokenge 2010 ***{published data only}***
Kokenge T, Lohofener C, Lange C, Grundemann C, Bergmann K, Januschkewitz K, et al.Efficacy and safety of a low-dose citrate catheter locking solution. A randomized double blind controlled trial. *NDT Plus* 2010;**3**(3):iii162.

Kotter 1996 ***{published data only}***
Kotter RW. Heparin vs saline for intermittent intravenous device maintenance in neonates. *Neonatal Network* 1996; **15**(6):43–7.

Kovacs 2005 ***{published data only}***
Kovacs MJ. A pilot study of central venous catheter survival in cancer patients using low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. http://clinicaltrials.gov/ct2/show/NCT00216866?term=The+Catheter+Study%3A+Central+Venous+Catheter+Survival+in+Cancer+Patients+Using+Low+Molecular+Weight+Heparin+%28Dalteparin%29+for+the+Treatrank=1 (accessed 6 October 2014) 2005.

Krafte-Jacobs 1995 ***{published data only}***
Krafte-Jacobs B, Sivit CJ, Mejia R, Pollack MM. Catheter-related thrombosis in critically ill children: comparison of catheters with and without heparin bonding. *Journal of Pediatrics* 1995;**126**(1):50–4.

Kristinsson 1985 ***{published data only}***
Kristinsson KG, Hastings JGM, Spencer RC. Is repeated flushing of Hickman catheters necessary?. *British Medical Journal* 1985;**291**(6490):282.

Kudsk 1985 ***{published data only}***
Kudsk KA, Powell C, Mirtallo JM, Fabri PJ, Ruberg RL. Heparin does not reduce catheter sepsis during total parenteral nutrition. *Journal of Parenteral and Enteral Nutrition* 1985;**9**(3):348–9.

Kulkarni 1994 ***{published data only}***
Kulkarni M, Elsner C, Ouellet D, Zeldin R. Heparinized saline versus normal saline in maintaining patency of the radial artery catheter. *Canadian Journal of Surgery* 1994;**37** (1):37–42.

Kyle 1999 ***{published data only}***
Kyle LA, Turner BS. Efficacy of saline vs heparin in maintaining 24-gauge intermittent intravenous catheters in a rabbit model. *Neonatal Network* 1999;**18**(6):49–54.

Lacasaña Bellmunt 2006 ***{published data only}***
Lacasaña Bellmunt P, Garcia Ortega MJ, Garcia Ruiz C, Palomino Gutierrez B, Toro Padilla R, Vila Sanchez A, Cánovas Galera P, Canals Tur R. Permeabilisation of peripheral venous catheters of intermittent use: with and without heparin [Permeabilización de catéteres venosos periféricos de uso intermitente: con y sin heparina]. *Metas de Enfermeria* 2006;**9**(7):10–6.

Lavau-Denes 2013 ***{published data only}***
Lavau-Denes S, Lacroix P, Maubon A, Preux PM, Genet D, Venat-Bouvet L, et al.Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study. *Cancer Chemotherapy and Pharmacology* 2013;**72**(1):65–73.

Le 2003 ***{published data only}***
Le Corre I, Delorme M, Cournoyer S. A prospective, randomized trial comparing a transparent dressing and a dry gauze on the exit site of long term central venous catheters of hemodialysis patients. *Journal of Vascular Access* 2003;**4** (2):56–61.

LeDuc 1997 ***{published data only}***
LeDuc K. Efficacy of normal saline solution versus heparin solution for maintaining patency of peripheral intravenous catheters in children. *Journal of Emergency Nursing* 1997;**23** (4):306–9.

Lee 2006 ***{published data only}***
Lee AY, Levine MN, Butler G, Webb C, Costantini L, Gu C, et al.Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. *Journal of Clinical Oncology* 2006;**24**(9):1404–8.

Lenhart 2001 ***{published data only}***
Lenhart C. Preventing central venous access device occlusions with saline only flush by use of an adapter. *Journal of Vascular Access Devices* 2001;**6**(2):29–31.

Leslie 1996 ***{published data only}***
Leslie GD, Jacobs IG, Clarke GM. Proximally delivered dilute heparin does not improve circuit life in continuous

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

venovenous haemodiafiltration. *Intensive Care Medicine* 2011;**22**(11):1261–4.

Liang 1998 ***{published data only}***
Liang Y, Wang Y, Li D. Clinical observation on normal saline of tube-sealing solution for vein permanent needle. *Shanxi Nursing Journal* 1998;**12**(2):80–1.

Liao 2002 ***{published data only}***
Liao S, Zhang Y, Chen L. Comparison of effects on sealing up the infusion tube by using three different solutions. *Chinese Nursing Research* 2002;**16**(2):87–8.

Lindblad 1994 ***{published data only}***
Lindblad B, Bergqvist D, Wakefield TW, Stanley JC. Time-related anticoagulation after regional and systemic administration of heparin in patients undergoing aortoiliac surgery. *European Journal of Vascular Surgery* 1994;**8**(5): 574–7.

Lok 2007 ***{published data only}***
Lok CE, Appleton D, Bhola C, Khoo B, Richardson RMA. Trisodium citrate 4%-an alternative to heparin capping of haemodialysis catheters. *Nephrology Dialysis Transplantation* 2007;**22**(2):477–83.

Lombardi 1988 ***{published data only}***
Lombardi TP, Gundersen B, Zammett LO, Walters JK, Morris BA. Efficacy of 0.9% sodium chloride injection with or without heparin sodium for maintaining patency of intravenous catheters in children. *Clinical Pharmacy* 1988;**7** (11):832–6.

Long 2006 ***{published data only}***
Long DA, Coulthard MG. Effect of heparin-bonded central venous catheters on the incidence of catheter-related thrombosis and infection in children and adults. *Anaesthesia and Intensive Care* 2006;**34**(4):481–4.

Lustig 2011 ***{published data only}***
Lustig A, Aflalu S. Novel catheter lock solution in prevention of hemodialysis catheter complications. *Journal of Clinical Pharmacology* 2011;**51**(9):1342.

Macrae 2008 ***{published data only}***
Macrae JM, Dojcinovic I, Djurdjev O, Jung B, Shalansky S, Levin A, Kiaii M. Citrate 4% versus heparin and the reduction of thrombosis study (CHARTS). *Clinical Journal of the American Society of Nephrology* 2008;**3**(2):369–74.

Maki 2011 ***{published data only}***
Maki DG, Ash SR, Winger RK, Lavin P, AZEPTIC Trial Investigators. A novel antimicrobial and antithrombotic lock solution for hemodialysis catheters: a multi-center, controlled,randomized trial. *Critical Care Medicine* 2011; **39**(4):613–20.

Male 2005 ***{published data only}***
Male C, Julian JA, Massicotte P, Gent M, Mitchell L, PROTEKT Study Group. Significant association with location of central venous line placement and risk of venous thrombosis in children. *Thrombosis and Haemostasis* 2005; **94**(3):516–21.

Malo 2010 ***{published data only}***
Malo J, Jolicoeur C, Theriault F, Lachaine J, Senecal L. Comparison between standard heparin and tinzaparin for haemodialysis catheter lock. *ASAIO Journal (American Society for Artificial Internal Organs)* 2010;**56**(1):42–7.

Marin 2000 ***{published data only}***
Marin MG, Lee JC, Skurnick JH. Prevention of nosocomial bloodstream infections: effectiveness of antimicrobial-impregnated and heparin-bonded central venous catheters. *Critical Care Medicine* 2000;**28**(9):3332–8.

Martin 2009 ***{published data only}***
Martin JM. Ethanol lock therapy for the prevention of catheter related blood stream infections. http:/ /clinicaltrials.gov/ct2/show/NCT00948441?term= Pediatric+Ethanol+Lock+Therapy+Study&rank=1 (accessed 6 October 2014) 2009.

Masroujeh 2008 ***{published data only}***
Masroujeh R, Shamseddeen W, Isma'eel H, Otrock ZK, Khalil IM, Taher A. Underutilization of venous thromboembolism prophylaxis in medical patients in a tertiary care center. *Journal of Thrombosis and Thrombolysis* 2008;**26**(2):138–41.

Massicotte 1996 ***{published data only}***
Massicotte P, Adams M, Marzinotto V, Brooker LA, Andrew M. Low-molecular-weight heparin in pediatric patients with thrombotic disease: a dose finding study. *Journal of Pediatrics* 1996;**128**(3):313–8.

Massicotte 2003 ***{published data only}***
Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtman B, et al.PROTEKT Study Group. An open-label randomized controlled trial of low molecular weight heparin for the prevention of central venous line-related thrombotic complications in children: the PROTEKT trial. *Thrombosis Research* 2003;**109**(2-3):101–8.

Mayo 1996 ***{published data only}***
Mayo DJ, Dimond EP, Kramer W, Horne MK III. Discard volumes necessary for clinically useful coagulation studies from heparinized Hickman catheters. *Oncology Nursing Forum* 1996;**23**(4):671–5.

McIntyre 2004 ***{published data only}***
McIntyre CW, Hulme LJ, Taal M, Fluck RJ. Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney International* 2004;**66**(2):801–5.

McMullen 1993 ***{published data only}***
McMullen A, Fioravanti ID, Pollack V, Rideout K, Sciera M. Heparinized saline or normal saline as a flush solution in intermittent intravenous lines in infants and children. *MCN: The American Journal of Maternal Child Nursing* 1993;**18**(2):78–85.

Meier 2011 ***{published data only}***
Meier P, Meier R, Turini P, Friolet R, Blanc E. Prolonged catheter survival in patients with acute kidney injury on continuous renal replacement therapy using a less thrombogenic micropatterned polymer modification. *Nephrology Dialysis Transplantation* 2011;**26**(2):628–35.

Mendarte 1997 ***{published data only}***
Mendarte L, Aguas M, Pons M, Torres MD. Use of sodium heparin vs physiological serum in permeability of peripheral vias. *Farmacia Hospitalaria* 1997;**21**(4):222–6.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Meyer 1995 *{published data only}*
Meyer BA, Little CJ, Thorp JA, Cohen GR, Yeast JD. Heparin versus normal saline as a peripheral line flush in maintenance of intermittent intravenous lines in obstetric patients. *Obstetrics and Gynecology* 1995;**85**(3):433–6.

Meyer 2010 *{published data only}*
Meyer AD, Jacobs BR. Prevention of catheter-related thrombosis after cardiac surgery: is heparin the answer?. *Pediatric Critical Care Medicine* 2010;**11**(4):531–2.

Mismetti 2003 *{published data only}*
Mismetti P, Mille D, Laporte S, Charlet V, Buchmuller-Cordier A, Jacquin JP, et al.CIP Study Group. Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial. *Haematologica* 2003;**88**(1):67–73.

Mitchell 2003 *{published data only}*
Mitchell L, Andrew M, Hanna K, Abshire T, Halton J, Wu J, et al.Trend to efficacy and safety using antithrombin concentrate in prevention of thrombosis in children receiving l-asparaginase for acute lymphoblastic leukemia: Results of the PARKAA study. *Thrombosis and Haemostasis* 2003;**90**(2):235–44.

Mok 2007 *{published data only}*
Mok E, Kwong TK, Chan MF. A randomized controlled trial for maintaining peripheral intravenous lock in children. *International Journal of Nursing Practice* 2007;**13**(1):33–45.

Monreal 1996 *{published data only}*
Monreal M, Alastrue A, Rull M, Mira X, Muxart J, Rosell R, et al.Upper extremity deep venous thrombosis in cancer patients with venous access devices--prophylaxis with a low molecular weight heparin (Fragmin). *Thrombosis and Haemostasis* 1996;**75**(2):251–3.

Moran 2012 *{published data only}*
Moran J, Sun S, Khababa I, Pedan A, Doss S, Schiller B. A randomized trial comparing gentamicin/citrate and heparin locks for central venous catheters in maintenance hemodialysis patients. *American Journal of Kidney Diseases* 2012;**59**(1):102–7.

Mortazavi 2011 *{published data only}*
Mortazavi M, Alsaeidi S, Sobhani R, Salimi F, Atapour A, Sharif N, et al.Succesful prevention of tunneled, central catheter infection by antibiotic lock therapy using cefotaxime. *Journal of Research in Medical Sciences* 2011;**16**(3):303–9.

Mudge 1998 *{published data only}*
Mudge B, Forcier D, Slattery MJ. Patency of 24-gauge peripheral intermittent infusion devices: a comparison of heparin and saline flush solutions. *Pediatric Nursing* 1998;**24**(2):142-5, 149.

Myrianthefs 2005 *{published data only}*
Myrianthefs P, Sifaki M, Samara I, Baltopoulos G. The epidemiology of peripheral vein complications: evaluation of the efficiency of differing methods for the maintenance of catheter patency and thrombophlebitis prevention. *Journal of Evaluation in Clinical Practice* 2005;**11**(1):85–9.

Na 2012 *{published data only}*
Na HS. Influence by heparinized flush solution of the radial artery catheter: INTEM and HEPTEM analysis. http://clinicaltrials.gov/ct2/show/NCT01522846?term=Heparin+Solution+and+INTEM%2FHEPTEM+Analysis&rank=1 (accessed 6 October 2014) 2012.

