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[Intervention Review]

Heparin versus normal saline for patency of arterial lines

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ABSTRACT

Background

For most patients who require intensive care, the success of clinical decision making and interventions is dependent on the accuracy of different physiological variables measured or obtained from samples using an arterial catheter. Maintaining the patency of these catheters is therefore essential for obtaining accurate measures, minimizing patient discomfort and reducing expenses incurred when an occluded catheter requires replacement. Uncertainty exists amongst clinicians as to best practice surrounding the contents of the arterial catheter flush solution (heparin or saline). The use of heparin is more expensive and is accompanied by significant risks such as haemorrhage, hypersensitivity and heparin-induced thrombocytopenia (HIT).

Objectives

The objective of this review was to evaluate whether normal saline is as efficacious and safe as heparin in maintaining the patency of arterial intravascular catheters in adult patients without a haematological disorder.

Search methods

Randomized clinical trials (RCTs) were identified through electronic database searches: Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 1, part of *The Cochrane Library*; MEDLINE (Ovid, 1966 to March 2013); EMBASE (Ovid, 1988 to March 2013) and CINAHL (1988 to March 2013), using specific strategies as advised by the Cochrane Anaesthesia Group search specialist. We contacted trial authors to ask for additional information as needed.

Selection criteria

Randomized controlled trials and quasi-randomized studies irrespective of blinding or language that compared an arterial catheter flush solution comprising any dose of heparin versus an infusion of normal saline only.

Data collection and analysis

Two review authors independently screened for methodological quality and extracted data from all identified studies that met the protocol inclusion criteria.

Main results

A total of seven studies (606 participants) met the inclusion criteria and measured the primary outcome of interest. All studies were at unclear to high risk of bias. Given the high degree of clinical and statistical heterogeneity of the included studies, no meta-analysis was completed. The results from individual studies that compared heparin at a dose of 1 to 2 IU/mL under continuous pressure were imprecise and do not provide definitive evidence of a difference. The observed difference with a dose of heparin increased to 4 IU/mL came from

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only one study of 30 participants, and the quality of the reported data was poor. Similarly, consistency in assessment and reporting of adverse events such as haematoma, insertion site infection and limb ischaemia was poor. Further research with well-defined primary and secondary outcome measures using a stratified sampling process that accommodates for the different heparin doses commonly used in clinical practice is needed to confirm the trends seen in research results now reported in the literature.

Authors' conclusions

The available evidence is of poor quality because of risk of bias and does not provide sufficient information to support the effects of adding heparin (1 to 2 IU/mL) to a maintenance solution (pressurized to deliver 3 mL of flush solution per hour) of 0.9% normal saline in maintaining the patency and functionality of arterial catheters.

PLAIN LANGUAGE SUMMARY

Heparin versus normal saline for maintaining an open (patent) arterial line

For most patients who require intensive care, the success of clinical decision making and interventions is dependent on the accuracy of blood pressure and pulse measurements of samples taken using an arterial catheter. Maintaining the patency of these catheters is therefore essential for minimizing both patient discomfort (blood clots and reduced blood flow to a limb, infection and scarring) and additional expenses incurred by the need to replace a blocked catheter. This summary of a Cochrane review presents what we know from the available research about which solution (heparin or normal saline) is more effective in maintaining the patency of arterial catheters in adult patients. Heparin is a powerful drug in terms of its ability to prevent clots from forming in the catheter, but its use is not without risk of bleeding, an allergic reaction and low platelet counts. Patients can experience serious adverse events when given heparin.

A total of seven randomized controlled studies met the inclusion criteria and enrolled a total of 606 participants. Because of differences in the way that the studies were designed, we were unable to combine their reported results. The results from individual studies that compared heparin at a dose of 1 to 2 IU/mL under continuous pressure were imprecise and do not provide definitive evidence of a difference. The effective dose of heparin has not yet been determined. This evidence needs to be confirmed in future trials. All studies had a moderate to high risk of methodological bias. The review of trials therefore revealed that more research is needed to determine exactly how long an arterial catheter maintained with a normal saline flush solution can be in place and remain functional (to accurately measure blood pressure and pulse and to provide blood samples that can be used to monitor oxygenation and other variables).

BACKGROUND

Description of the condition

Most patients admitted to an intensive care unit require an arterial catheter to enable accurate monitoring of blood pressure, regular blood sampling and assessment of arterial blood oxygenation. Patients typically are admitted to an intensive care unit because of unstable haemodynamics requiring continuous monitoring (more frequently than every five minutes). The most common indications for insertion of an arterial catheter are sepsis and associated hypotension, hypertensive crisis, use of potent vasoactive drugs such as noradrenaline (norepinephrine) or dobutamine and the need for frequent arterial blood sampling (Garretson 2005). In the European Prevalence of Infection in Intensive Care study, for example, 44% of critically ill participants underwent arterial catheterization (Vincent 1995).

Over years of clinical practice, the manufacturers of arterial catheters have actively researched variables that can impact the safety profile and functionality of arterial catheters. The most frequently researched variables include site of insertion and insertion technique, composition of the catheter, types of anticoagulant and fluid used to flush the internal lumen of the catheter and the amount of external pressure applied to the flush solution in an effort to prevent the backflow of arterial blood into the arterial cannula and transducer tubing. Inflating the pressure infuser bag to a constant 300 mmHg has become standard practice (Brozek 2008). A variety of catheters available on the market are composed of hypothyrombotic materials or are impregnated with antiplatelet and/or antithrombotic drugs. These catheters have not become commonplace, most likely because of their unknown cost/benefit profile. The most common site of insertion is the radial artery, given the ease of access and patient safety described in comparison with alternate sites such as the carotid or femoral artery (Cines 2010; Garrettson 2005).

