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

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[Intervention Review]

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

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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.

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.

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]	

	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.

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-

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.

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.

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

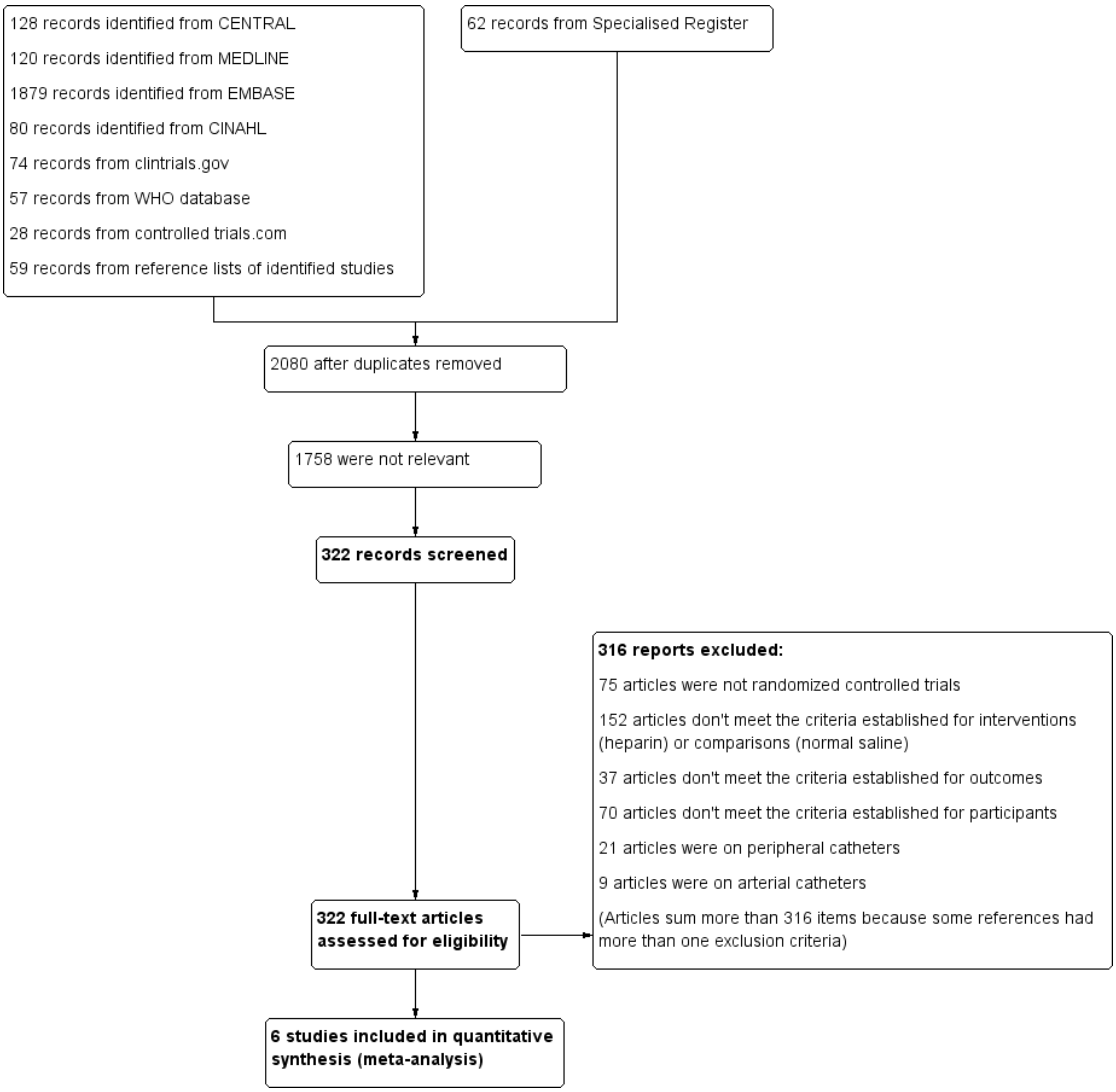
Description of studies

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.

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

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.