Niers 2007 *{published data only}*
Niers TMH, Di Nisio M, Klerk CPW, Baarslag HJ, Buller HR, Biemond BJ. Prevention of catheter-related venous thrombosis with nadroparin in patients receiving chemotherapy for hematologic malignancies: a randomized, placebo-controlled study. *Journal of Thrombosis and Haemostasis* 2007;**5**(9):1878–82.

Niesen 2003 *{published data only}*
Niesen KM, Harris DY, Parkin LS, Henn LT. The effects of heparin versus normal saline for maintenance of peripheral intravenous locks in pregnant women. *Journal of Obstetric Gynecologic and Neonatal Nursing* 2003;**32**(4):503–8.

Nieto-Rodriguez 1992 *{published data only}*
Nieto-Rodriguez JA, Garcia-Martin MA, Barreda-Hernandez MD, Hervas MJ, Cano-Real O. Heparin and infusion phlebitis: a prospective study. *Annals of Pharmacotherapy* 1992;**26**(10):1211–4.

NIH Clinical Centers 2002 *{published data only}*
NIH Clinical Centers. Heparin vs. lepirudin flushes in preventing withdrawal occlusion of tunneled, open-ended venous access devices: a blinded, randomized, clinical trial. http://clinicaltrials.gov/ct2/show/NCT00039767?term=Heparin+Versus+Lepirudin+Flushes+in+Preventing+Blockage+of+Venous+Access+Devices&rank=1 (accessed 6 October 2014) 2002.

Nori 2006 *{published data only}*
Nori US, Manoharan A, Yee J, Besarab A. Comparison of low-dose gentamicin with minocycline as catheter lock solutions in the prevention of catheter-related bacteremia. *American Journal of Kidney Diseases* 2006;**48**(4):596–605.

Ociepa 2010 *{published data only}*
Ociepa T, Maloney E, Urasinski T, Sawicki M. Thrombotic complications of tunneled central lines in children with malignancy. *Journal of Pediatric Hematology/Oncology* 2010;**32**(2):88–92.

Oguzhan 2012 *{published data only}*
Oguzhan N, Pala C, Sipahioglu MH, Cilan H, Durmaz S, Percin D, et al.Locking tunneled hemodialysis catheters with hypertonic saline (26% NaCl) and heparin to prevent catheter-related bloodstream infections and thrombosis: a randomised, prospective trial. *Renal Failure* 2012;**34**(2):181–8.

Ojala 2007 *{published data only}*
Ojala TH, Lehtonen L. A preliminary report-heparin counteracts indomethacin effect on ductus arteriosus in very low birthweight infants. *Pediatric Critical Care Medicine* 2007;**8**(3):258–60.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Onder 2009 *{published data only}*
Onder AM, Chandar J, Billings A, Simon N, Gonzalez J, Francoeur D, et al.Prophylaxis of catheter-related bacteremia using tissue plasminogen activator-tobramycin locks. *Pediatric Nephrology* 2009;**24**(11):2233–43.

Oran 2008 *{published data only}*
Oran NT, Eser I. Impact of heparin locking frequency on preventing temporary dialysis catheter dysfunction in haemodialysis patients. *Journal of Renal Care* 2008;**34**(4): 199–202.

Paisley 1997 *{published data only}*
Paisley MK, Stamper M, Brown J, Brown N, Ganong LH. The use of heparin and normal saline flushes in neonatal intravenous catheters. *Pediatric Nursing* 1997;**23**(5):521-4, 527.

Periard 2008 *{published data only}*
Periard D, Monney P, Waeber G, Zurkinden C, Mazzolai L, Hayoz D, et al.Randomized controlled trial of peripherally inserted central catheters vs. peripheral catheters for middle duration in-hospital intravenous therapy. *Journal of Thrombosis and Haemostasis* 2008;**6**(8):1281–8.

Pervez 2002 *{published data only}*
Pervez A, Ahmed M, Ram S, Torres C, Work J, Zaman F, et al.Antibiotic lock technique for prevention of cuffed tunnel catheter associated bacteremia. *Journal of Vascular Access* 2002;**3**(3):108–13.

Petersen 2001 *{published data only}*
Petersen C. Clinical issues. Heparin v saline locks; "hosing"; reading in the OR; sterility of dropped packages; trays as prep table covers. *AORN Journal* 2001;**74**(6):900–3.

Pierce 2000 *{published data only}*
Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Medicine* 2000;**26** (7):967–72.

Pouw 1995 *{published data only}*
Pouw L, Kilsby D, Francis P, Tulloh B. Heparin thromboprophylaxis via indwelling subcutaneous teflon cannula. *Australian and New Zeland Journal of Surgery* 1995;**65**(11):793–5.

Power 2009 *{published data only}*
Power A, Duncan N, Singh SK, Brown W, Dalby E, Edwards C, et al.Sodium citrate versus heparin catheter locks for cuffed central venous catheters: a single-center randomized controlled trial. *American Journal of Kidney Diseases* 2009;**53**(6):1034–41.

Powers 1999 *{published data only}*
Powers JM. Obtaining blood samples for coagulation studies from a normal saline lock. *American Journal of Critical Care* 1999;**8**(4):250–3.

Pucheu 1996 *{published data only}*
Pucheu A, Leduc B, Sillet-Bach I, Payen C, Assaf W, Pucheu M. Experimental prevention of deep venous thrombosis with low-molecular-weight heparin using implantable infusion devices [Prevention experimental de la thrombose veineuse profonde avec de l'heparine de bas poids moleculaire en usant dispositifs d'infusion implantables]. *Annales de Cardiologie et d Angeiologie* 1996;**45**(2):59–63.

Puiggros 2012 *{published data only}*
Puiggròs C, Cuerda C, Virgili N, Chicharro ML, Martínez C, Garde C, Grupo NADYA-SENPE. Catheter occlusion and venous thrombosis prevention and incidence in adult home parenteral nutrition (HPN) programme patients [Prevención e incidencia de oclusión del catéter y trombosis venosa en pacientes adultos con nutrición parenteral domiciliaria (NPD)]. *Nutricion Hospitalaria* 2012;**27**(1): 256–61.

Quenot 2013 *{published data only}*
Quenot JP. Citrate versus heparin for the lock of non-tunneled hemodialysis catheters in patients hospitalised in ICU. Multicentre, controlled, randomised superiority trial. http://clinicaltrials.gov/ct2/show/NCT01962116?term=Citrate+Versus+Heparin+for+the+Lock+of+Non-tunneled+Hemodialysis+Catheters+in+Patients+Hospitalised+in+ICU&rank=1 (accessed 6 October 2014) 2013.

Rackoff 1995 *{published data only}*
Rackoff WR, Weiman M, Jakobowski D, Hirschl R, Stallings V, Bilodeau J, et al.A randomized, controlled trial of the efficacy of a heparin and vancomycin solution in preventing central venous catheter infections in children. *Journal of Pediatrics* 1995;**127**(1):147–51.

Rajani 1979 *{published data only}*
Rajani K, Goetzman BW, Wennberg RP, Turner E, Abildgaard C. Effect of heparinization of fluids infused through an umbilical artery catheter on catheter patency and frequency of complications. *Pediatrics* 1979;**63**(4): 552–6.

Randon 2006 *{published data only}*
Randon C. Prospective study which compares the use of a closing system without a needle and with positive pressure to a heparin lock with positive pressure for patients with a catheter for chemotherapy. http://clinicaltrials.gov/ct2/show/NCT00386451?term=Comparing+a+Closing+System+Without+a+Needle+With+Positive+Pressure+to+a+Heparin+L
rank=1 (accessed 6 October 2014) 2006.

Rao 1981 *{published data only}*
Rao PS, Thapar MK, Rogers JH, Jr, Strong WB, Lutcher CL, Nesbit RR, Jr, et al.Effect of intraarterial injection of heparin on the complications of percutaneous arterial catheterization in infants and children. *Catheterization and Cardiovascular Diagnosis* 1981;**7**(3):235–46.

Ray 1999 *{published data only}*
Ray CE Jr, Shenoy SS, McCarthy PL, Broderick KA, Kaufman JA. Weekly prophylactic urokinase instillation in tunneled central venous access devices. *Journal of Vascular and Interventional Radiology* 1999;**10**(10):1330–4.

Reeves 2009 *{published data only}*
Reeves AM. Comparison of heparin vs. no heparin on duration of peripherally inserted central catheter patency in neonates. http://clinicaltrials.gov/ct2/show/NCT00879957?term=Hep-

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

arin+Versus+no+Heparin+on+Duration+of+Peripherally+Inserted+Central+Catheters&rank=1 (accessed 6 October 2014) 2009.

Reichardt 2002 *{published data only}*
Reichardt P, Kretzschmar A, Biakhov M, Irwin D, Slabber C, Miller L, et al.A phase III double-blind, placebo-controlled study evaluating the efficacy and safety of daily low-molecular-weight heparin (dalteparin sodium, Fragmin) in preventing catheter-related complications in cancer patients with central venous catheters [abstract]. Journal of Clinical Oncology 2002; Vol. 21 (Suppl):703a, Abstract 1474.

Renaud 2009 *{published data only}*
Renaud CJ, Serret D, Sinon E. Antimicrobial locks in tunneled hemodialysis catheters: from clinical trials to clinical practice. *Hemodialysis International* 2009;**13**(3): 375.

Rijnders 2005 *{published data only}*
Rijnders BJ, Van WE, Vandecasteele SJ, Stas M, Peetermans WE. Treatment of long-term intravascular catheter-related bacteraemia with antibiotic lock: randomized, placebo-controlled trial. *Journal of Antimicrobial Chemotherapy* 2005;**55**(1):90–4.

Roberts 1994 *{published data only}*
Roberts GW, Holmes MD, Staugas RE, Day RA, Finlay CF, Pitcher A. Peripheral intravenous line survival and phlebitis prevention in patients receiving intravenous antibiotics: heparin/hydrocortisone versus in-line filters. *Annals of Pharmacotherapy* 1994;**28**(1):11–6.

Robertson 1994 *{published data only}*
Robertson J. Intermittent intravenous therapy: a comparison of two flushing solutions. *Contemporary Nurse* 1994;**3**(4):174–9.

Robinson 2009 *{published data only}*
Robinson M, Healey JS, Eikelboom J, Schulman S, Morillo CA, Nair GM, et al.Postoperative low-molecular-weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. *Pacing and Clinical Electrophysiology* 2009;**32**(3):378–82.

Ruggiero 1983 *{published data only}*
Ruggiero RP, Aisenstein TJ. Central catheter fibrin sleeve-heparin effect. *JPEN Journal of Parenteral and Enteral Nutrition* 1983;**7**(3):270–3.

Sahin Balcik 2011 *{published data only}*
Sahin Balcik O, Akkaya C, Uz B, Aksoy C, Guvenc B, Dincer S. The efficacy and safety of hypertonic citrate as catheter-locking solution in hematopoietic stem cell transplant recipients [Hipertonik Sitrat›n Hematopoetik Kök Hücre Transplant Alıcılarında Kateter Kapatma Solüsyonu Olarak Etkinlik ve Güvenirliği]. *Turkiye Klinikleri Journal of Cardiovascular Sciences* 2011;**23**(1): 48–53.

Sanders 2008 *{published data only}*
Sanders J, Pithie A, Ganly P, Surgenor L, Wilson R, Merriman E, Loudon G, Judkins R, Chambers S. A prospective double-blind randomized trial comparing intraluminal ethanol with heparinized saline for the prevention of catheter-associated bloodstream infection in immunosuppressed haematology patients. *Journal of Antimicrobial Chemotherapy* 2008;**62**(4):809–15.

Sang Sook 2012 *{published data only}*
Sang Sook H, Jee Eun P, Nam Eun K, Hwa Ja K. Effects of normal saline for maintenance of arterial lines of surgical patients. *Journal of Korean Academy of Nursing* 2012;**42**(6): 791–8.

Saxena 2005 *{published data only}*
Saxena AK, Panhotra BR. The impact of catheter-restricted filling with cefotaxime and heparin on the lifespan of temporary hemodialysis catheters: a case controlled study. *Journal of Nephrology* 2005;**18**(6):755–63.

Saxena 2006 *{published data only}*
Saxena AK, Panhotra BR, Sundaram DS, Al-Hafiz A, Naguib M, Venkateshappa CK, et al.Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement. *Kidney International* 2006;**70**(9): 1629–35.

Saxena 2006a *{published data only}*
Saxena AK, Panhotra BR, Sundaram DS, Morsy MN, Al-Ghamdi AM. Enhancing the survival of tunneled haemodialysis catheters using an antibiotic lock in the elderly: a randomised, double-blind clinical trial. *Nephrology* 2006;**11**(4):299–305.

Scherr 2002 *{published data only}*
Scherr K, Guenther C, Koshal A, Finegan B. Effects of heparinized vs nonheparinized flush solutions on patency of arterial and central pressure monitoring lines in the postoperative cardiac surgical patient. *American Journal of Critical Care* 2002;**11**(3):277.

Schilling 2006 *{published data only}*
Schilling S, Doellman D, Hutchinson N, Jacobs BR. The impact of needleless connector device design on central venous catheter occlusion in children: a prospective, controlled trial. *JPEN Journal of Parenteral and Enteral Nutrition* 2006;**30**(2):85–90.