Arterial cannulation, similar to all medical interventions, is associated with risk. A landmark study conducted in 1967 by Mortensen reported a 16% complication rate amongst 3193 participants (Mortensen 1967). This result is contentious; however, no follow-up studies of a similar magnitude have been conducted. In a comprehensive review of radial artery complications, Brzezinski 2009 reported permanent ischaemic complications at a rate of 0.09%. The most common complication was clotting at the entry site (20 participants; 0.6%), which resulted in reduced blood flow to the distal limb (Mortensen 1967). Poor patency of arterial catheters can result in vascular clotting, scarring of surrounding tissues and infection (Randolph1998). In spite of these risks, arterial catheterization affords the multidisciplinary healthcare team invaluable information about the patient's condition. Determination of the success of medical decision making and interventions is dependent on the accuracy of data received from blood samples and of physiological measurements observed on bedside monitors connected to the arterial catheter. Maintaining the patency of these catheters is therefore essential in minimizing patient discomfort and additional expenses incurred if repeated replacement of a blocked catheter should be required (Tuncali 2005).

Description of the intervention

The anticoagulant properties of heparin led clinicians to use heparinized saline infusions as a means of preventing the blood from clotting inside the arterial catheter or on the external surface and creating risk of embolization when the catheter is flushed or removed and/or causing the catheter to malfunction. A patient who receives the minimum dose of heparin flush solution of 1 IU/h plus a 5-mL flush/h following hourly arterial blood gas analysis will receive approximately 192 IU of heparin/24 h. Despite its beneficial antithrombotic effects, heparin use is not without risks. In 3% of patients who use heparin at therapeutic doses, an autoimmune-mediated thrombocytopenia can occur that greatly increases the risk of clotting events (Cines 2010; Rice 2005). Other risks include allergic reactions and increased potential for bleeding (Whitta 2006).

For some patients admitted to hospital, the only exposure to heparin and its potential risks occurs through the arterial flush solution. Following publication of the results of the 1998 systematic review and meta-analysis performed by Randolph and colleagues, normal saline flush has replaced heparin as the standard flush solution for peripheral venous catheters in most clinical settings (Randolph1998). However, the use of 0.9% sodium chloride (normal saline) as an arterial flush solution, with or without heparin, to minimize thrombus formation and prolong the patency of the catheter began before any research was conducted to determine its efficacy in this setting (Randolph1998; Tuncali 2005). Over the years, numerous research projects have been conducted with varying and sometimes contradictory outcomes (de Neef 2002; Randolph1998). Many ideas as to the reasons for these variances have been proposed (e.g. heparin dose, catheter insertion site), all of which inform the hypothesis for another research study. Hence clinicians remain uncertain as to best practice surrounding the use of heparin or normal saline as a flush solution for maintaining the patency of arterial catheters.

How the intervention might work

Interest in the use of normal saline only as the flush solution for arterial catheters arose as the result of increasing knowledge about the risks associated with the use of heparin. Numerous clinical trials and case series argue the benefits associated with use of normal saline alone instead of heparin (AACN 1993; Whitta 2006). These benefits include decreased risk of potential medication errors, elimination of the risk of drug incompatibilities and overall simplification of nursing procedures (AACN 1993; Whitta 2006). However, normal saline has no inherent anticoagulant properties; thus poor patency of catheters, vascular thrombosis, scarring and infection remain constant concerns.

Why it is important to do this review

No systematic review of the literature has been conducted to synthesize conflicting results from randomized controlled trials (RCTs) comparing heparin solutions versus normal saline only for maintaining the patency of arterial catheters in the adult population. Therefore, it is prudent to determine whether the benefits of heparin outweigh the potential risks associated with its use versus normal saline in the arterial flush solution.

OBJECTIVES

The objective of this review was to evaluate whether normal saline is as efficacious and safe as heparin in maintaining the patency of arterial intravascular catheters in adult patients without a haematological disorder.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and/or quasi-randomized studies.

Types of participants

We included adult patients (as defined by the individual study protocol) without a haematological disorder (e.g. acquired or inherited coagulation or haemostasis disorders).

Types of interventions

The experimental intervention of interest was 0.9% sodium chloride (normal saline) flush solution with no added heparin versus a control of normal saline solution with heparin added at any dose. The flush solution needed to be given as a continuous infusion (typically under 300 mmHg to achieve a constant infusion rate of 3 mL/h).

We excluded from this review any study in which the intervention or control flush solution was delivered on an intermittent basis.

Types of outcome measures

Primary outcomes

- Duration of arterial line utility (i.e. reliability of arterial pressure and waveform quality, the ease with which the flush solution can be infused and arterial blood withdrawn).

Secondary outcomes

- All-cause mortality.
- Presence of clots, infection, inflammation (arteritis) or ischaemia of the limb.
- Number of adverse events (e.g. bleeding total number of participants who had one or more episodes of bleeding), bruising (total number of participants who had one or more episodes of bruising)).

Studies that did not clearly specify timing of and reasons for discontinuation of the arterial line were excluded from the review.

Search methods for identification of studies

Electronic searches

The choice of which subject matter database to search and the design of a suitable search strategy for each of these databases were guided by the Cochrane Anaesthesia Group search specialist. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 1, part of *The Cochrane Library*; MEDLINE (Ovid, 1966 to March 2013); EMBASE (Ovid, 1988 to March 2013) and CINAHL (1988 to March 2013) using specific strategies as advised by the Cochrane Anaesthesia Group search specialist (see [Appendix](#)

1 (CENTRAL), [Appendix 2](#) (MEDLINE, CINAHL) and [Appendix 3](#) (EMBASE)).

In addition, we combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy phases one and two, as contained in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Our MEDLINE searches included both free-text terms (including alternative spellings) and Medical Subject Heading (MeSH) terms. We exploded MeSH headings.

From the search results, we identified all relevant articles on PubMed and critiqued the MeSH terms for new terms to be included in the search strategies. We fed all new terms back into the search strategy before rerunning the search. We handsearched reference lists from identified published trials, abstracts of relevant conference proceedings and reference lists of relevant articles to identify further clinical trials. We did not impose a language restriction. We emailed each of the primary authors noted on the publications in an attempt to identify additional studies and unpublished reports. No additional information was identified.

Searching other resources

We searched the following Websites for relevant ongoing trials and 'grey' literature ([Ryan 2007](#)).