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

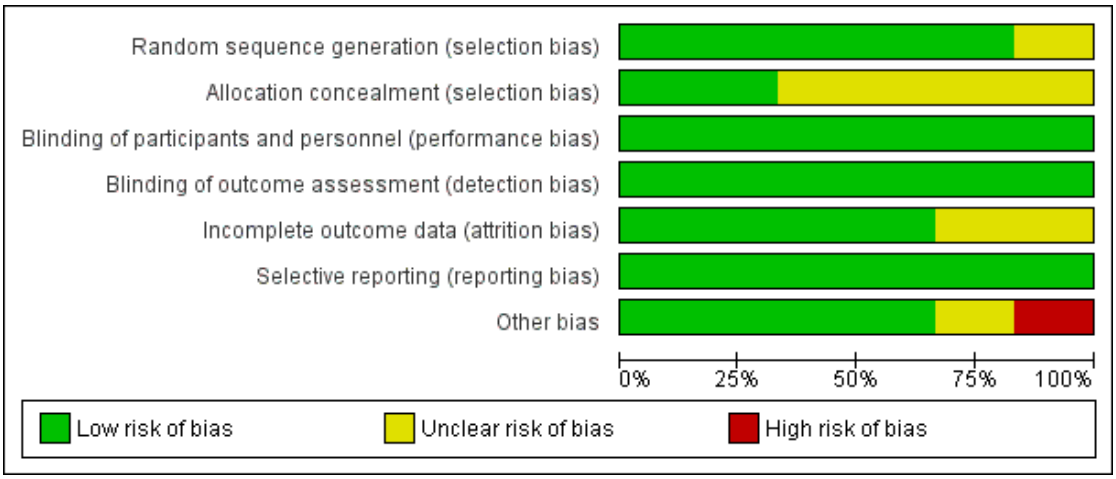
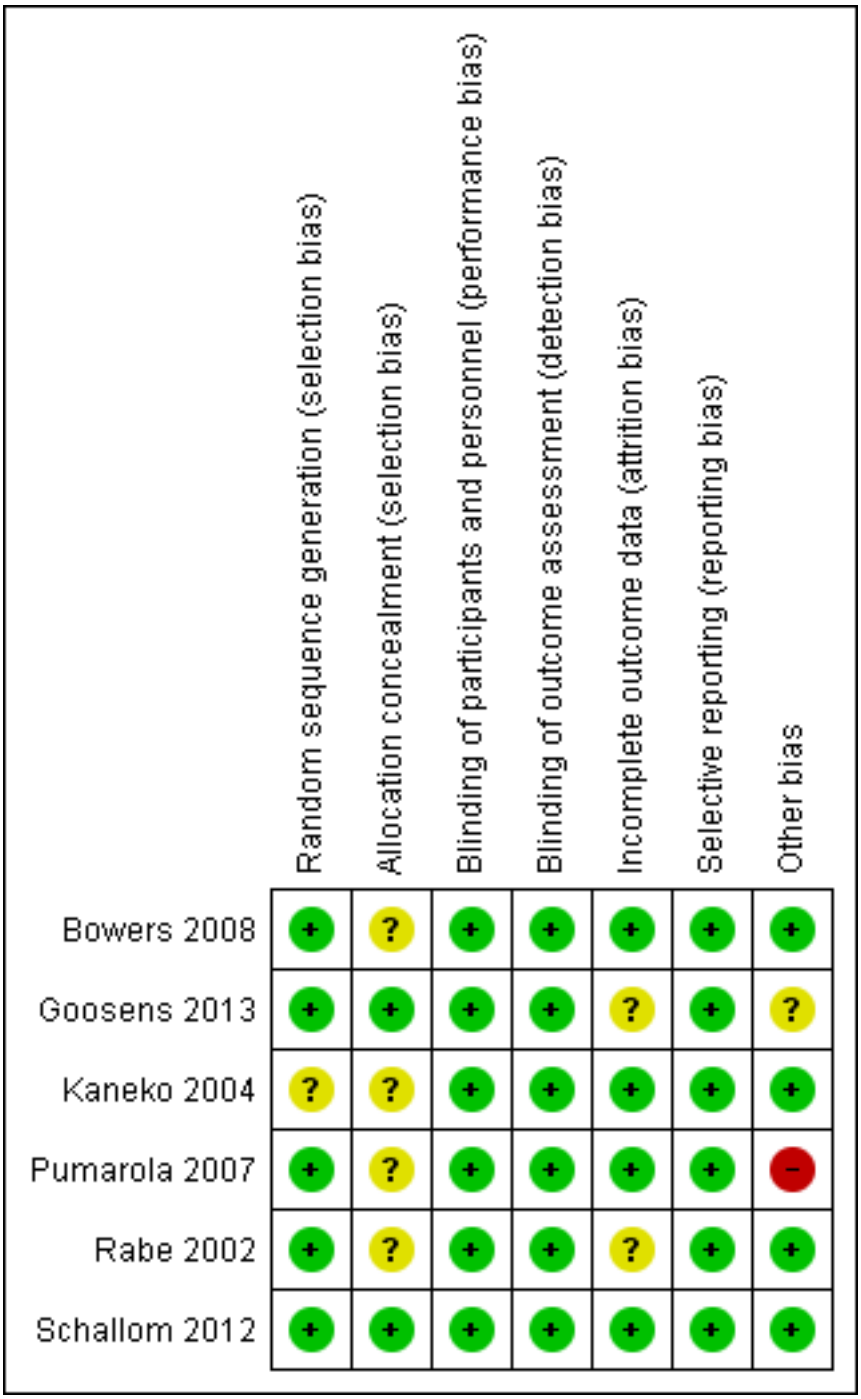