Schouten 2013 *{published data only}*
Schouten H. Concentrated citrate locking to reduce the incidence of central venous catheter-related infections and thrombosis: a randomized phase III study in a hematological patient population. http://clinicaltrials.gov/ct2/show/NCT01820962?term=Concentrated+Citrate+Locking+to+Reduce+the+Incidence+of+CVC-related+Complications+in+Hematological+Patients&rank=1 (accessed 6 October 2014) 2013.

Schroder 2008 *{published data only}*
Schroder H. A randomised study of taurolock for the locking of tunneled central venous catheters in children with malignant diseases. http://clinicaltrials.gov/ct2/show/NCT00735813?term=Tauroli-

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

dine+Lock+Solution+in+the+Prevention+of+Catheter+Related+Bacteremia&infections in patients undergoing hemodialysis: a clinical rank=1 (accessed 6 October 2014) 2008.

Schroeder 2010 *{published data only}*
Schroeder AR, Axelrod DM, Silverman NH, Rubesova E, Merkel E, Roth SJ. A continuous heparin infusion does not prevent catheter-related thrombosis in infants after cardiac surgery. *Pediatric Critical Care Medicine* 2010;**11**(4):489–95.

Schultz 2002 *{published data only}*
Schultz AA, Drew D, Hewitt H. Comparison of normal saline and heparinized saline for patency of IV locks in neonates. *Applied Nursing Research* 2002;**15**(1):28–34.

Schwartz 1990 *{published data only}*
Schwartz C, Henrickson KJ, Roghmann K, Powell K. Prevention of bacteremia attributed to luminal colonization of tunneled central venous catheters with vancomycin-susceptible organisms. *Journal of Clinical Oncology* 1990;**8**(9):1591–7.

Seguin 1994 *{published data only}*
Seguin J, Fletcher MA, Landers S, Brown D, Macpherson T. Umbilical venous catheterizations: audit by the Study Group for Complications of Perinatal Care. *American Journal of Perinatology* 1994;**11**(1):67–70.

Seliem 2010 *{published data only}*
Seliem W, Abdel-Hady H, El-Nady G. Amikacin-heparin lock for prevention of catheter-related bloodstream infection in neonates with extended umbilical venous catheters use: a randomized controlled trial. *Journal of Neonatal-Perinatal Medicine* 2010;**3**(1):33–41.

Serrano 2009 *{published data only}*
Serrano Ruiz A, Saboya Sánchez S, Latorre Marco I, Bragado León M, Cabrerizo Osorio E, Solis Muñoz M, et al.Efficacy of a sealing solution with saline solution at 0, 9% versus heparin to maintain permeability of a central venous catheter at the ICU [Eficacia de una solución de sellado con suero salino al 0,9% versus heparina sobre la permeabilidad del catéter venoso central no permanente en pacientes críticos]. *Educare21* 2009;**53**(7):http://www.enfermeria21.com/publicaciones/educare (accessed May 2012).

Shah 2007a *{published data only}*
Shah PS, Kalyn A, Satodia P, Dunn MS, Parvez B, Daneman A, et al.A randomized, controlled trial of heparin versus placebo infusion to prolong the usability of peripherally placed percutaneous central venous catheters (PCVCs) in neonates: the HIP (Heparin Infusion for PCVC) study. *Pediatrics* 2007;**119**(1):e284–91.

Shen 2013 *{published data only}*
Shen J, Montez-Rath M, Mitani A, Winkelmayer W. Correlates of and variation in heparin dosage for maintenance hemodialysis in older U.S. patients. *American Journal of Kidney Diseases* 2013;**61**(4):A89.

Shirzad 2013 *{published data only}*
Shirzad M, Espahbodi F, Baboli MT, Samakoosh MA, Khalilian A. Effects of heparin lock-antibiotics to prevent trial. *Journal of Mazandaran University of Medical Sciences* 2013;**22**(96):99–104.

Shively 1997 *{published data only}*
Shively M, Riegel B, Waterhouse D, Burns D, Templin K, Thomason T. Testing a community level research utilization intervention. *Applied Nursing Research: ANR* 1997;**10**(3):121–7.

Shoaf 1992 *{published data only}*
Shoaf J, Oliver S. Efficacy of normal saline injection with and without heparin for maintaining intermittent intravenous site. *Applied Nursing Research* 1992;**5**(1):9–12.

Sierra 2010 *{published data only}*
Sierra Diaz R. Sealing catheters with gelafundin compared to sodium heparin [Sellado de catéteres con gelafundina versus heparina sódica]. *Revista de la Sociedad Española de Enfermeria Nefrologica* 2010;**13**(4):242–5.

Silva 2008 *{published data only}*
Silva J, Teixeira e Costa, Baptista A, Ramos A, Ponce P. Catheter-related bacteremia in hemodialysis: which preventive measures to take?. *Nephron* 2008;**110**(4):251–7.

Silva 2013 *{published data only}*
Silva TNV, Mendes ML, Abrao JMG, Caramori JT, Ponce D. Successful prevention of tunneled central catheter infection by antibiotic lock therapy using cefazolin and gentamicin. *International Urology and Nephrology* 2013;**45**(5):1405–13.

Skofic 2009 *{published data only}*
Skofic N, Buturovic-Ponikvar J, Kovac J, Premru V, Knap B, Pernat AM, et al.Hemodialysis catheters with citrate locking in critically ill patients with acute kidney injury treated with intermittent online hemofiltration or hemodialysis. *Therapeutic Apheresis and Dialysis* 2009;**13**(4):327–33.

Smith 1990 *{published data only}*
Smith I, Hathaway M, Goldman C, Ng J, Brunton J, Simor AE, et al.A randomized study to determine complications associated with duration of insertion of heparin locks. *Research in Nursing and Health* 1990;**13**(6):367–73.

Smith 1991 *{published data only}*
Smith S, Dawson S, Hennessey R, Andrew M. Maintenance of the patency of indwelling central venous catheters: is heparin necessary?. *American Journal of Pediatric Hematology/Oncology* 1991;**13**(2):141–3.

Sofroniadou 2012 *{published data only}*
Sofroniadou S, Revela I, Smirloglou D, Makriniotou I, Zerbala S, Kouloubinis A, et al.Linezolid versus vancomycin antibiotic lock solution for the prevention of nontunneled catheter-related blood stream infections in hemodialysis patients: a prospective randomized study. *Seminars in Dialysis* 2012;**25**(3):344–50.

Solomon 2001 *{published data only}*
Solomon B, Moore J, Arthur C, Prince HM. Lack of efficacy of twice-weekly urokinase in the prevention of complications associated with Hickman catheters: a

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

multicentre randomised comparison of urokinase versus heparin. *European Journal of Cancer* 2001;**37**(18):2379–84.

Solomon 2010 ***{published data only}***
Solomon LR, Cheesbrough JS, Ebah L, Al-Sayed T, Heap M, Millband N, et al.A randomized double-blind controlled trial of taurolidine-citrate catheter locks for the prevention of bacteremia in patients treated with hemodialysis. *American Journal of Kidney Diseases* 2010;**55**(6):1060–8.

Solomon 2012 ***{published data only}***
Solomon LR, Cheesbrough JS, Bhargava R, Mitsides N, Heap M, Green G, et al.Observational study of need for thrombolytic therapy and incidence of bacteremia using taurolidine-citrate-heparin, taurolidine-citrate and heparin catheter locks in patients treated with hemodialysis. *Seminars in Dialysis* 2012;**25**(2):233–8.

Sona 2012 ***{published data only}***
Sona C, Prentice D, Schallom L. National survey of central venous catheter flushing in the intensive care unit. *Critical Care Nurse* 2012;**32**(1):e12–9.

Stas 2001 ***{published data only}***
Stas KJF, Vanwalleghem J, De MB, Keuleers H. Trisodium citrate 30% vs heparin 5% as catheter lock in the interdialytic period in twin- or double-lumen dialysis catheters for intermittent haemodialysis. *Nephrology Dialysis Transplantation* 2001;**16**(7):1521–2.

Steczko 2009 ***{published data only}***
Steczko J, Ash SR, Nivens DE, Brewer L, Winger RK. Microbial inactivation properties of a new antimicrobial/antithrombotic catheter lock solution (citrate/methylene blue/parabens). *Nephrology Dialysis Transplantation* 2009;**24**(6):1937–45.

Stephens 1997 ***{published data only}***
Stephens LC, Haire WD, Tarantolo S, Reed E, Schmit-Pokorny K, Kessinger A, et al.Normal saline versus heparin flush for maintaining central venous catheter patency during apheresis collection of peripheral blood stem cells (PBSC). *Transfusional Science* 1997;**18**(2):187–93.

Taylor 1989 ***{published data only}***
Taylor J, Shannon R, Kilbride HW. Heparin lock intravenous line. Use in newborn infants. *Clinical Pediatrics* 1989;**28**(5):237–40.

Thomson 2011 ***{published data only}***
Thomson PC, Morris ST, Mactier RA. The effect of heparinized catheter lock solutions on systemic anticoagulation in hemodialysis patients. *Clinical Nephrology* 2011;**75**(3):212–7.

Thurlimann 1992 ***{published data only}***
Thurlimann B, Bachmann I. Effective prevention of chemotherapy-induced phlebitis by low-dose heparin: a prospective randomised trial. *Annals of Oncology* 1992;**3**(4):311–3.

Tolar 1996 ***{published data only}***
Tolar B, Gould JR. The timing and sequence of multiple device-related complications in patients with long-term indwelling Groshong catheters. *Cancer* 1996;**78**(6):1308–13.

Treas 1992 ***{published data only}***
Treas LS, Latinis-Bridges B. Efficacy of heparin in peripheral venous infusion in neonates. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 1992;**21**(3):214–9.

Trivedi 1997 ***{published data only}***
Trivedi HS, Twardowski ZJ. Use of double-lumen dialysis catheters. Loading with locked heparin. *ASAIO Journal (American Society for Artificial Internal Organs)* 1997;**43**(6):900–3.

Trottier 1995 ***{published data only}***
Trottier SJ, Veremakis C, O'Brien J, Auer AI. Femoral deep vein thrombosis associated with central venous catheterization: results from a prospective, randomized trial. *Critical Care Medicine* 1995;**23**(1):52–9.

Tuncali 2005 ***{published data only}***
Tuncali BE, Kuvaki B, Tuncali B, Capar E. A comparison of the efficacy of heparinized and nonheparinized solutions for maintenance of perioperative radial arterial catheter patency and subsequent occlusion. *Anesthesia and Analgesia* 2005;**100**(4):1117–21.

Tuten 1991 ***{published data only}***
Tuten SH, Gueldner SH. Efficacy of sodium chloride versus dilute heparin for maintenance of peripheral intermittent intravenous devices. *Applied Nursing Research* 1991;**4**(2):63–71.

Unal 2012 ***{published data only}***
Unal S, Ekici F, Cetin II, Bilgin L. Heparin infusion to prevent umbilical venous catheter related thrombosis in neonates. *Thrombosis Research* 2012;**130**(5):725–8.

Uslu 2010 ***{published data only}***
Uslu S, Ozdemir H, Comert S, Bolat F, Nuhoglu A. The effect of low-dose heparin on maintaining peripherally inserted percutaneous central venous catheters in neonates. *Journal of Perinatology* 2010;**30**(12):794–9.

Van Rooden 2004 ***{published data only}***
Van Rooden CJ, Rosendaal FR, Meinders AE, Van Oostayen JA, Van Der Meer FJ, Huisman MV. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. *Haematologica* 2004;**89**(2):201–6.

Vegting 2012 ***{published data only}***
Vegting IL, Tabbers MM, Benninga MA, Wilde JC, Serlie MJ, Tas TA, et al.Prophylactic anticoagulation decreases catheter-related thrombosis and occlusion in children with home parenteral nutrition. *JPEN Journal of Parenteral and Enteral Nutrition* 2012;**36**(4):456–62.

Venditto 2010 ***{published data only}***
Venditto M, du Montcel ST, Robert J, Trystam D, Dighiero J, Hue D, et al.Effect of catheter-lock solutions on catheter-related infection and inflammatory syndrome in hemodialysis patients: heparin versus citrate 46% versus heparin/gentamicin. *Blood Purification* 2010;**29**(3):268–73.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Vercaigne 2011 *{published data only}*
Vercaigne L. Efficacy and safety of an ethanol/sodium citrate locking solution to prevent hemodialysis catheter-related infections: a pilot study. http://clinicaltrials.gov/ct2/show/NCT01394458?term=Efficacy+and+Safety+of+an+Ethanol%2FSodium+Citrate+Locking+Solution%3A+A+Pilot+Study&rank=1 (accessed 6 October 2014) 2011.

Verso 2005 *{published data only}*
Verso M, Agnelli G, Bertoglio S, Di Somma FC, Paoletti F, Ageno W, et al.Enoxaparin for the prevention of venous thromboembolism associated with central vein catheter: a double-blind, placebo-controlled, randomized study in cancer patients. *Journal of Clinical Oncology* 2005;**23**(18): 4057–62.