- www.controlled-trials.com.
- www.clinicalstudyresults.org.
- www.webarchive.nationalarchives.gov.uk.
- www.joannabriggs.edu.au.
- <http://clinicaltrials.gov/ct2/search>.
- <http://www.who.int/entity/en/>.

We searched the following grey literature and conference proceedings.

- New York Academy of Science Grey Source: A Selection of Web-based Resources in Grey Literature (also checking the subset called 'Grey Literature Report').
- Clinical Medicine Netprints Collection Index to Theses Canada Portal Networked Digital Library of Theses and Dissertations.
- Australian Digital Thesis Program Proquest.
- Digital Theses ISTP on Web of Science British Library INSIDE (www.bl.uk/insideSIGLE).
- <http://international.inist.fr/article55.html>, www.science.gov, www.scirus.com.

Data collection and analysis

Two of the review authors (VF and GM) independently screened all identified studies against the protocol inclusion criteria. Marked differences between the identified studies in terms of methodological quality, dose of heparin given and timing and route of arterial flush solution were noted; therefore a meta-analysis was not completed (see Risk of bias [Figure 1](#) and [Figure 2](#)). The review team's statistician (WG) attempted to bring together the three pairs of published survival graphs onto the same page. The result is a "composite survival graph from the original publications." However, because some data on the original graphs were ambiguous as the result of overlapping and/or criss-crossing of graph segments, it is an impossible task to properly indicate censored points. Therefore, we chose to omit this graph

from the review; however, the graph is available on request. The graph, which is best described as an illustration of key features from the original research graphs, conveys the relative times and

magnitudes of various events so that the reader can develop some sort of visual comparison of how the different studies relate to each other.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Budz 1995	+	+	+	+	+
Clifton 1991	?	?	?	+	+
Del Cutillo 2008	+	?	+	?	?
Goh 2011	?	+	?	+	+
Kulkarni 1994	-	?	+	+	?
Tuncali 2005	+	?	+	+	?
Whitta 2006	?	?	+	+	?

Selection of studies

The search and selection of studies followed a three-step process. First, two review authors (GM and VF) independently scanned the titles and abstracts of reports identified by the above search

strategy. Second, handsearching and snowballing from reference lists of key articles were performed. Third, focused searches based on expert advice were completed. All studies that did not meet the inclusion criteria were discarded (see [Figure 3](#) for search results and [Appendix 4](#) for the study retrieval form).

Figure 3. Study selection and inclusion.

Data extraction and management

Both review authors extracted data using a standardized tool for primary outcomes and risk of bias quality assessments and accuracy and completeness of data (see [Appendix 5](#) for the data extraction form). Discrepancies were resolved by having the third review author (SR-M) independently review the paper. For each included trial, information was extracted regarding the location and methods of the trial, participant characteristics (age range, eligibility criteria), the nature of the interventions and data related to the outcomes specified above. When information regarding any of the above was unclear, emails were sent to the authors of the

original reports to request further details. SR-M entered data into Review Manager software [RevMan 5.1](#); GM checked the accuracy of data entry.

Assessment of risk of bias in included studies

Two of the review authors (VF and GM) independently assessed each of the included studies using the RevMan 5.2 risk of bias tool ([Higgins 2011](#)). Five of the six criteria are reported in graphical format ([Figure 1](#); [Figure 2](#)) and include the following: sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. The assessment process was

not blinded to authorship or to journal of publication; however, each review author paid particular attention to the clarity with which each of the five assessment criteria was reported. Each study was defined as having low risk of bias only if each of the five criteria was adequately fulfilled. Additional details about risk assessment for each of the included studies can be found in the results section of this review.

Measures of treatment effect

The effect measure of choice was the risk ratio for benefits gained and/or the risk ratio for harms avoided. Each of the seven included studies (Budz 1995; Clifton 1991; Del Cotillo 2008; Goh 2011; Kulkarni 1994; Tuncali 2005; Whitta 2006) measured the primary outcome of interest. Three studies (Budz 1995; Tuncali 2005; Whitta 2006) used a continuous variable: mean duration of catheter in place. Four studies (Clifton 1991; Del Cotillo 2008; Goh 2011; Kulkarni 1994) used survival analysis (Table 1). Catheter functionality (i.e. difficulty flushing, aspiration of blood, dampening and/or loss of arterial waveform) was measured in six of the seven studies by a scoring system of numbers of events reported during a given period of time (typically an eight-hour intensive care unit work shift).

Unit of analysis issues

Each of the included studies randomly assigned at the level of the participant; however, the unit of analysis consisted of arterial catheter duration and functionality. Each of the included studies followed a simple parallel-group design whereby each participant was randomly assigned to a maintenance solution containing heparin or to normal saline without heparin. Catheter duration is reported as a single measurement per participant; however, inconsistency across the included studies was noted regarding how this was measured. Three studies (Budz 1995; Kulkarni 1994; Tuncali 2005) measured the mean duration of the arterial catheter. Three studies (Clifton 1991; Del Cotillo 2008; Goh 2011) captured catheter survival (count) over time. All included studies analysed catheter functionality in different ways. Four studies (Budz 1995; Clifton 1991; Del Cotillo 2008; Kulkarni 1994) measured functionality according to the occurrence (count) of individual events such as difficulty flushing, aspiration of blood and dampening and/or loss of arterial waveform. Tuncali 2005 reported the mean number of corrective manipulations of the catheter to maintain functionality, and Whitta 2006 reported a functional score of mean percentage.

Dealing with missing data

Intention-to-treat analysis and management of missing data were discussed by the authors of three included studies. Goh 2011 recruited and analysed data from 70 participants. Kulkarni 1994 chose to exclude from the final analysis participants with missing data and the Del Cotillo 2008 survival analysis censored participants in the normal saline arm who had to be treated with heparin.

Assessment of heterogeneity

The major source of heterogeneity between studies was clinical. No two studies measured catheter functionality and duration in the same way. Therefore pooling of data was not possible because of variation between studies in the dose of heparin given and/or

the scale of measurement used to report catheter functionality and duration.