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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.

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

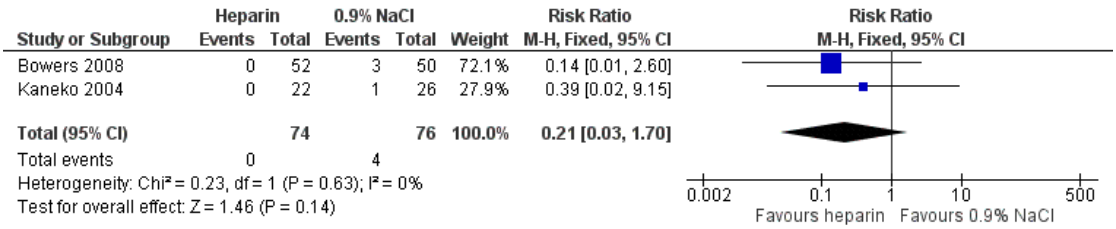
See: **Summary of findings for the main comparison** Heparin for central venous catheters

Primary outcomes

Occlusion of CVCs

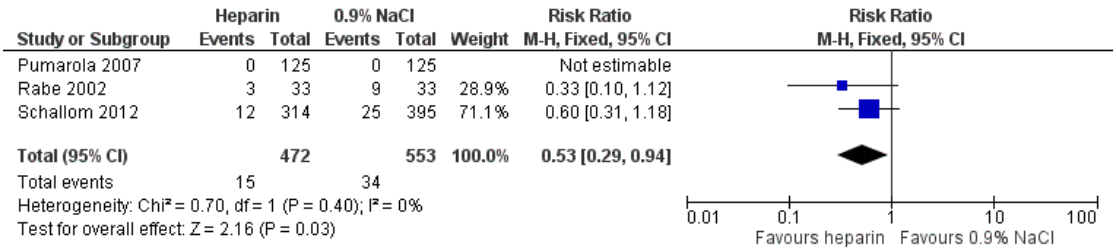
- Two studies were focused on *participant as unit of analysis* (Bowers 2008; Kaneko 2004), including 76 participants. Findings are pooled in Figure 4. Analysis performed using a Mantel-Haenszel (M-H) fixed-effect model yielded an RR of 0.21 (95% CI 0.03 to 1.70) (i.e. a non-significant effect), with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



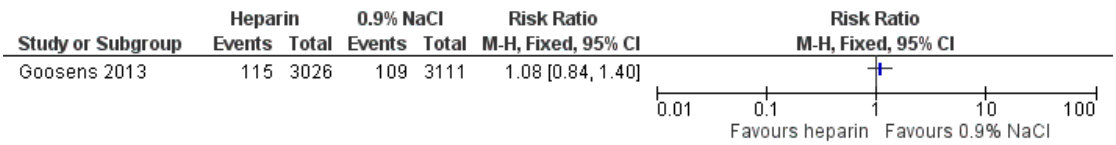
- Three studies were focused on *catheter as unit of analysis* (Pumarola 2007; Rabe 2002; Schallom 2012), totaling 1025 observations. Findings are pooled in Figure 5, demonstrating a favourable effect of heparin when results were analysed by means of an M-H fixed-effect model (RR 0.53, 95% CI 0.29 to 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

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.

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

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

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.

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* *Indicates the major publication for the study*

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

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

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

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

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

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

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)

(*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)

(*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

(*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)

(*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)

(*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)

(*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)

(*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)

(*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)

(*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)

(*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

(*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

(*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)

(*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

(*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.