Verso 2008 *{published data only}*
Verso M, Agnelli G, Kamphuisen PW, Ageno W, Bazzan M, Lazzaro A, et al.Risk factors for upper limb deep vein thrombosis associated with the use of central vein catheter in cancer patients. *Internal and Emergency Medicine* 2008;**3** (2):117–22.

Vertrees 2001 *{published data only}*
Vertrees RA, Zwischenberger JB, Woodson LC, Bedell EA, Deyo DJ, Chernin JM. Veno-venous perfusion-induced systemic hyperthermia: case report with perfusion considerations. *Perfusion* 2001;**16**(3):243–8.

Wan 2012 *{published data only}*
Wan XL, Zeng LN. Heparin added in total nutrient admixture for preventing peripherally inserted central catheter occlusion in neonate: A case report. *Chinese Journal of Evidence-Based Medicine* 2012;**12**(10):1275–8.

Wang 2012 *{published data only}*
Wang R, Luo O, He L, Li JX, Zhang MG. Preservative-free 0.9% sodium chloride for flushing and locking peripheral intravenous access device: a prospective controlled trial. *Journal of Evidence-Based Medicine* 2012;**5**(4):205–8.

Warkentin 1998 *{published data only}*
Warkentin TE, Ling E, Ho A, Sheppard JI. 'Incidental' unfractionated heparin (UFH) vs normal saline (NS) flushes for intraoperative invasive catheters and the frequency of formation of heparin induced thrombocytopenia IgG antibodies (HIT-IgG): A randomized controlled trial. *Blood* 1998;**92**(10 Suppl 1 (Pt 2)):91.

Wassenaar 2008 *{published data only}*
Wassenaar T, Black J, Kahl B, Schwartz B, Longo W, Mosher D, et al.Acute promyelocytic leukaemia and acquired alpha-2-plasmin inhibitor deficiency: a retrospective look at the use of epsilon-aminocaproic acid (Amicar) in 30 patients. *Hematological Oncology* 2008;**26**(4):241–6.

Weijmer 2005 *{published data only}*
Weijmer MC, van den Dorpel MA, Van de Ven PJ, ter Wee PM, van Geelen JA, Groeneveld JO, et al.Randomized, clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients. *Journal of the American Society of Nephrology* 2005; **16**(9):2769–77.

White 2011 *{published data only}*
White M, Crawley J, Rennie E, Lewandowski L. Examining the effectiveness of 2 solutions used to flush capped pediatric peripheral intravenous catheters. *Journal of Infusion Nursing* 2011;**34**(4):260–70.

Whitta 2006 *{published data only}*
Whitta RK, Hall KF, Bennetts TM, Welman L, Rawlins P. Comparison of normal or heparinised saline flushing on function of arterial lines. *Critical Care and Resuscitation* 2006;**8**(3):205–8.

Willicombe 2010 *{published data only}*
Willicombe MK, Vernon K, Davenport A. Embolic complications from central venous hemodialysis catheters used with hypertonic citrate locking solution. *American Journal of Kidney Diseases* 2010;**55**(2):348–51.

Winnett 2008 *{published data only}*
Winnett G, Nolan J, Miller M, Ashman N. Trisodium citrate 46.7% selectively and safely reduces staphylococcal catheter-related bacteraemia. *Nephrology Dialysis Transplantation* 2008;**23**(11):3592–8.

Witkovski 2010 *{published data only}*
Witkovski MC. Continuous or intermittent for keeping arterial catheter in children: a randomized clinical trial. http://clinicaltrials.gov/ct2/show/NCT01097031?term=Continuous+or+Intermittent+for+Keeping+Arterial+Catheter+in+Children%3A+A+Randomiz
rank=1 (accessed 6 October 2014) 2010.

Wolf 2011 *{published data only}*
Wolf J. A double-blind, randomized, placebo-controlled trial of ethanol lock therapy for treatment and secondary prophylaxis of central line associated bloodstream infection (CLABSI) in children and adolescents. http://clinicaltrials.gov/ct2/show/NCT01472965?term=Ethanol+Lock+Therapy+for+Treatment+and+Secondary+Prophylaxis+of+Central+Lin
Associated+Bloodstream+Infection&rank=1 (accessed 6 October 2014) 2011.

Wolley 2010 *{published data only}*
Wolley M, Freeman J, Zoysa DJ, Wei J. Antimicrobial locks in a dialysis unit: reduction in gram negative catheterassociated bloodstream infection without significant impact on rates of S. Aureus infection. *Nephrology* 2010;**15** (4):35.

Wong 2009 *{published data only}*
Wong FSY, Cheng YL, Chow NY, Cheung ALC, Chau SK, Ngai MS, et al.Effect of 3 different solutions used for locking hemodialysis catheter on systemic coagulation: a randomized study. *Hemodialysis International* 2009;**13**(3): 403.

Wooldridge 1988 *{published data only}*
Wooldridge JB, Jackson JG, Wooldridge JB, Jackson JG. Evaluation of bruises and areas of induration after two techniques of subcutaneous heparin injection. *Heart and Lung* 1988;**17**(5):476–82.

Worly 2004 *{published data only}*
Worly JM, Fortenberry JD, Hansen I, Chambliss CR, Stockwell J. Deep venous thrombosis in children with

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

diabetic ketoacidosis and femoral central venous catheters. *Pediatrics* 2004;**113**(1):e57–e60.

Wright 1995 *{published data only}*
Wright A, Hecker J, McDonald G. Effects of low-dose heparin on failure of intravenous infusions in children. *Heart & Lung* 1995;**24**(1):79–82.

Yevzlin 2007 *{published data only}*
Yevzlin AS, Sanchez RJ, Hiatt JG, Washington MH, Wakeen M, Hofmann RM, et al.Concentrated heparin lock is associated with major bleeding complications after tunneled hemodialysis catheter placement. *Seminars in Dialysis* 2007;**20**(4):351–4.

Yilmaz 2010 *{published data only}*
Yilmaz KB, Akinci M, Dogan L, Yologlu Z, Atalay C, Kulacoglu H. Central venous catheter-associated thrombosis in the perioperative period: a frequent complication in cancer patients that can be detected early with Doppler examination. *Tumori* 2010;**96**(5):690–4.

Yon 2013 *{published data only}*
Yon CK, Low CL. Sodium citrate 4% versus heparin as a lock solution in hemodialysis patients with central venous catheters. *America Journal of Health-System Pharmacy* 2013; **70**(2):131–6.

Young 2009 *{published data only}*
Young AM, Billingham LJ, Begum G, Kerr DJ, Hughes AI, Rea DW, et al.WARP Collaborative Group, UK. Warfarin thromboprophylaxis in cancer patients with central venous catheters (WARP): an open-label randomised trial. *Lancet* 2009;**373**(9663):567–74.

Zacharski 2005 *{published data only}*
Zacharski LR, Prandoni P, Monreal M. Warfarin versus low-molecular-weight heparin therapy in cancer patients. *Oncologist* 2005;**10**(1):72–79.

Zhang 2009 *{published data only}*
Zhang P, Yuan J, Tan HZ, Lv R, Chen JH. Successful prevention of cuffed hemodialysis catheter-related infection using an antibiotic lock technique by strictly catheter-restricted antibiotic lock solution method. *Blood Purification* 2009;**27**(2):206–11.

Additional references

Battistelli 2010
Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. *The American Journal of Surgery* 2010;**199**(1):43–51.

Bern 1990
Bern MM, Lokich JJ, Wallach SR, Bothe A, Benotti PN, Arkin CF, et al.Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. *Annals of Internal Medicine* 1990;**112**(6): 423–8.

Bishop 2009
Bishop L. Aftercare and management of central venous access devices. In: Hamilton H, Bodenham A editor(s). *Central venous catheters*. 1st Edition. Chichester: Wiley & Blackwell, 2009:221–37.

Bradford 2014
Bradford NK, Edwards RM, Chan RJ. Heparin versus 0.9% sodium chloride intermittent flushing for the prevention of occlusion in long term central venous catheters in infants and children. *Cochrane Database of Systematic Reviews* 2014, Issue 2. [DOI: 10.1002/14651858.CD010996]

Burns 2008
Burns KE, McLaren A. A critical review of thromboembolic complications associated with central venous catheters. *Canadian Journal of Anaesthesia* 2008;**55**(8):532–41.

Goode 1991
Goode CJ, Titler M, Rakel B, Ones DS, Kleiber C, Small S, et al.A meta-analysis of effects of heparin flush and saline flush: quality and cost implications. *Nursing Research* 1991; **40**(6):324–30.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altmann DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**(7414):557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Chichester: Cochrane Handbook for Systematic Reviews of Interventions, 2011.

Jacobs 2003
Jacobs BR. Central venous catheter occlusion and thrombosis. *Critical Care Clinics* 2003;**19**(3):489–514..

Klerk 2003
Klerk CPW, Smorenburg SM, Büller HR. Thrombosis prophylaxis in patient populations with a central venous catheter. *Archives of Internal Medicine* 2003;**163**(16): 1913–21.

Lee 2007
Lee DH, Warkentin TE. Frequency of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A editor (s). *Heparin-Induced Thrombocytopenia*. 4th Edition. New York: Informa Healthcare, 2007:67–116.

López-Briz 2005
Lopez-Briz E, Ruiz-Garcia V. Effectiveness of heparin versus NaCl 0,9% in central venous catheter flushing. a systematic review [Heparina frente a cloruro sódico 0,9% para mantener permeables los catéteres venosos centrales. Una revisión sistemática]. *Farmacia Hospitalaria* 2005;**29** (4):258–64.

López-Briz 2010
López-Briz E, Ruiz Garcia V, Cabello JB, Bort-Marti S, Carbonell Sanchis R, Burls A. Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD008462]

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Martel 2005
Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005;**106**(8):2710–5.

McNulty 2005
McNulty I, Katz E, Kim KY. Thrombocytopenia following heparin flush. *Progress in Cardiovascular Nursing* 2005;**20** (4):143–7.

McQuay 1997
McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Annals of Internal Medicine* 1997;**126**(9):712–20.

Mermel 2000
Mermel LA. Prevention of intravascular catheter-related infections. *Annals of Internal Medicine* 2000;**132**(5): 391–402.

Merrer 2001
Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy E, Barre E, et al. French Catheter Study Group in Intensive Care. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA* 2001;**286**(6):700–7.

Mitchell 2009
Mitchell MD, Anderson BJ, Williams K, Umscheid CA. Heparin flushing and other interventions to maintain patency of central venous catheters: a systematic review. *Journal of Advanced Nursing* 2009;**65**(10):2007–21.

Raad 1997
Raad I, Darouiche R, Dupuis J, Abi-Said D, Gabrielli A, Hachem R, et al.Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections. A randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Annals of Internal Medicine* 1997; **127**(4):267–74.

Randolph 1998a
Randolph AG. An evidence-based approach to central venous catheter management to prevent catheter-related infection in critically ill patients. *Critical Care Clinics* 1998; **14**(3):411–21.

Randolph 1998b
Randolph AG, Cook DJ, Gonzales CA, Andrew M. Benefit of heparin in central venous and pulmonary artery catheters: a meta-analysis of randomized controlled trials. *Chest* 1998; **113**(1):165–71..

Shah 2008
Shah PS, Shah VS. Continuous heparin infusion to prevent thrombosis and catheter occlusion in neonates with peripherally placed percutaneous central venous catheters. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD002772.pub3]

Smith 2013
Smith RN. Central venous catheters. *BMJ* 2013;**347**:f6570. [DOI: 10.1136/bmj.f6570]

Valerio 1981
Valerio D, Hussey JK, Smith FW. Central vein thrombosis associated with intravenous feeding-a prospective study. *JPEN Journal of Parenteral and Enteral Nutrition* 1981;**5**(3): 240–2.

Veenstra 1999
Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999;**281**(3):261–7.

Verso 2003
Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *Journal of Clinical Oncology* 2003;**21**(19): 3665–75.

Warkentin 2007
Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A editor (s). *Heparin-Induced Thrombocytopenia*. 4th Edition. New York: Informa Healthcare, 2007:21–66.