Assessment of reporting biases

Reporting bias was assessed according to the five criteria detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- Selective omission of outcomes from reports.
- Selective selection of data for an outcome.
- Selective reporting of analyses using the same data.
- Selective reporting of subsets of the data.
- Selective under-reporting of data.

Reporting bias was unclear for all seven studies.

Data synthesis

We intended to present pooled data as mean differences (MDs) with 95% confidence intervals (CIs) if the included trials used similar scales of measurement, and standardized mean differences (SMDs) would be used with different scales of measurement. For dichotomous data, we planned to calculate risk ratios (RRs) of pooled data inclusive of 95% CIs, and the Peto odds ratio would be used if the pooled outcome effect was very small (< 1%). Given the clinical variation between studies, pooling of data into a meta-analysis would be misleading and therefore was not undertaken. A summary of the included studies is provided in narrative and tabular formats.

Subgroup analysis and investigation of heterogeneity

No subgroup analysis was undertaken.

Sensitivity analysis

We had planned to perform sensitivity analysis based on the dose of heparin used in different trials and differences between randomized and quasi-randomized studies. However, because of the high degree of clinical heterogeneity of the included studies, a meta-analysis was not undertaken.

RESULTS

Description of studies

No differences in data extraction were noted between review authors (GM and VF). A complete summary of each included study and reasons for exclusion of studies can be found in the tables *Characteristics of included studies* and *Characteristics of excluded studies*.

Results of the search

We identified 23 full-text studies as potentially suitable. From these identified studies, we excluded 16 and included seven studies. No disagreement between review authors regarding inclusion of studies was observed. See Figure 3 for further details.

Included studies

Study design

All studies used a parallel design. Six studies included two groups (Clifton 1991; Del Cotillo 2008; Goh 2011; Kulkarni 1994; Tuncali

2005; Whitta 2006). One study had three arms (Budz 1995). Comparative groups varied between studies in the dose of heparin used.

Sample sizes

Studies included in the review ranged in sample size from 30 (Budz 1995; Clifton 1991) to 200 (Tuncali 2005).

Study location and source of participants

Two studies were conducted in Canada (Budz 1995; Kulkarni 1994), one study in Spain (Del Cotillo 2008), one in the United States (Clifton 1991), one in Singapore (Goh 2011), one in Turkey (Tuncali 2005) and one in New Zealand (Whitta 2006).

Participants

All participants were recruited from an intensive care setting. Two studies were conducted in a mixed medical/surgical intensive care unit (Del Cotillo 2008; Whitta 2006) and included a total of 198 participants, one study was conducted in a neuroscience intensive care unit (Goh 2011) and included a total of 70 participants, two studies were conducted in a general surgical intensive care unit (Kulkarni 1994; Tuncali 2005) and included a total of 141 participants, one study of 30 participants was conducted in a general medical intensive care unit (Clifton 1991) and one study of 30 participants was conducted in a cardiac intensive care unit (Budz 1995). The site of arterial cannulation varied between included studies. Four studies used the radial artery (Budz 1995; Clifton 1991; Kulkarni 1994; Tuncali 2005), and two studies used a variety of sites (radial, brachial, femoral, pedal) (Del Cotillo 2008; Whitta 2006).

Types of interventions

The dose of heparin used varied between groups. Five studies used a dose of 1 IU/mL of heparin (Budz 1995; Del Cotillo 2008; Goh 2011; Tuncali 2005; Whitta 2006), two studies used a dose of 2 IU/mL of heparin (Budz 1995; Kulkarni 1994) and one study used a dose of 4 IU/mL of heparin (Clifton 1991).

Outcome measures

Arterial catheter utility was measured differently amongst the studies. Four studies (Clifton 1991; Del Cotillo 2008; Goh 2011; Kulkarni 1994) used survival analysis (hours) without the log rank data (clarity of censored data) available for statistical comparison of how the different studies relate to each other; two studies used the mean (min/h) duration of catheter in place (Budz 1995; Tuncali 2005) and one study used the mean duration of catheter survival against the central limits theorem at the 95% CI (Whitta 2006). All of the included studies, except for Goh 2011, assessed catheter functionality by counting one or all of the following events within a specified period: arterial haemodynamic waveform dampening, resistance to manual flushing or blood withdrawal from the arterial cannula and the need for manipulation of the arterial catheter (position change, etc). Tuncali 2005 was the only study that reported assessment of the secondary outcomes of interest: risk of haematoma, insertion site infection and limb ischaemia. Budz 1995 was the only study that assessed the presence of clots on the arterial catheter upon removal. Although five of the included studies (Budz 1995; Clifton 1991; Goh 2011; Kulkarni 1994; Whitta 2006) monitored participant coagulation profiles throughout the

trial—prothrombin time, partial thromboplastin time and platelet count—no comparative analysis on risk of bleeding was performed.

Excluded studies

Reasons for exclusion of studies can be broken down into four categories. Ten studies followed a different protocol. For example, the AACN 1993 study used normal saline (94.5%), lactated Ringer's (2.3%), glucose (1.5%) and other (1.7%) base flush solutions without providing subgroup analyses of the different solutions. Branson 1993 reviewed sodium citrate for maintenance of the arterial line, Hook 1987 compared heparin versus lactated Ringer's, Kaye 2001 used only normal saline without comparison versus heparin, Bolgiano 1990 compared two different strengths of heparin as opposed to heparin versus saline and Hall 2006 is a duplicate publication of Whitta 2006. Ouellet 1992 was excluded, as no participant data were provided in published or unpublished works. Further breakdown of excluded studies, outlining specifics of design and outcomes, can be seen in [Characteristics of excluded studies](#).

Risk of bias in included studies

All of the included studies were conducted within a hospital setting and received ethical approval from the hospital's central research and ethics committee. An overall assessment of risk of bias for each outcome across studies was used in making judgements about the quality of evidence. In this assessment, the key study-level domains were sequence generation, concealment of sequence allocation (related to selection bias) and completeness of outcome data (related to attrition bias). The key outcome-level domains were blinding and selective reporting.

For researcher-assessed outcomes (duration of catheter functionality; incidence of haematoma, arteritis, presences of clots and limb ischaemia), four of the six included studies reported adequate blinding and a small loss to follow-up.