RCT: randomised controlled trial.
SC: subcutaneous.

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]

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)

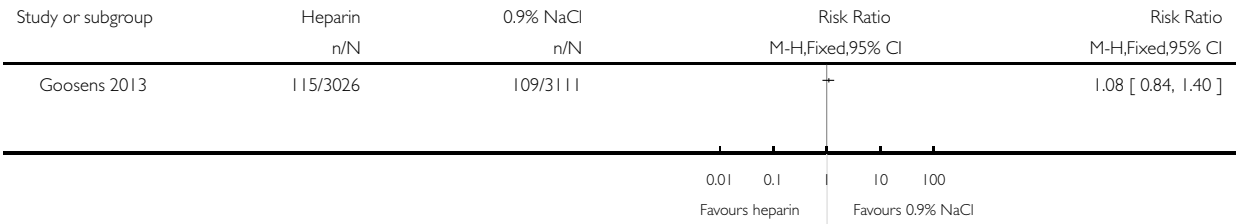
Test for subgroup differences: Not applicable

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)



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

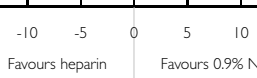
Outcome: 1 Duration of catheter patency (unit of analysis participant)

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



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)

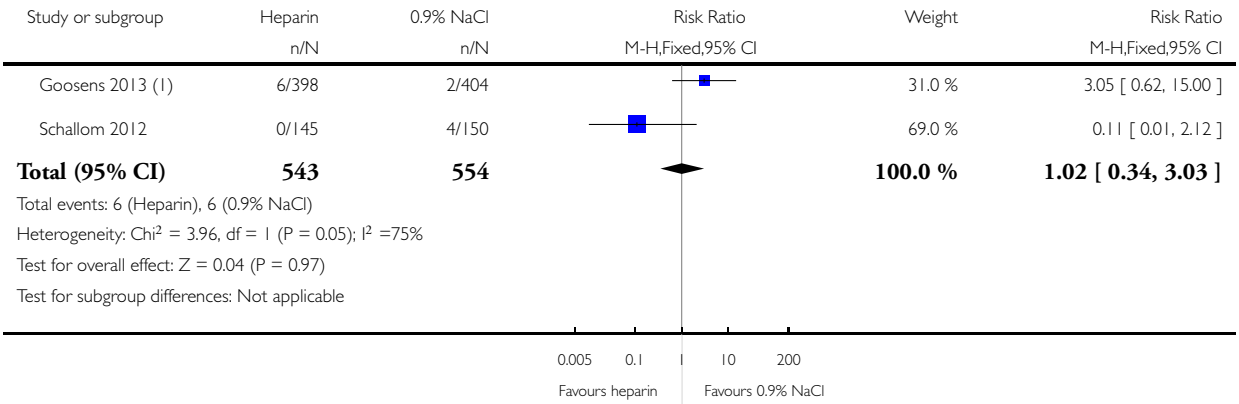
Test for subgroup differences: Not applicable

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



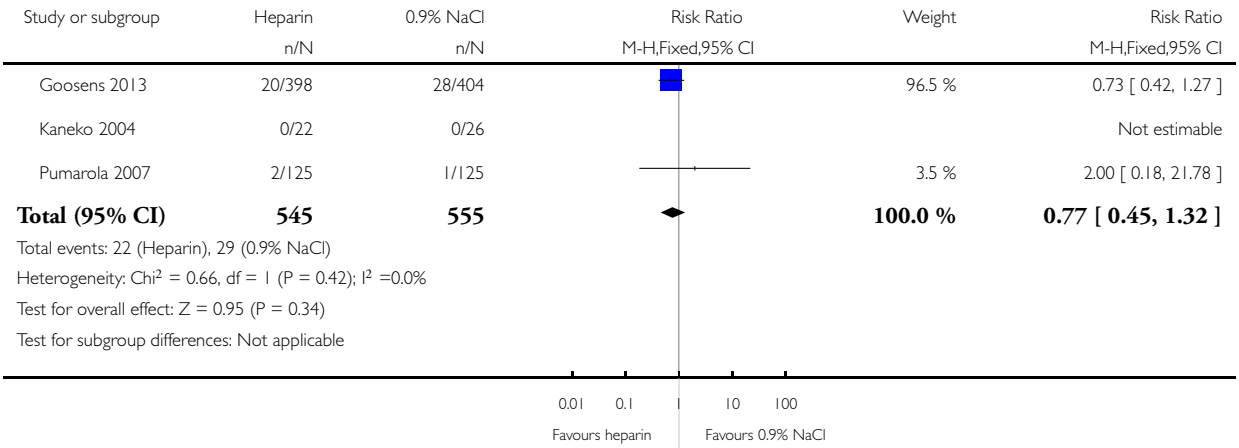
(1) *Staphylococcus aureus 2, Staphylococcus epidermidis 3, Candida glabatra 1 in Heparin group and Staphylococcus epidermidis 1 and Staphylococcus homini 1 in saline groups*