* *Indicates the major publication for the study*

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bowers 2008

Methods	Randomised open-label controlled trial
Participants	102 participants with single-lumen peripherally inserted central catheters (PICCs) with luer-activated devices
Interventions	Flushing with: • Heparin 100 IU/mL flushing (3 mL) • 0.9% sodium chloride flushing (10 mL)
Outcomes	Occlusion of PICCs, average duration of catheter
Notes	Follow-up until the first of the following: event (occlusion) or discharge No data on use of systemic anticoagulation, as stated by study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A random block design with concealment was used"
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement. Method of concealment is not described or is not described in sufficient detail to allow a definitive judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label trial, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Other bias	Low risk	Study appears to be free of other sources of bias

Goosens 2013

Methods	Randomised open-label non-inferiority controlled trial
Participants	802 participants older than 1 year with an onco-haematological malignancy
Interventions	Flushing with: • 10 mL 0.9% NaCl and after 3 mL heparin (100 IU/mL) • 10 mL 0.9% NaCl
Outcomes	Primary outcome: withdrawal occlusion at access (i.e. inability to aspirate blood while injection is easy) Secondary outcomes: catheter-related bacteraemia within 180 days, duration of catheter
Notes	Follow-up 180 days Following contact with the trialists, we obtained additional raw data, which have been used in the analysis Use of heparin IV was an exclusion criterion

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation computer generated
Allocation concealment (selection bias)	Low risk	Allocation concealment by means of sequentially numbered participant cards, stored in a separate room
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, but the outcome is categorical (blood aspiration possible or not) and is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, but the outcome is categorical (blood aspiration possible or not) and is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement: no information on number of catheters losing patency in each group

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Goosens 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	All prespecified outcomes of the study were reported in the prespecified way
Other bias	Unclear risk	No separate analyses for children (3.5%) and adults. Not enough information to permit judgement of other bias

Kaneko 2004

Methods	Randomised open-label controlled trial
Participants	48 participants under haemodialysis with double-lumen central venous catheter
Interventions	Flushing with: • 20 mL 0.9% NaCL+ 2 mL heparin 1000 IU/mL lock • 20 mL 0.9% NaCl
Outcomes	Thrombotic occlusion, catheter survival, catheter patency time, haematological and coagulation markers, safety
Notes	Low molecular weight heparin (dalteparin, parnaparin or reviparin) was used during each haemodialysis session Follow-up not clearly reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information about sequence generation process insufficient to permit judgement
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kaneko 2004 (*Continued*)

Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study appears to be free of other sources of bias

Pumarola 2007

Methods	Randomised blinded controlled trial
Participants	250 patients in intensive care unit (ICU) with 3-lumen central venous catheter
Interventions	Flushing with: • 5 mL 0.9% NaCl • 5 mL heparin 20 IU/mL
Outcomes	Catheter patency at 24 hours, at 72 hours and at discharge from ICU (mean 4.74, SD 5)
Notes	2-Phase trial: In the first phase, 2 different dosages of heparin were compared; in the second phase, heparin was compared with 0.9% NaCl Follow-up until first of the following: event (occlusion) or discharge Systemic anticoagulant use was exclusion criterion

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation computer generated (software Aleator®)
Allocation concealment (selection bias)	Unclear risk	Information was insufficient to permit judgement. Method of concealment is not described or is not described in sufficient detail to allow a definitive judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label trial, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Pumarola 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	High risk	Study may be underpowered: Only 38 and 57 participants per group were analysed, but predetermined sample size was 185 participants per group. Study was stopped early in 74 participants pertaining to the heparin group and in 52 participants pertaining to the 0.9% NaCl group

Rabe 2002

Methods	Randomised open-label controlled trial
Participants	91 intensive care unit patients in whom 99 3-lumen central venous catheters were implanted
Interventions	Catheter lock with 0.5 mL of: • Heparin 5000 IU/mL • 0.9% NaCl • Vitamin C 200 mg/mL
Outcomes	Catheter patency (tested every 2 days)
Notes	Follow-up 20 days Prophylactic or therapeutic anticoagulation was used in the 3 groups but with non-significant differences

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation list prepared by study authors using a random number generator
Allocation concealment (selection bias)	Unclear risk	Information insufficient to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label trial, but the outcome is not likely to be influenced by lack of blinding

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Rabe 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reporting of attrition/exclusions insufficient to permit judgement: no information about number of catheters losing patency in each group
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study appears to be free of other sources of bias

Schallom 2012

Methods	Randomised controlled open-label trial
Participants	295 patients (326 catheters, 709 lumens) from medical or surgical intensive care unit in whom a 3- or 4-lumen central venous catheter was inserted
Interventions	Flushes every 8 hours with: • 3 mL heparin 10 IU/mL • 10 mL 0.9% NaCl
Outcomes	Rate of lumen non-patency, blood loss return, flush failure, rate of catheter-related bloodstream infection, heparin-induced thrombocytopaenia
Notes	Follow-up 22 days Prophylactic or therapeutic anticoagulation was used in both groups with non-significant differences

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Investigators used a computerised random number generator in MS Excel®
Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed until the card was retrieved upon obtaining patient consent" Follow-up 1-27 days

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Schallom 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment, but outcome measurement is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but it is clear that published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study appears to be free of other sources of bias

ICU: intensive care unit.
PICCs: peripherally inserted central catheters.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
AACCN 1993	Arterial catheters were used
Abbas 2009	Study is not an RCT
Abdelkefi 2004	Interventions do not fulfil inclusion criteria (continuous infusion)
Abdelkefi 2005	Interventions do not fulfil inclusion criteria (continuous infusion); outcomes do not fulfil inclusion criteria (infection)
Abdelkefi 2005a	Interventions do not fulfil inclusion criteria (heparin-coated catheters)
Abdelkefi 2007	Interventions do not fulfil inclusion criteria (heparin-bonded catheter + normal saline vs non-coated catheter + continuous infusion heparin)
Abdelkefi 2008	Interventions do not fulfil inclusion criteria (impregnated catheters)
Agnelli 2009	Interventions do not fulfil inclusion criteria (systemic nadroparin)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Akyuz 2010	Comparison does not fulfil inclusion criteria (heparin vs taurolidine + citrate)
Alexander 2010	Peripheral catheters were used
Alpan 1984	Participants do not fulfil inclusion criteria (children)
Andersen 1992	Study is not an RCT
Ankola 1993	Arterial catheters were used; interventions do not fulfil inclusion criteria
Anton 2009	Participants and intervention do not fulfil inclusion criteria (children, heparin-bonded catheters)
Appelgren 1995	Study is not an RCT
Appelgren 1996	Interventions do not fulfil inclusion criteria (heparin-bonded catheters)
Aquino 2002	Interventions do not fulfil inclusion criteria (urokinase flushes), outcomes do not fulfil inclusion criteria (prevention of bacteraemia)
Araujo 2008	Interventions do not fulfil inclusion criteria (catheter comparison)
Arnts 2011	Peripheral catheters were used. Participants do not fulfil inclusion criteria (neonates)
Arone 2012	Study is not an RCT
Arrants 1999	Interventions do not fulfil inclusion criteria (saline lock only), outcomes do not fulfil inclusion criteria (obtaining blood samples)
Ashton 1990	Peripheral catheters were used
Aslam 2008	Study is not an RCT
Aslam 2010	Study is not an RCT
Aslam 2011	Comparisons do not fulfil inclusion criteria (heparin or citrate vs heparin + tigecycline + N-acetylcysteine)
Bailey 1979	Interventions do not fulfil inclusion criteria (continuous perfusion of heparin), outcomes do not fulfil inclusion criteria (sepsis prevention)
Balduini 2010	Peripheral catheters were used
Baltrons 2008	Study is not an RCT (retrospective study)
Barrett 1990	Interventions do not fulfil inclusion criteria (peripheral catheters)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Barriga 1997	Interventions do not fulfil inclusion criteria (heparin with or without vancomycin), outcomes do not fulfil inclusion criteria (prevention of bacteraemia)
Bayes 1999	Study is not an RCT
Beecroft 1997	Participants do not fulfil inclusion criteria (children)
Bennegard 1982	Interventions do not fulfil inclusion criteria (heparin-coated vs non-coated catheters)
Bertoglio 2012	Study is not an RCT
Bertolino 2012	Peripheral catheters were used
Betjes 2004	Comparison does not fulfil inclusion criteria (heparin vs citrate-taurolidine), outcomes do not fulfil inclusion criteria (prevention of sepsis)
Betremieux 1988	Participants do not fulfil inclusion criteria (children)
Birch 2010	Participants do not fulfil inclusion criteria (neonates)
Bisseling 2010	Comparison does not fulfil inclusion criteria (heparin vs taurolidine)
Bleyer 2005	Comparison interventions do not fulfil inclusion criteria (heparin vs minocycline + EDTA)
Bolgiano 1990	Arterial catheters were used
Bookstaver 2009	Study is not an RCT
Bossert 1994	Study is not an RCT
Bracho-Blanchet 2010	Participants do not fulfil inclusion criteria (children)
Branger 2011	Interventions do not fulfil inclusion criteria (arteriovenous fistula vs tunnelled jugular vein catheter)
Branson 1993	Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate)
Brismar 1982	Interventions do not fulfil inclusion criteria (systemic heparin)
Broom 2009	Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol), outcomes do not fulfil inclusion criteria (prevention of infection)
Broom 2012	Outcomes do not fulfil inclusion criteria (prevention of infection)
Brown-Smith 1990	Study is not an RCT
Butt 1987	Arterial catheters were used