See [Figure 1](#) and [Figure 2](#) for a graphical summary of the risk of bias assessments of the included studies as performed by the review authors. No study was deemed to have low risk of bias in all domains. Most of the studies included in the review had methodological weaknesses, in particular, poor clarity in reporting of allocation and concealment. Despite efforts to procure additional information by emailing the primary trial authors, no additional data were forthcoming.

Allocation

Six of the seven studies provided a brief description of the method used to generate a sequence for random assignment and/or concealment of this randomization process (Budz 1995; Del Cotillo 2008; Goh 2011; Kulkarni 1994; Tuncali 2005; Whitta 2006). Clifton 1991 provided no description.

Blinding

Four of the six studies provided details about the blinding process (Budz 1995; Del Cotillo 2008; Kulkarni 1994; Whitta 2006). No description was provided by Clifton 1991 or Whitta 2006.

Incomplete outcome data

Each of the included studies analysed the same numbers of participants as the numbers initially randomly assigned to

treatment and control groups. However, only one study (Goh 2011) reported intention-to-treat analyses. Therefore, irrespective of the ability to gauge attrition bias from the tables of data reported for each study, the degree of risk that attrition bias plays in this review remains unclear.

Selective reporting

Overall, selective reporting of outcomes for each of the six included studies was assessed as unclear.

Effects of interventions

Total duration of catheter functionality (min/h/d)

The stated outcome for five of the seven studies that measured this primary outcome of interest (Del Cotillo 2008; Goh 2011; Kulkarni 1994; Tuncali 2005; Whitta 2006) was that 0.9% saline is as effective as heparin in maintaining the patency and functionality of the arterial catheter. Del Cotillo 2008 used 1 IU/mL of heparin for comparison with normal saline and reported a median duration of catheter in place as 5.1 days (interquartile range (IQR) = 8.1) in the heparin group and 5.4 days (IQR = 7.3) in the saline group. This finding was not statistically significant, with a P value > 0.5 (P value 0.7). Tuncali 2005 used 1 IU/mL of heparin for comparison with normal saline during the perioperative period and reported that the mean duration of cannulation for the heparin group was 378 minutes ($\pm$ 159.0 standard deviation (SD)) compared with 332 minutes ($\pm$ 154.6 SD) for the normal saline group and stated that no statistically significant difference was found between the two groups. Whitta 2006 used 1 IU/mL of heparin for comparison with normal saline and reported that the mean study duration was 6.6 days for the heparin group and 5.8 days for the normal saline group with no significant difference in study duration noted with use of the Student's *t* test. However, given the poor reporting of the sampling and random sequence generation for all of the included studies, the risk of bias is high; therefore caution must be used in interpreting these results. An additional table- (Table 1) has been constructed by the review authors in an attempt to provide an 'overview' of the important elements of each of the included studies. The final column in this table provides a summary of the primary outcome: duration of catheter function using a single measurement: hours.

We were not able to perform meta-analyses as planned on any of the outcomes. The only two studies that used the same data measurement for catheter patency (Clifton 1991; Kulkarni 1994) used different heparin doses and therefore introduced too much heterogeneity to warrant pooled analysis. Kulkarni 1994 used 2 IU/mL of heparin, whilst Clifton 1991 used 4 IU/mL. Both studies combined the heparin with 1000 mL of 0.9% saline and pressurized the solution to maintain a continuous flow at 3 mL/h. Kulkarni 1994 concluded that no difference between the two different maintenance solutions was observed. Clifton 1991, on the other hand, stopped the trial early on the observation that heparin proved to significantly improve catheter duration and functionality, with a catheter survival rate of 86% at 96 hours compared with a rate of 52% after 40 hours with 0.9% normal saline. The significant difference in the dose of heparin used in Clifton's study should be considered when the study results are reviewed. Many of the secondary outcomes were measured at very different time points, and some studies reported highly skewed data. Amidst this heterogeneity, we did not perform a pooled analysis with any of

the secondary data and therefore chose to give only a narrative description of the results. We provide numerical data for each study result, which can be found in both the table titled [Characteristics of included studies](#) and [Table 1](#), Duration of catheter functionality.

Presence of clot on removal of arterial catheter

Budz 1995 was the only study that measured the presence of clot on removal of the arterial catheter; investigators reported a rate of 30% in the normal saline group and a rate of 0% in the heparin group.

Insertion site infection (arteritis) (follow-up: seven days)

Tuncali 2005 was the only study that measured the incidence of infection and reported that no participant in the normal saline and heparin groups experienced insertion site infection.

Limb ischaemia (follow-up: seven days)

Tuncali 2005 was the only study that measured the incidence of distal limb ischaemia; investigators reported that no participant in the normal saline and heparin groups experienced limb ischaemia.

Risk of bleeding

Four of the included studies (Budz 1995; Clifton 1991; Kulkarni 1994; Whitta 2006) monitored participants' coagulation profiles throughout the trial—prothombin time, partial thromboplastin time, platelet count—but none of these studies measured the outcome of 'risk of bleeding.'

Risk of haematoma at 24 hours (follow-up: seven days)

Tuncali 2005 was the only study that measured the incidence of haematoma at 24 hours; investigators found that haematoma was present in one participant in the normal saline group and in two participants in the heparin group and concluded that the incidence of haematoma after decannulation and at 24 hours was similar in the two groups.

DISCUSSION

Summary of main results

This present review compares 0.9% normal saline versus heparin for the prevention of clotting in arterial lines. The most important outcome for the patient is arterial catheter functional duration, as this results in accurate clinical data to guide clinical decision making and a reduced number of painful, invasive procedures whenever a non-functional arterial catheter needs to be replaced and/or frequent radial artery 'stabs' for arterial blood gas analysis are needed. Therefore, the primary outcome that we assessed was duration of catheter functionality (meaning the ability to accurately assess physiological measurements needed for patient care). Five of the included studies (Budz 1995; Del Cotillo 2008; Goh 2011; Tuncali 2005; Whitta 2006) compared normal saline versus 1 U/mL of heparin, and each concluded that no benefit was gained from the use of heparin (please refer to [Table 1](#): Overview of studies). Clifton 1991, on the other hand, who used a higher dose of heparin, recommends the use of heparin to improve catheter survival and functionality, whilst Kulkarni 1994, who used only 2 U/mL, suggests that no observable benefit was evident at 96 hours when heparin was added to the maintenance flush solution.