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

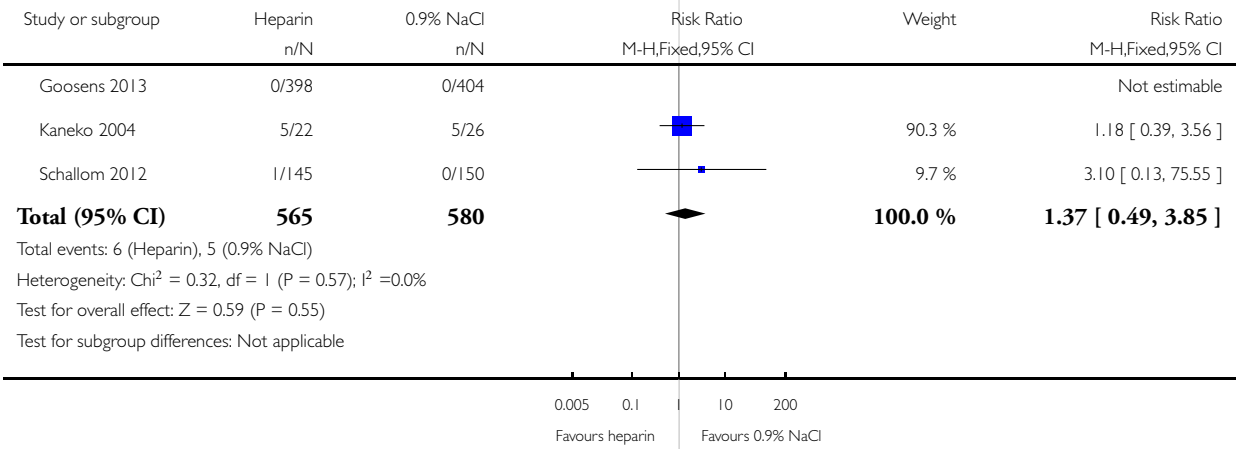


Analysis 3.4. Comparison 3 Safety, Outcome 4 Haemorrhage from any site.

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

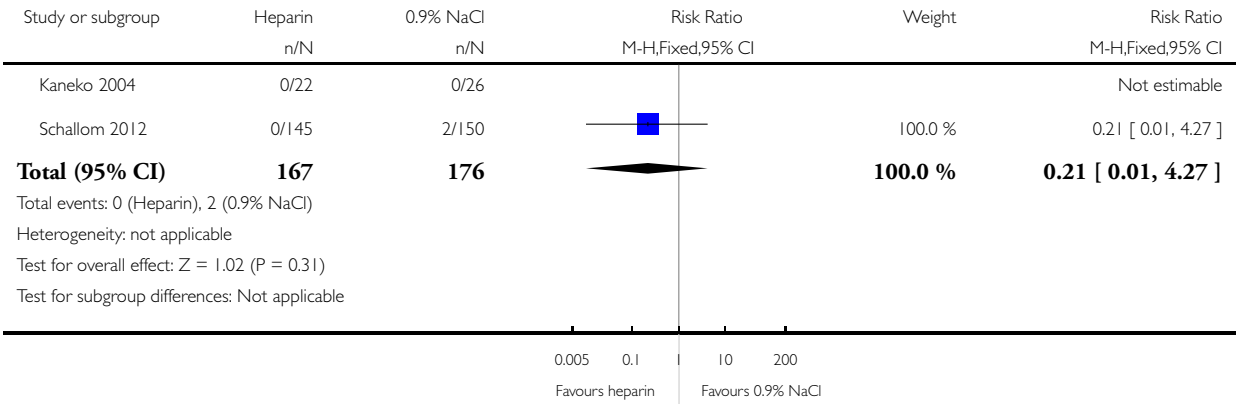


Analysis 3.5. Comparison 3 Safety, Outcome 5 Heparin-induced thrombocytopaenia.

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

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

(*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)

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)

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

(*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

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.

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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