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Buturovic 1998	Comparison interventions do not fulfil inclusion criteria (heparin vs citrate vs polygeline)
Cabrita 2011	Study is not an RCT
Calderero 2009	Study is not an RCT
Campbell 2011	Participants do not fulfil inclusion criteria (children)
Campos 2011	Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol). Outcomes do not fulfil inclusion criteria (catheter-related bacteraemia)
Cardinal 2000	Outcomes do not fulfil inclusion criteria (acid-base and electrolyte measurements)
Carrasco 2004	Interventions do not fulfil inclusion criteria (heparin-coated catheter)
Carratala 1999	Interventions do not fulfil inclusion criteria (heparin vs heparin + vancomycin), outcomes do not fulfil inclusion criteria (prevention of infection)
Carrero 2012	Study is not an RCT
Casale 2009	Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)
Catorze 2011	Arterial catheters were used
Catton 2006	Peripheral catheters were used
Cesaro 2009	Participants do not fulfil inclusion criteria (paediatric participants)
Chang 1997	Outcomes do not fulfil inclusion criteria (intraventricular haemorrhage ratio)
Cheronis 2013	Comparisons do not fulfil inclusion criteria (heparin vs trimetoprim + EDTA + ethanol)
Chu 2009	Comparisons do not fulfil inclusion criteria (heparin vs heparin + gentamicin)
Clark 2009	Study is not an RCT
Clifton 1991	Interventions do not fulfil inclusion criteria (heparin continuous flush)
Coli 2006	Interventions do not fulfil inclusion criteria (oral anticoagulant drugs)
Conte 2003	Interventions do not fulfil inclusion criteria (systemic low molecular weight heparin)
Coplon 2007	Comparisons do not fulfil inclusion criteria (heparin vs gentamicin + citrate)
Corbett 2013	Comparisons do not fulfil inclusion criteria (heparin vs taurolidine + heparin + citrate)
Cortes 2006	Comparisons do not fulfil inclusion criteria (heparin vs minocycline + EDTA)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Cottee 1995	Study is not an RCT
Crews 1997	Participants do not fulfil inclusion criteria (paediatric participants)
Daghistani 1996	Participants do not fulfil inclusion criteria (children)
Danek 1992	Participants do not fulfil inclusion criteria (children)
Daniell 1973	Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)
Davanipur 2011	Comparison does not fulfil inclusion criteria (heparin vs cloxacillin + heparin). Outcomes do not fulfil inclusion criteria (prevention of infection)
David 1981	Participants do not fulfil inclusion criteria (children)
De Cicco 2009	Interventions do not fulfil inclusion criteria (acenocumarine vs dalteparin vs no treatment)
de la Torre 2012	Peripheral catheters were used
de Neef 2002	Participants do not fulfil inclusion criteria (children)
del Cotillo 2008	Interventions do not fulfil inclusion criteria (arterial catheters)
del Pozo 2012	Interventions do not fulfil inclusion criteria (comparison of antibiotic concentrations)
Dias 2000	Participants do not fulfil inclusion criteria (children)
Dillon 2004	Participants do not fulfil inclusion criteria (children), comparison interventions do not fulfil inclusion criteria (heparin vs urokinase)
Dogra 2002	Comparison interventions do not fulfil inclusion criteria (heparin vs gentamicin + citrate), outcomes do not fulfil inclusion criteria (prevention of infection)
Donham 1987	Peripheral catheters were used
Duemichen 2012	Participants do not fulfil inclusion criteria (children). Comparison interventions do not fulfil inclusion criteria (heparin vs taurolidine). Outcomes do not fulfil inclusion criteria (prevention of infection)
Duncan 2005	Comparison interventions do not fulfil inclusion criteria (heparin vs citrate)
Duncan 2010	Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)
Dunser 2005	Interventions do not fulfil inclusion criteria (coated vs non-coated catheters), outcomes do not fulfil inclusion criteria (prevention of infection)
Dupuis 2012	Study is not an RCT, comparison interventions do not fulfil inclusion criteria (heparin vs citrate)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Edstrom 2002	Participants do not fulfil inclusion criteria (children), outcomes do not fulfil inclusion criteria (analytical determinations)
Eloy 1987	Interventions do not fulfil inclusion criteria (catheter comparison)
Epperson 1984	Interventions do not fulfil inclusion criteria (peripheral catheters)
Everts 2004	Study is not an RCT
Ferreira 2011	Participants do not fulfil inclusion criteria (children)
Festini 2013	Participants do not fulfil inclusion criteria (children) (peripheral catheters)
Filippi 2007	Participants do not fulfil inclusion criteria (children), interventions do not fulfil inclusion criteria (heparin + fusidic acid), outcomes do not fulfil inclusion criteria (prevention of infection)
Fonseca 2010	Study is not an RCT
Fort 2011	Participants do not fulfil inclusion criteria (children)
Fratino 2002	Participants do not fulfil inclusion criteria (children)
Garay Rubio 2011	Peripheral catheters were used
Garland 2005	Participants do not fulfil inclusion criteria (neonates), comparison interventions do not fulfil inclusion criteria (heparin vs heparin + vancomycin), outcomes do not fulfil inclusion criteria (prevention of infection)
Garrelts 1989	Peripheral catheters were used
Gillies 1985	Study is not an RCT
Gittins 2007	Participants do not fulfil inclusion criteria (children), comparison interventions do not fulfil inclusion criteria (heparin vs alteplase)
Glaspy 2000	Interventions do not fulfil inclusion criteria (systemic dalteparin)
Goh 2011	Interventions do not fulfil inclusion criteria (IV continuous heparin administration)
Golberg 1999	Participants do not fulfil inclusion criteria (neonates)
Gomez Palomar 2005	Study is not an RCT
Goode 1993	Peripheral catheters were used
Griffin 2005	Interventions do not fulfil inclusion criteria (papaverine)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Grosso 1989	Interventions do not fulfil inclusion criteria (calcium heparin)
Guillet 1997	Study is not an RCT
Gyr 1995	Interventions do not fulfil inclusion criteria (peripheral catheters)
Hall 2006	Interventions do not fulfil inclusion criteria (continuous flush), outcomes do not fulfil inclusion criteria (platelet count)
Hamilton 1988	Peripheral catheters were used
Handrup 2012	Comparison interventions do not fulfil inclusion criteria (heparin vs taurolidine). Participants do not fulfil inclusion criteria (children)
Handrup 2013	Participants do not fulfil inclusion criteria (children)
Hanrahan 1994	Participants do not fulfil inclusion criteria (children)
Harlev 2010	Participants do not fulfil inclusion criteria (children)
Harter 2002	Interventions do not fulfil inclusion criteria (coated vs non-coated catheters), outcomes do not fulfil inclusion criteria (prevention of infection)
Haynes 2002	Interventions do not fulfil inclusion criteria (SC device)
Heilskov 1998	Participants do not fulfil inclusion criteria (neonates)
Hemmelgarn 2006	Study is not an RCT
Hemmelgarn 2011	Comparison interventions do not fulfil inclusion criteria (heparin vs alteplase)
Hendrickx 2001	Comparison interventions do not fulfil inclusion criteria (citrate vs heparin)
Heng 2011	Interventions do not fulfil inclusion criteria (ethanol lock)
Henrickson 2000	Participants do not fulfil inclusion criteria (children), outcomes do not fulfil inclusion criteria (prevention of infection)
HGU Gregorio Marañón 2010	Comparisons do not fulfil inclusion criteria (heparin vs ethanol)
Hill 2011	Participants do not fulfil inclusion criteria (children)
Hoffer 1999	Interventions do not fulfil inclusion criteria (valved vs non-valved catheters)
Hook 1987	Study is not an RCT
Horgan 1987	Participants do not fulfil inclusion criteria (infants)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Horne 1995	Comparison interventions do not fulfil inclusion criteria (heparin vs lepirudin)
Horne 2006	Study is not an RCT
Hryszko 2013	Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)
Hu 2011	Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)
Imamovic 2009	Comparisons do not fulfil inclusion criteria (heparin vs citrate)
Ishii 2013	Interventions do not fulfil inclusion criteria (heparin continuous administration)
Israel Ministry of Health	Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)
Jaksic 2010	Comparisons do not fulfil inclusion criteria (heparin vs ethanol). Participants do not fulfil inclusion criteria (children)
James 1994	Study is not an RCT
Jasinsky 2007	Interventions do not fulfil inclusion criteria (antireflux device)
Jeppesen 2013	Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)
Johnson 2002	Interventions do not fulfil inclusion criteria (mupirocin), outcomes do not fulfil inclusion criteria (prevention of infection)
Jonker 2010	Study is not an RCT (retrospective cohort)
Jonkers 2012	Comparison interventions do not fulfil inclusion criteria (heparin vs taurolidine)
Jowett 1986	Peripheral catheters were used
Kalmanti 2002	Study is not an RCT, participants do not fulfil inclusion criteria (children)
Kamala 2002	Participants do not fulfil inclusion criteria (neonates)
Kankanala 2012	Comparison does not fulfil inclusion criteria (heparin vs citrate)
Karthaus 2006	Interventions do not fulfil inclusion criteria (systemic dalteparin)
Kleiber 1993	Participants do not fulfil inclusion criteria (children)
Klenner 2003	Participants do not fulfil inclusion criteria (children)
Knofler 1999	Study is not an RCT, participants do not fulfil inclusion criteria (children)
Kokenge 2010	Comparison does not fulfil inclusion criteria (heparin vs citrate)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Kotter 1996	Participants do not fulfil inclusion criteria (neonates)
Kovacs 2005	Interventions do not fulfil inclusion criteria (systemic dalteparin)
Krafte-Jacobs 1995	Participants do not fulfil inclusion criteria (children)
Kristinsson 1985	Study is not an RCT
Kudsk 1985	Interventions do not fulfil inclusion criteria (heparin administered in continuous perfusion)
Kulkarni 1994	Interventions do not fulfil inclusion criteria (continuous flush)
Kyle 1999	Study is not an RCT
Lacasaña Bellmunt 2006	Peripheral catheters were used
Lavau-Denes 2013	Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)
Le 2003	Interventions do not fulfil inclusion criteria (dressings)
LeDuc 1997	Participants do not fulfil inclusion criteria (children)
Lee 2006	Study is not an RCT
Lenhart 2001	Study is not an RCT
Leslie 1996	Comparisons do not fulfil inclusion criteria (comparison of 2 heparin concentrations)
Liang 1998	Peripheral catheters were used
Liao 2002	Peripheral catheters were used
Lindblad 1994	Interventions do not fulfil inclusion criteria (systemic heparin), outcomes do not fulfil inclusion criteria (anticoagulation)
Lok 2007	Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate)
Lombardi 1988	Participants do not fulfil inclusion criteria (children)
Long 2006	Interventions do not fulfil inclusion criteria (heparin-bonded catheters)
Lustig 2011	Comparisons do not fulfil inclusion criteria (heparin vs citrate + ethanol + methylene blue)
Macrae 2008	Comparison does not fulfil inclusion criteria (heparin vs citrate)
Maki 2011	Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate + methylene blue + methylparaben + propylparaben)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Male 2005	Study is not an RCT
Malo 2010	Comparison interventions do not fulfil inclusion criteria (heparin vs tinzaparin)
Marin 2000	Interventions do not fulfil inclusion criteria (heparin-bonded catheters), outcomes do not fulfil inclusion criteria (prevention of infection)
Martin 2009	Participants do not fulfil inclusion criteria (children). Interventions do not fulfil inclusion criteria (ethanol vs heparin)
Masroujeh 2008	Study is not an RCT
Massicotte 1996	Participants do not fulfil inclusion criteria (children)
Massicotte 2003	Interventions do not fulfil inclusion criteria (systemic raveparin), participants do not fulfil inclusion criteria (children)
Mayo 1996	Study is not an RCT
McIntyre 2004	Comparison interventions do not fulfil inclusion criteria (heparin vs heparin + gentamicin), outcomes do not fulfil inclusion criteria (prevention of infection)
McMullen 1993	Interventions do not fulfil inclusion criteria (peripheral catheters), participants do not fulfil inclusion criteria (children)
Meier 2011	Interventions do not fulfil inclusion criteria (catheter comparison)
Mendarte 1997	Study is not an RCT
Meyer 1995	Interventions do not fulfil inclusion criteria (peripheral catheters)
Meyer 2010	Participants do not fulfil inclusion criteria (children)
Mismetti 2003	Interventions do not fulfil inclusion criteria (systemic dalteparin), comparison interventions do not fulfil inclusion criteria (warfarin)
Mitchell 2003	Participants do not fulfil inclusion criteria (children)
Mok 2007	Participants do not fulfil inclusion criteria (children)
Monreal 1996	Interventions do not fulfil inclusion criteria (systemic nadroparin)
Moran 2012	Comparison interventions do not fulfil inclusion criteria (gentamicin + citrate vs heparin)
Mortazavi 2011	Comparison interventions do not fulfil inclusion criteria (heparin vs heparin + cefotaxime), outcomes do not fulfil inclusion criteria (prevention of infection)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Mudge 1998	Interventions do not fulfil inclusion criteria (peripheral catheters)
Myrianthefs 2005	Study is not an RCT
Na 2012	Arterial catheters were used
Niers 2007	Interventions do not fulfil inclusion criteria (systemic nadroparin)
Niesen 2003	Interventions do not fulfil inclusion criteria (peripheral catheters)
Nieto-Rodriguez 1992	Peripheral catheters were used
NIH Clinical Centers 2002	Comparisons do not fulfil inclusion criteria (heparin vs lepirudin)
Nori 2006	Comparison does not fulfil inclusion criteria (gentamicin vs minocycline). Outcomes do not fulfil inclusion criteria (prevention of infection)
Ociepa 2010	Participants do not fulfil inclusion criteria (children)
Oguzhan 2012	Interventions do not fulfil inclusion criteria (heparin + NaCl 26% vs heparin)
Ojala 2007	Study is not an RCT
Onder 2009	Study is not an RCT
Oran 2008	Comparison interventions do not fulfil inclusion criteria (heparin lock 3 times a week vs heparin lock 6 times a week)
Paisley 1997	Participants do not fulfil inclusion criteria (children)
Periard 2008	Interventions do not fulfil inclusion criteria (catheter comparison)
Pervez 2002	Comparison interventions do not fulfil inclusion criteria (heparin vs sodium citrate + gentamicin) , outcomes do not fulfil inclusion criteria (prevention of infection)
Petersen 2001	Study is not an RCT
Pierce 2000	Participants do not fulfil inclusion criteria (children)
Pouw 1995	Interventions do not fulfil inclusion criteria (systemic heparin)
Power 2009	Comparison interventions do not fulfil inclusion criteria (heparin vs citrate)
Powers 1999	Outcomes do not fulfil inclusion criteria (analytical results)
Pucheu 1996	Study is not an RCT

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Puiggros 2012	Study is not an RCT
Quenot 2013	Comparisons do not fulfil inclusion criteria (heparin vs citrate)
Rackoff 1995	Particpants do not fulfil inclusion criteria (children), comparison interventions do not fulfil inclusion criteria (heparin vs heparin + vancomycin), outcomes do not fulfil inclusion criteria (prevention of infection)
Rajani 1979	Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)
Randon 2006	Comparisons do not fulfil inclusion criteria (heparin vs non-needle system)
Rao 1981	Participants do not fulfil inclusion criteria (children)
Ray 1999	Comparison interventions do not fulfil inclusion criteria (heparin vs urokinase)
Reeves 2009	Participants do not fulfil inclusion criteria (neonates)
Reichardt 2002	Interventions do not fulfil inclusion criteria (systemic heparin)
Renaud 2009	Study is not an RCT
Rijnders 2005	Interventions do not fulfil inclusion criteria (antibiotics vs placebo)
Roberts 1994	Peripheral catheters were used
Robertson 1994	Participants do not fulfil inclusion criteria (children)
Robinson 2009	Study is not an RCT
Ruggiero 1983	Interventions do not fulfil inclusion criteria (heparin continuous)
Sahin Balcik 2011	Study is not an RCT
Sanders 2008	Comparison interventions do not fulfil inclusion criteria (heparin vs ethanol), outcomes do not fulfil inclusion criteria (prevention of infection)
Sang Sook 2012	Arterial catheters were used
Saxena 2005	Study is not an RCT
Saxena 2006	Comparison does not fulfil inclusion criteria (heparin vs cefotaxime + heparin)
Saxena 2006a	Comparison does not fulfil inclusion criteria (heparin vs cefotaxime + heparin)
Scherr 2002	Arterial catheters were used