Available evidence suggests that no observable difference occurs when 0.9% normal saline is used compared with 1 to 2 U/mL heparin for maintaining catheter patency and functionality. However, significant differences are observed when the heparin dose is increased to 4 U/mL. This result was observed in only one study of 30 participants, and the quality of the reported data was poor. Death and/or all-cause mortality was not reported in any of the included studies. Emails were sent to the primary trial authors to seek further details on study methods; no response was received.

Failure in catheter functionality was commonly defined as catheter clotting and/or arterial pressure waveform dampening. Such definitions are unlikely to provide a reliable indication as to the duration of catheter function. These endpoints are highly subjective and do not necessarily translate to detriments experienced by the patient. No major adverse events were reported in association with the higher dose of heparin of 4 U/mL.

We therefore conclude that the limited available evidence suggests that a maintenance solution (pressurized to deliver 3 mL/h) of 0.9% normal saline is as effective as 1 or 2 U/mL of heparin in maintaining the patency and functionality of arterial catheters when positioned in the radial artery (Goh 2011; Kulkarni 1994; Tuncali 2005). A number of clinical variables are suggested to impact the duration and functionality of catheters, such as receipt of other anticoagulants or thrombolytics, use of a catheter longer than two inches and femoral insertion site, all of which need to be taken into consideration when arterial catheterization of patients is planned (Budzy 1995; Clifton 1991; Del Cutillo 2008; Goh 2011; Kulkarni 1994; Tuncali 2005; Whitta 2006).

Overall completeness and applicability of evidence

The limitations of our analysis may originate from the quality of data reported in available studies and from our analysis of these data. Of these, we emphasize the lack of a consistent and comparable method for measuring catheter patency across studies. Arterial catheter duration, with or without the more subjective assessments of dampening of arterial pressure waveform and presence of haematoma, needs to be reported comparatively in all trials for future research results to improve reliability and use of the evidence obtained for the question at hand.

Quality of the evidence

The methodological quality of all included studies was low, based on the criteria set forth in the risk of bias table provided in the Review Manager software (please refer to Figure 1 and Figure 2). Most studies were double-blinded; however, losses to follow-up were not adequately described, and allocation concealment was unclear. None of the study authors discussed intention-to-treat analysis. The study authors described their funding sources, which were not related to industry.

Potential biases in the review process

The search strategy used to find relevant studies was not limited to English and would have identified studies in other languages, thereby avoiding language bias. However, although studies not available in English were identified during the search process, none fit the inclusion criteria, and all studies included in the review were published in English.

Grey literature bias and studies published in non-indexed journals, particularly in developing countries, may result in lack of identification of all relevant studies. Searching was performed and two review authors were used to critically appraise the quality of included studies; in addition, the authors of included studies were contacted for information on unpublished or ongoing studies, but none were found. It is not possible to quantify the effect that publication bias may have had in this review.

Agreements and disagreements with other studies or reviews

Two existing studies have become a consistent reference in the discussion of strategies to maintain the patency of arterial catheters: AACN 1993 and Randolph1998. In 1993, the American Association of Critical-Care Nurses (AACN) (AACN 1993) published the results of a large-scale randomized clinical trial (Thunder I Project) conducted to evaluate the effects of heparinized and non-heparinized flush solutions on the patency of arterial pressure monitoring catheters. This multi-centre RCT included studies from a total of 198 critical care units in a variety of locations in the United States, Canada and Australia. A total of 5139 participants were included in the final analysis. The conclusions of the trial authors are supportive of this review in that use of a heparin flush did not guarantee patency of the catheter. Randolph and co-workers (Randolph1998) conducted a systematic review and meta-analysis of 26 RCTs that evaluated the effects of heparin (intermittent use or continuous infusion) on duration of catheter patency and prevention of complications associated with its use in peripheral venous and arterial catheters. Two of the 13 included studies used peripheral arterial catheters, and the rest used peripheral venous catheters. The conclusion of Randolph1998 that infusion of low-dose heparin significantly prolongs the patency of radial artery catheters conflicts with the results of this review. The reasons for this difference may relate to the fact that three of the six studies included in this review (Del Cutillo 2008; Tuncali 2005; Whitta 2006) were not published and therefore were not included in the Randolph1998 review.

AUTHORS' CONCLUSIONS

Implications for practice

The existing evidence is of poor quality but suggests that a maintenance solution (pressurized to deliver 3 mL/h) of 0.9% normal saline is as effective as heparin 1 to 2 U/mL in maintaining the patency and functionality of arterial catheters when positioned in the radial artery (Goh 2011; Kulkarni 1994; Tuncali 2005).

Implications for research

Randomized controlled trials are needed to help guide the choice of arterial line maintenance infusion solutions for the critically ill patient. We found the evidence to be suggestive, but not conclusive, that normal saline is as effective as heparin in maintaining the functional patency of arterially inserted catheters (Goh 2011; Kulkarni 1994; Tuncali 2005; Whitta 2006). Additional research is needed to determine the upper time limit for the use of normal saline flush solution in maintaining the function of an arterially inserted catheter. Attention should also be paid to determining which insertion site is optimal. Of particular note for future research is the inconsistency that currently exists in practice related to measurement of catheter functionality. It is essential that future

researchers design studies that gather data on outcomes that are clinically relevant to the patient and the clinician. Consensus on the minimum criteria will strengthen future research efforts.