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Schilling 2006	Participants do not fulfil inclusion criteria (children)
Schouten 2013	Comparisons do not fulfil inclusion criteria (heparin vs citrate)
Schroder 2008	Comparisons do not fulfil inclusion criteria (heparin vs taurolidine)
Schroeder 2010	Participants do not fulfil inclusion criteria (infants)
Schultz 2002	Participants do not fulfil inclusion criteria (children)
Schwartz 1990	Participants do not fulfil inclusion criteria (children), outcomes do not fulfil inclusion criteria (prevention of infection)
Seguin 1994	Study is not an RCT
Seliem 2010	Participants do not fulfil inclusion criteria (children)
Serrano 2009	Study is not an RCT
Shah 2007a	Participants do not fulfil inclusion criteria (neonates)
Shen 2013	Study is not an RCT
Shirzad 2013	Comparisons do not fulfil inclusion criteria (heparin vs heparin + cefazolin)
Shively 1997	Study is not an RCT
Shoaf 1992	Study is not an RCT
Sierra 2010	Study is not an RCT
Silva 2008	Interventions do not fulfil inclusion criteria (antibiotic ointment vs antibiotic lock)
Silva 2013	Comparison does not fulfil inclusion criteria (heparin vs heparin + cefazolin + gentamicin)
Skofic 2009	Study is not an RCT
Smith 1990	Interventions do not fulfil inclusion criteria (heparin lock left in place)
Smith 1991	Study is not an RCT, participants do not fulfil inclusion criteria (neonates)
Sofroniadou 2012	Comparison does not fulfil inclusion criteria (heparin vs heparin + vancomycin vs heparin + linezolid)
Solomon 2001	Comparison does not fulfil inclusion criteria (heparin vs urokinase)
Solomon 2010	Comparison does not fulfil inclusion criteria (heparin vs taurolidine + citrate)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Solomon 2012	Study is not an RCT
Sona 2012	Study is not an RCT
Stas 2001	Comparison does not fulfil inclusion criteria (heparin vs citrate)
Steczko 2009	Study is not an RCT
Stephens 1997	Study is not an RCT
Taylor 1989	Participants do not fulfil inclusion criteria (children)
Thomson 2011	Comparison interventions do not fulfil inclusion criteria (different concentrations of heparin)
Thurlimann 1992	Interventions do not fulfil inclusion criteria (peripheral catheters)
Tolar 1996	Interventions do not fulfil inclusion criteria (no heparin use)
Treas 1992	Participants do not fulfil inclusion criteria (children)
Trivedi 1997	Study is not an RCT
Trottier 1995	Interventions do not fulfil inclusion criteria (different catheterisation sites)
Tuncali 2005	Interventions do not fulfil inclusion criteria (arterial catheters, continuous flushing)
Tuten 1991	Peripheral catheters were used
Unal 2012	Participants do not fulfil inclusion criteria (children)
Uslu 2010	Partoicipants and interventions do not fulfil inclusion criteria (children, heparin continuous infusion)
Van Rooden 2004	Study is not an RCT
Vegting 2012	Study is not an RCT
Venditto 2010	Comparison interventions do not fulfil inclusion criteria (heparin vs citrate vs heparin + gentamicin)
Vercaigne 2011	Comparisons do not fulfil inclusion criteria (heparin vs citrate + ethanol)
Verso 2005	Interventions do not fulfil inclusion criteria (systemic enoxaparin)
Verso 2008	Study is not an RCT
Vertrees 2001	Study is not an RCT

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

Wan 2012	Study is not an RCT
Wang 2012	Peripheral catheters were used
Warkentin 1998	Outcomes do not fulfil inclusion criteria (formation of hepatin antibodies)
Wassenaar 2008	Study is not an RCT
Weijmer 2005	Comparison does not fulfil inclusion criteria (heparin vs citrate)
White 2011	Participants do not fulfil inclusion criteria (children)
Whitta 2006	Interventions do not fulfil inclusion criteria (continuous heparin flushing)
Willicombe 2010	Study is not an RCT
Winnett 2008	Study is not an RCT
Witkovski 2010	Arterial catheters were used
Wolf 2011	Comparisons do not fulfil inclusion criteria (heparin vs ethanol)
Wolley 2010	Study is not an RCT
Wong 2009	Outcomes do not fulfil inclusion criteria (changes in activated partial thromboplastin time)
Wooldridge 1988	Study is not an RCT
Worly 2004	Study is not an RCT, participants do not fulfil inclusion criteria (children)
Wright 1995	Participants do not fulfil inclusion criteria (children)
Yevzlin 2007	Study is not an RCT, outcomes do not fulfil inclusion criteria (bleeding complications)
Yilmaz 2010	Study is not an RCT
Yon 2013	Study is not an RCT, interventions do not fulfil inclusion criteria (citrate vs heparin)
Young 2009	Interventions do not fulfil inclusion criteria (warfarin)
Zacharski 2005	Interventions do not fulfil inclusion criteria (warfarin vs low molecular weight heparin)
Zhang 2009	Interventions do not fulfil inclusion criteria (heparin vs gentamicin + heparin), outcomes do not fulfil inclusion criteria (infection)

EDTA: ethylenediaminetetraacetic acid.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

RCT: randomised controlled trial.
SC: subcutaneous.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

Comparison 1. Occlusion of CVCs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Occlusion of CVCs (unit of analysis participant)	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.70]
2 Occlusion of CVCs (unit of analysis catheter)	3	1025	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.29, 0.94]
3 Occlusion of CVCs (unit of analysis line access)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Duration of catheter patency

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of catheter patency (unit of analysis participant)	3	952	Mean Difference (IV, Fixed, 95% CI)	0.41 [-1.29, 2.12]
2 Duration of catheter patency (unit of analysis catheter)	2	752	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.20, 0.99]

Comparison 3. Safety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CVC-related thrombosis	2	1097	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.74, 1.99]
2 CVC-related sepsis	2	1097	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.34, 3.03]
3 Mortality	3	1100	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.45, 1.32]
4 Haemorrhage from any site	3	1145	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.49, 3.85]
5 Heparin-induced thrombocytopaenia	2	343	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.27]

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1 Occlusion of CVCs, Outcome 1 Occlusion of CVCs (unit of analysis participant).

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 1 Occlusion of CVCs

Outcome: 1 Occlusion of CVCs (unit of analysis participant)

Study or subgroup	Heparin n/N	0.9% NaCl n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bowers 2008	0/52	3/50		72.1 %	0.14 [0.01, 2.60]
Kaneko 2004	0/22	1/26		27.9 %	0.39 [0.02, 9.15]
Total (95% CI)	**74**	**76**		**100.0 %**	**0.21 [0.03, 1.70]**

Total events: 0 (Heparin), 4 (0.9% NaCl)

Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Occlusion of CVCs, Outcome 2 Occlusion of CVCs (unit of analysis catheter).

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 1 Occlusion of CVCs

Outcome: 2 Occlusion of CVCs (unit of analysis catheter)

Study or subgroup	Heparin n/N	0.9% NaCl n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Pumarola 2007	0/125	0/125			Not estimable
Rabe 2002	3/33	9/33		28.9 %	0.33 [0.10, 1.12]
Schallom 2012	12/314	25/395		71.1 %	0.60 [0.31, 1.18]
Total (95% CI)	**472**	**553**		**100.0 %**	**0.53 [0.29, 0.94]**

Total events: 15 (Heparin), 34 (0.9% NaCl)

Heterogeneity: $Chi^2 = 0.70$, df = 1 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 2.16 (P = 0.031)

Test for subgroup differences: Not applicable

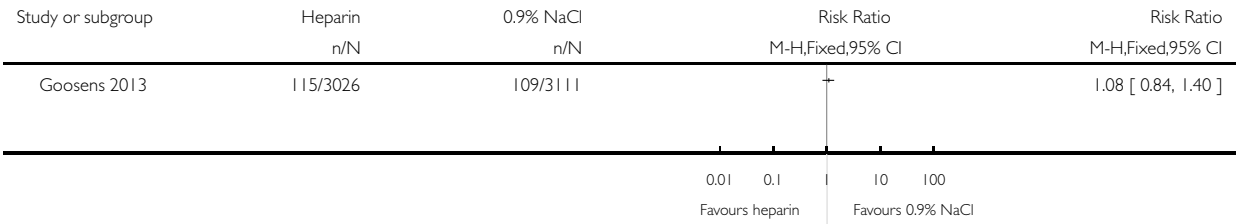
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.3. Comparison 1 Occlusion of CVCs, Outcome 3 Occlusion of CVCs (unit of analysis line access).

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 1 Occlusion of CVCs

Outcome: 3 Occlusion of CVCs (unit of analysis line access)



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 2.1. Comparison 2 Duration of catheter patency, Outcome 1 Duration of catheter patency (unit of analysis participant).

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 2 Duration of catheter patency

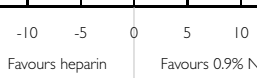
Outcome: 1 Duration of catheter patency (unit of analysis participant)

Study or subgroup	Heparin N	Mean(SD)	0.9% NaCl N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bowers 2008	52	2.9 (5.7)	50	2.1 (4)		80.1 %	0.80 [-1.11, 2.71]
Goosens 2013	398	150.9 (40.7)	404	152.4 (37.9)		9.8 %	-1.50 [-6.94, 3.94]
Kaneko 2004	22	17.3 (8.85)	26	18.1 (10.15)		10.1 %	-0.80 [-6.18, 4.58]
Total (95% CI)	**472**		**480**			**100.0 %**	**0.41 [-1.29, 2.12]**

Heterogeneity: $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 2.2. Comparison 2 Duration of catheter patency, Outcome 2 Duration of catheter patency (unit of analysis catheter).

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 2 Duration of catheter patency

Outcome: 2 Duration of catheter patency (unit of analysis catheter)

Study or subgroup	Heparin N	Mean(SD)	0.9% NaCl N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Pumarola 2007	25	4.87 (5)	18	4.55 (4)		4.9 %	0.32 [-2.37, 3.01]
Schallom 2012	314	8 (4)	395	7.6 (4.3)		95.1 %	0.40 [-0.21, 1.01]
Total (95% CI)	**339**		**413**			**100.0 %**	**0.40 [-0.20, 0.99]**

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Safety, Outcome 1 CVC-related thrombosis.

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 3 Safety

Outcome: 1 CVC-related thrombosis

Study or subgroup	Heparin n/N	0.9% NaCl n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Goosens 2013	13/398	11/404		41.0 %	1.20 [0.54, 2.65]
Schallom 2012	19/145	16/150		59.0 %	1.23 [0.66, 2.29]
Total (95% CI)	**543**	**554**		**100.0 %**	**1.22 [0.74, 1.99]**

Total events: 32 (Heparin), 27 (0.9% NaCl)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

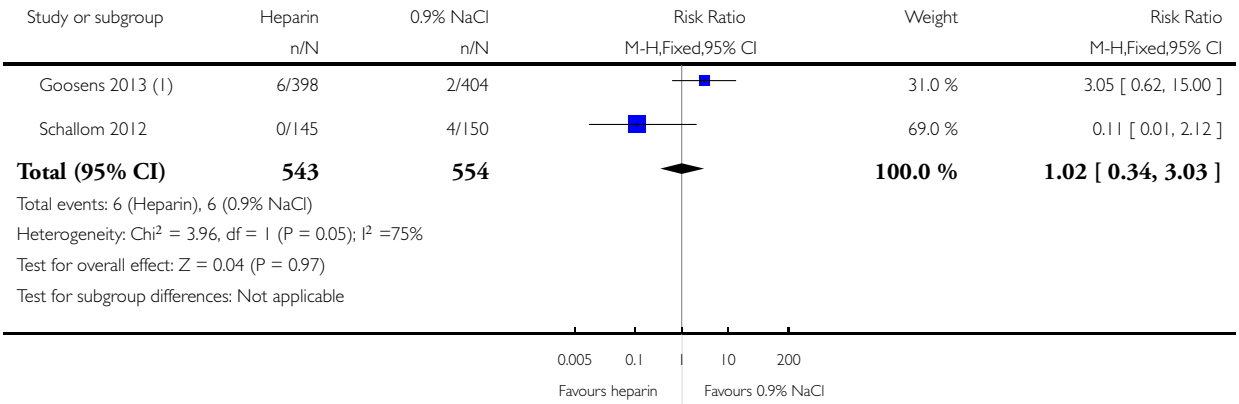
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.2. Comparison 3 Safety, Outcome 2 CVC-related sepsis.

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 3 Safety

Outcome: 2 CVC-related sepsis



(1) *Staphylococcus aureus 2, Staphylococcus epidermidis 3, Candida glabatra 1 in Heparin group and Staphylococcus epidermidis 1 and Staphylococcus homini 1 in saline groups*

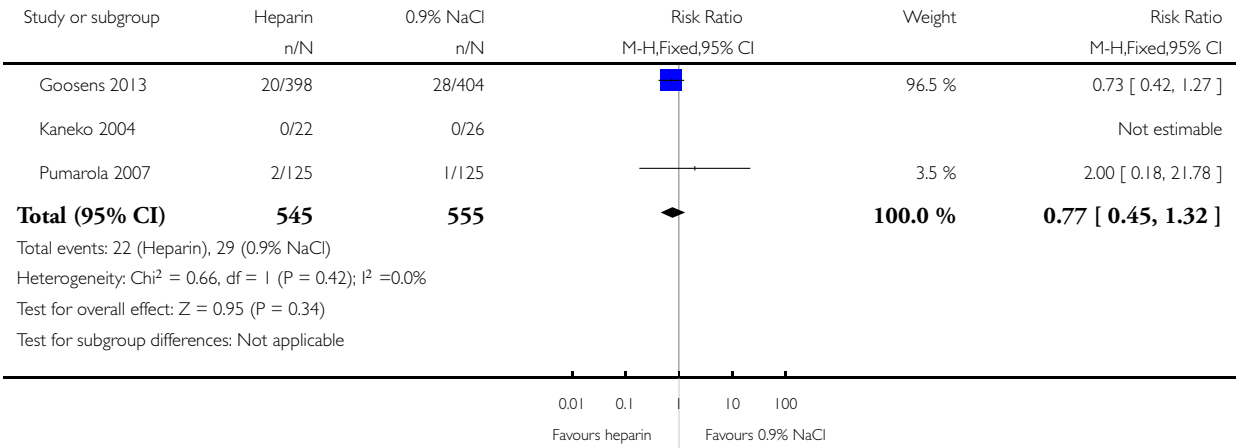
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.3. Comparison 3 Safety, Outcome 3 Mortality.