Further, methodological challenges exist, including heterogeneity of the patient population (patients receiving subcutaneous heparin, co-morbidities, admission diagnosis, age) and the large sample size required to show a clinical difference. Nevertheless, future multi-centre trials are urgently needed. These must ensure methodological rigour by examining potential risks for bias at the design stage, for example, in both random sequence generation and concealment, as well as in blinding of outcome assessors and use of outcome measures that are less prone to biased assessments or reporting.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Budz 1995

Methods	Randomized, double-blind
Participants	30 participants
	Cardiac surgery intensive care unit at a tertiary care hospital, Canada
Gender	

Heparin versus normal saline for patency of arterial lines (Review)

Budz 1995 (Continued)

- 6:24 male

Mean age distribution, years

- Heparin 1 U/mL: 63.2
- Heparin 2 U/mL: 62.1
- Saline: 64.4

Inclusion criteria

- First-time coronary artery bypass graft surgery
- Admitted to cardiac surgery ICU postoperatively
- Age between 35 and 75 years
- No chronic illness other than coronary artery disease
- No known coagulation disorders
- Had taken acetylsalicylic acid (ASA) before hospital admission
- Cannulation with a #20 Teflon radial artery catheter before surgery
- Normal PT, PTT and platelets preoperatively
- Able to understand English

No exclusion criteria provided

Pressurized bag to achieve continuous flow rate of 3 mL/h

Insertion site

- Radial artery

Interventions	<p>Gp 1 (n = 10) 2 IU/mL of heparin (the control group)</p> <p>Gp 2 (n = 10) 1 IU/mL of heparin</p> <p>Gp 3 (n = 10) N/saline</p> <p>Coagulation tests were performed preoperatively and at time intervals of 24 and 48 hours post surgery</p>
Outcomes	<p>Primary outcomes of interest</p> <p>1. Difference in occlusion risk of the radial arterial catheter among the flush solution</p> <p><i>Mean duration and (SD) of catheter in situ</i></p> <p>Gp 1 (2 IU/mL hep): 39.15 (7.55)</p> <p>Gp 2 (1 IU/mL hep): 36.10 (8.11)</p> <p>Gp 3 (normal saline): 37 (12.17)</p> <p>2. Difference in frequency of occlusion of the radial arterial catheter among flush solutions (P value 0.05)</p> <p><i>Difficulty flushing; aspiration; dampened waveform; loss of arterial waveform</i></p> <p>Gp 1: 5 counts</p> <p>Gp 2: 6 counts</p> <p>Gp 3: 17 counts</p> <p>3. Reasons for catheter removal (P value 0.01)</p> <p><i>Catheter no longer required; inability to withdraw blood; arterial spasm</i></p> <p>Gp 1: 9/10; 1/10; 0/10</p>

Budz 1995 (Continued)

Gp 2: 9/10; 0/10; 1/10

Gp 3: 5/10; 5/10; 0/10

Notes	Results of this study tend to indicate that heparin continues to be required in the flush solution to maintain arterial catheter patency
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a random numbers table, the pharmacist assigned each subject to one of the 2 experimental groups or control. Reference codes were sealed until completion of study
Allocation concealment (selection bias)	Low risk	Reference codes identifying the type of flush solution were sealed until completion of the study
Blinding (performance bias and detection bias) All outcomes	Low risk	It was reported that both the researcher and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All missing data were reported and accounted for
Selective reporting (reporting bias)	Low risk	The results for all proposed outcomes were reported

Clifton 1991

Methods	<p>Double-blind, randomized design</p> <p>Participants were consecutively entered into the study and were randomly assigned to receive heparin or normal saline flush solution</p>
Participants	<p>15 participants were enrolled into each treatment group from a general adult medical intensive care unit</p> <p>Gender: 7:8 men</p> <p>Age: 56.2 (±15.1):48 (±17)</p> <p>The study was originally planned for 40 participants. <i>The study was stopped after 30 participants because investigators detected a significant difference in patency rates</i></p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> Radial artery only with adequate collateral circulation <p>Exclusion criteria</p> <ul style="list-style-type: none"> Coag disorders Platelet count < 50,000 mm³ Systemic anticoagulants <p>Insertion site: radial artery</p>
Interventions	Gp 1: (15) N/saline

Heparin versus normal saline for patency of arterial lines (Review)

Clifton 1991 (Continued)

Gp 2: (15) 4 IU/mL Hep

Pressurized bag to achieve continuous flow rate of 3 mL/h

Outcomes	<p>Primary outcomes</p> <p>1. <i>Catheter duration</i></p> <ul style="list-style-type: none"> Survival analysis <p>2. <i>Catheter functionality</i></p> <ul style="list-style-type: none"> Dampened waveform (count) Catheter occlusion: <i>inability to draw blood freely</i> (count) Corrective manipulation (% per 8-hour shift) Frequency of manipulation (count/8-hour shift) according to scoring system: <p>0 times, 1-5 times, 5-6 times, 6-10 times, >10 times per 8-hour shift</p>
Notes	<p>Catheter failures</p> <p>Gp 1 (normal saline) = 5/15 = 52% patency @ 40 hours</p> <p>Gp 2 (4 IU/mL Hep) 1/15 = 100% patency at 40 hours</p> <p>Use of heparin-containing flush solution resulted in a catheter survival rate (Kaplan-Meier P value < 0.05) of 86% at 96 hours compared with a rate of 52% after 40 hours with normal saline. Heparin-flushed catheters required significantly less manipulation to prevent catheter occlusion and arterial pressure/waveform dampening. Use of normal saline as a continuous flush is associated with an increase in frequency of catheter occlusion and malfunction, and is not recommended in patients with abnormal coagulation and platelet count</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study authors were contacted via email for further clarification with no response
Allocation concealment (selection bias)	Unclear risk	Study authors were contacted via email for further clarification with no response
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study authors were contacted for clarification with no response
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data remained consistent and accounted for throughout analysis and reporting
Selective reporting (reporting bias)	Low risk	Results for all proposed outcomes were reported

Del Cutillo 2008

Methods	Randomized, double-blind, placebo-controlled
Participants	133 patients from a third-level intensive care unit

Heparin versus normal saline for patency of arterial lines (Review)

Del Cotillo 2008 (Continued)

>18 years of age

1 arterial cath/patient

Gender: 71%:66% men

Age, years: 63.5 (± 15.6):62.7 (± 15.8)