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 3 Safety

Outcome: 3 Mortality

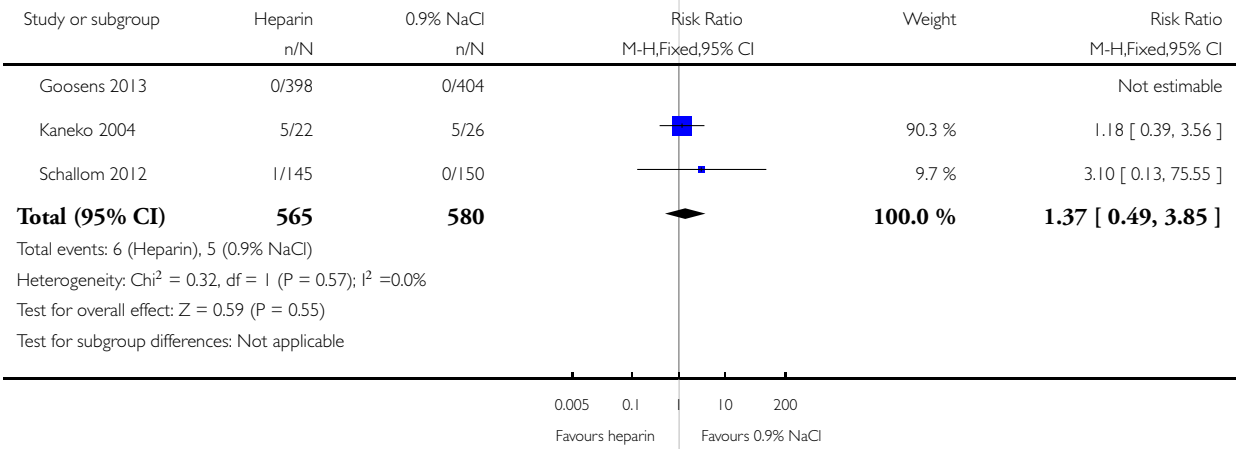


Analysis 3.4. Comparison 3 Safety, Outcome 4 Haemorrhage from any site.

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 3 Safety

Outcome: 4 Haemorrhage from any site



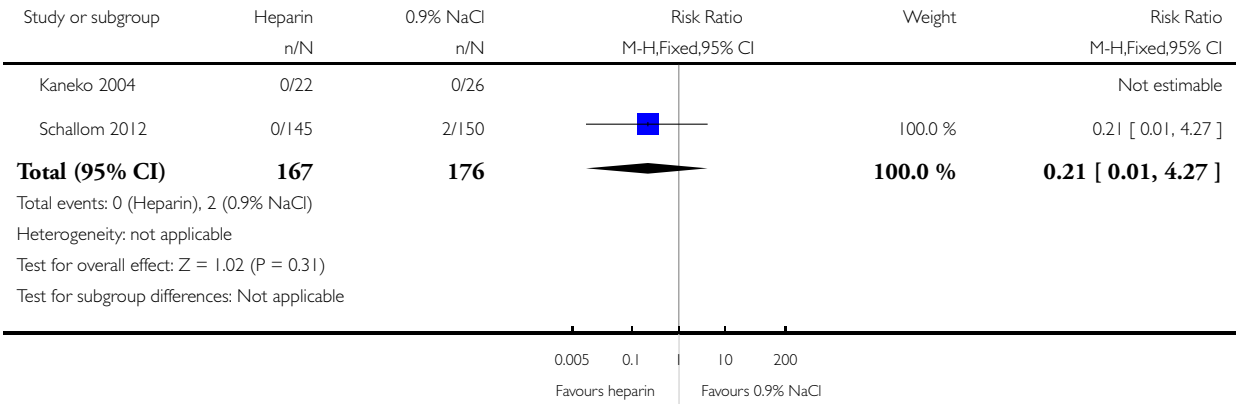
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.5. Comparison 3 Safety, Outcome 5 Heparin-induced thrombocytopaenia.

Review: Heparin versus 0.9% sodium chloride intermittent flushing for prevention of occlusion in central venous catheters in adults

Comparison: 3 Safety

Outcome: 5 Heparin-induced thrombocytopaenia



ADDITIONAL TABLES

Table 1. Secondary outcomes

Study	CVC-related thrombosis		CVC-related sepsis		Mortality		Coagulation parameters		HIT		Haemorhage	
	H	NS	H	NS	H	NS	H	NS	H	NS	H	NS
Bowers 2008	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Goosens 2013	13/398	11/404	6/398	2/404	20/398	28/404	NR	NR	NR	NR	0	0
Kaneko 2004	NR	NR	NR	NR	0	0	ACT in-	ACT un-	0	0	5/22	5/26

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Secondary outcomes (*Continued*)

							creased* APTT increased† PT increased‡	changed APTT unchanged PT unchanged				
Pumarola 2007	NR	NR	NR	NR	2/125	1/125	NR	NR	NR	NR	NR	NR
Rabe 2002	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schallom 2012	19/145	16/150	0/145	4/150	NR	NR	NR	NR	0/145	2/150	1/145	0/150

ACT: activated coagulation time.
APTT: activated partial thromboplastin time.
CVC: central venous catheter.
H: heparin.
HIT: heparin-induced thrombocytopaenia.
NR: not reported.
NS: normal saline (0.9% NaCl).
PT: prothrombin time.
*P value < 0.001 for comparison with NS group; †P value 0.001 for comparison with NS group; ‡Non-significant difference for comparison with NS group (P value 0.187).

APPENDICES

Appendix 1. CENTRAL search strategy

#1	MeSH descriptor: [Heparin] explode all trees	3995
#2	(hep* or UH or UFH or LMWH):ti,ab,kw	26525
#3	MeSH descriptor: [Sodium Chloride] this term only	1757
#4	MeSH descriptor: [Saline Solution, Hypertonic] explode all trees	360

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

#5	saline*:ti,ab,kw	13508
#6	sodium:ti,ab,kw	19429
#7	NaCl:ti,ab,kw	1189
#8	#1 or #2	26756
#9	#3 or #4 or #5 or #6 or #7	31063
#10	#8 and #9	1030
#11	MeSH descriptor: [Catheterization, Central Venous] this term only	721
#12	MeSH descriptor: [Catheterization] this term only	1415
#13	MeSH descriptor: [Catheters, Indwelling] explode all trees	908
#14	catheter*:ti,ab,kw	11675
#15	cannula*:ti,ab,kw	1456
#16	CVC* or PICC:ti,ab,kw	273
#17	venous near/3 access	318
#18	#11 or #12 or #13 or #14 or #15 or #16 or #17	12715
#19	#10 and #18 in Trials	128

Appendix 2. MEDLINE search strategy

Database: Ovid MEDLINE(R) <1946 to November Week 3 2013>
Search strategy:
---
1 exp Heparin/ (57389)
2 (hep$ or UH or UFH or LMWH).ti,ab. (627845)
3 Sodium Chloride/ (50802)
4 Saline Solution, Hypertonic/ (5000)
5 saline.ti,ab. (131343)
6 sodium.ti,ab. (261605)
7 NaCl.ti,ab. (44546)
8 1 or 2 (644714)
9 or/3-7 (440904)
10 8 and 9 (21343)
11 Catheterization, Central Venous/ (11904)
12 Catheterization/ (46418)
13 Catheters, Indwelling/ (16134)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

14 cannul$.ti,ab. (33065)
15 catheter$.ti,ab. (147967)
16 (CVC or PICC).ti,ab. (2879)
17 (venous adj3 access).ti,ab. (3589)
18 or/11-17 (208806)
19 10 and 18 (1058)
20 randomized controlled trial.pt. (390995)
21 controlled clinical trial.pt. (90070)
22 randomized.ab. (288395)
23 placebo.ab. (157299)
24 clinical trials as topic.sh. (175750)
25 randomly.ab. (200079)
26 trial.ti. (124923)
27 or/20-26 (897019)
28 exp animals/ not humans.sh. (4066609)
29 27 not 28 (826166)
30 19 and 29 (120)

Appendix 3. EMBASE search strategy

Database: Embase <1980 to 2013 Week 50>
Search strategy:
---
1 exp heparin/ (111566)
2 (hep$ or UH or UFH or LMWH).ti,ab. (773397)
3 1 or 2 (830780)
4 sodium chloride/ (119646)
5 hypertonic solution/ (4892)
6 (saline or sodium or NaCl).ti,ab. (487934)
7 or/3-6 (1333259)
8 3 and 7 (830780)
9 central venous catheterization/ (7513)
10 catheterization/ (36817)
11 catheter thrombosis/pc [Prevention] (183)
12 intravenous catheter/ or catheter/ or peripherally inserted central venous catheter/ (36105)
13 (catheter$ or cannul$).ti,ab. (230742)
14 (CVC or PICC).ti,ab. (4479)
15 (venous adj3 access).ti,ab. (5380)
16 or/9-15 (256005)
17 8 and 16 (17487)
18 random$.ti,ab. (864687)
19 factorial$.ti,ab. (22152)
20 (crossover$ or cross over$ or cross-over$).ti,ab. (68906)
21 placebo$.ti,ab. (198520)
22 (doubl$ adj blind$).ti,ab. (142411)
23 (singl$ adj blind$).ti,ab. (14177)
24 assign$.ti,ab. (235808)
25 allocat$.ti,ab. (81397)
26 volunteer$.ti,ab. (175670)
27 CROSSOVER PROCEDURE/ (39190)
28 DOUBLE-BLIND METHOD/ (119131)
29 RANDOMIZED CONTROLLED TRIALS/ (43057)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

30 SINGLE-BLIND METHOD/ (18632)
31 or/18-30 (1358554)
32 17 and 31 (1879)

Appendix 4. CINAHL search strategy

Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	Search modes - Find all my search terms	
S32	S13 AND S23 AND S31	80
S31	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30	40,125
S30	TX venous N3 access	1,007
S29	TX (CVC or PICC)	1,046
S28	TX catheter*	38,099
S27	TX cannul*	2,913
S26	(MH "Catheters")	2,666
S25	(MH "Catheterization")	2,725
S24	(MH "Catheterization, Central Venous")	2,802
S23	S21 AND S22	1,079
S22	S16 OR S17 OR S18 OR S19 OR S20	22,046
S21	S14 OR S15	55,265
S20	TX NaCl	479
S19	TX sodium	15,578
S18	TX saline	7,258
S17	(MH "Saline Solution, Hypertonic")	586
S16	(MH "Sodium Chloride")	2,008
S15	TX (hep* or UH or UFH or LMWH)	55,259

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

S14	(MH "Heparin+")	6,072
S13	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12	332,461
S12	single blind	10,305
S11	double blind	31,977
S10	triple blind	227
S9	latin square	267
S8	placebo*	29,457
S7	(MH "Placebos")	8,466
S6	follow-up stud*	63,187
S5	alloca*	18,840
S4	random*	171,810
S3	clin* N2 trial*	135,194
S2	(MH "Random Assignment")	36,178
S1	(MH "Clinical Trials+")	168,712

Appendix 5. Clinicaltrials.gov search

catheter AND heparin	74 studies found

Appendix 6. International Clinical Trials Registry Platform (WHO database)

heparin AND catheter	56 records for 53 trials found

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Appendix 7. Controlled-trials.com search

catheter AND heparin	28

CONTRIBUTIONS OF AUTHORS

E López-Briz (ELB): conception of the review; protocol design; identification, qualification and analysis of studies; interpretation of analysis; draft of the final review; update of the review.

V Ruiz Garcia (VRG): conception of the review; protocol design; identification, qualification and analysis of studies; interpretation of analysis; draft of the final review; update of the review.

JB Cabello (JBC): protocol design; identification, qualification and analysis of studies; interpretation of analysis; draft of the final review.

S Bort-Marti (SBM): identification of trials; analysis of studies; draft of the final review.

R Carbonell Sanchis (RCS): protocol design; third author in cases of disagreement about study qualifications; interpretation of analysis.

A Burls (AB): protocol design; interpretation of analysis; draft of the final review.

DECLARATIONS OF INTEREST

ELB: none known.

VRG: none known.

JBC: none known.

SBM: none known.

RCS: none known.

AB: none known.

SOURCES OF SUPPORT

Internal sources

- This work was not supported or granted, Spain.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

External sources

- This work was not supported or granted, Spain.
- Chief Scientist Office, Scottish Government Health Directorates, the Scottish Government, UK.

The PVD Group editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When the present systematic review was planned, and as a result of clinical considerations, the unit of analysis was assumed to be the participant. When the literature search was performed, three studies were found wherein the unit of analysis was the catheter, whereas in only two studies, the unit of analysis was the participant, and in one study, the unit of analysis was line access (every time that a line was used to provide drugs, blood, etc.). In view of this, all included studies were analysed separately for each different unit of analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Catheter Obstruction [statistics & numerical data]; *Catheterization, Central Venous; *Central Venous Catheters; Anticoagulants [*administration & dosage]; Heparin [*administration & dosage]; Sodium Chloride [*administration & dosage]; Therapeutic Irrigation [methods]

MeSH check words

Adult; Humans

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.