Exclusion criteria

- Hypersensitivity to heparin
- > 5 insertion attempts @ same site
- Thrombocytopenia $< 100,000/\text{mm}^3$
- Full-dose anticoag or fibrinolytics
- Concurrent participation in another study

Catheter insertion site

- Radial: 62% of Hep group; 57% saline
- Femoral: 38% Hep; 38% saline
- Pedal: 0% Hep; 3% saline
- Humeral: 0% Hep; 2% saline

Interventions	<p>Gp 1 (n = 65): 1 IU/mL Hep</p> <p>Gp 2 (n = 68): N/saline</p> <p>Arterial catheter functionality was compared in the groups every 8 hours and at catheter removal</p>
Outcomes	<p>Primary outcomes</p> <p>1. Catheter patency as measured by:</p> <ul style="list-style-type: none"> • Reliability of arterial pressure % • Curve quality % • Number of manipulations to maintain patency % (lavage of catheter, mobilization or both) <p>2. Catheter survival as measured by:</p> <ul style="list-style-type: none"> • Median duration of catheter in days - Kaplan-Meier (P value < 0.05)
Notes	<p>Catheter patency at time of removal (P value 0.09)</p> <p>Gp 1: 92%</p> <p>Gp 2: 82%</p> <p>Catheter survival - median (P value 0.7)</p> <p>Gp 1: 5.1 days</p> <p>Gp 2: 5.4 days</p> <p>Use of heparinized solutions for arterial catheter maintenance does not appear to be justified. Heparin did not increase the duration of catheters nor improve their functionality</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The pharmacy department randomly assigned, masked and dispensed the saline vials

Heparin versus normal saline for patency of arterial lines (Review)

Del Cotillo 2008 (Continued)

Allocation concealment (selection bias)	Unclear risk	No details were provided
Blinding (performance bias and detection bias) All outcomes	Low risk	It was reported that both the researcher and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details were provided
Selective reporting (reporting bias)	Unclear risk	No details were provided

Goh 2011

Methods	Randomized controlled trial
Participants	<p>70 patients in neuroscience intensive care unit (NSICU) at the Singapore General Hospital in Singapore from August 2008 to February 2009</p> <p>Heparin: 22 male:12 female</p> <p>Saline: 20 male:16 female</p> <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Allergy to heparin • Those receiving anticoagulant, thrombolytic or platelet therapy • Those who had a history of HITTS <p>Cannulation site</p> <ul style="list-style-type: none"> • Radial: 54 • Brachial: 14 • Dorsalis pedis: 2
Interventions	<p>Group 1 (n = 34): 1 IU/mL Hep</p> <p>Group 2 (n = 36): N/saline</p> <p>Continuous pressure of 300 mmHg and a flow rate of 3 mL/h</p>
Outcomes	<p>Arterial line patency</p> <p>At 72 hours (P value 0.578)</p> <p>Gp1 Hep: 34/34 heparin</p> <p>Gp 2 N/saline: 35/36 N/saline</p> <p>At 120 hours (P value 0.328)</p> <p>Gp 1 Hep: 31/34 heparin</p> <p>Gp 2 N/saline: 30/34 N/saline</p>
Notes	

Heparin versus normal saline for patency of arterial lines (Review)

Goh 2011 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information was not reported
Allocation concealment (selection bias)	Low risk	Sealed envelope was prepared by someone not involved in the study
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study was single-blinded (participants)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Seventy patients were recruited for this study, and all completed the study with no dropouts
Selective reporting (reporting bias)	Low risk	Reporting was transparent

Kulkarni 1994

Methods	Randomized, double-blind trial Randomly assigned according to date of admission: even dates received normal saline; odd dates received heparin
Participants	78 adults Trial was performed in surgical ICU within a university-affiliated hospital Gender <ul style="list-style-type: none"> Heparin (n = 40): 11:29 male Saline (n = 38): 13:25 male Mean age, years <ul style="list-style-type: none"> Heparin: 66.7 (21-87) Saline: 65.9 (38-86) Exclusion criteria <ul style="list-style-type: none"> Emergency admissions Therapeutic use of anticoagulants Thrombolytic therapy or antiplatelet therapy Arterial line site other than radial artery Site could not be cannulated within five attempts Incomplete data Consent not obtained Site of catheterization: radial
Interventions	Gp 1 (n = 40): 2 IU/mL heparin Gp 2 (n = 38): N/saline

Heparin versus normal saline for patency of arterial lines (Review)

Kulkarni 1994 (Continued)

- All participants underwent baseline, daily and post-catheter removal assessment of:
 - * Allen's test
 - * Measurement of finger pulse waveform
 - * Measurement of bilateral digit temperature on first, middle and little digits
 - * Assessment of radial artery flow
 - * Coagulation assessment
 - * Site appearance
 - * Arterial pressure waveform
 - * Blood withdrawal and flushing ability
 - * Number of times blood withdrawn from system
 - * Accuracy of intra-arterial BP measurement compared with brachial artery cuff measurement

Outcomes	Primary outcome of interest 1. Catheter patency as measured by: <ul style="list-style-type: none"> • Mean duration of arterial catheter (hours) • Kaplan-Meier for distribution of time until blockage • Frequency of events (accuracy of intra-arterial pressure vs cuff pressure)
Notes	Results <i>Mean duration</i> Gp 1 Hep 2 IU: 98 hours Gp 2 N/saline: 80 hours Proportion of catheters patent at 72 hours (Fisher's exact test ($P = 0.05 > P \text{ value} \leq 0.16$, X^2 test)) Gp 1 Hep 2 IU: 93% Gp 2 N/saline: 82% (CI -0.643 to +0.283)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomly allocated to 2 groups according to the date of admission: Group A (Heparin) for participants admitted on odd-number days; Group B (normal saline) for participants admitted on even-number days
Allocation concealment (selection bias)	Unclear risk	No details were provided
Blinding (performance bias and detection bias) All outcomes	Low risk	It was reported that both the researcher and clinicians were blinded
Incomplete outcome data (attrition bias)	Low risk	All data remained consistent and accounted for throughout analysis and reporting

Heparin versus normal saline for patency of arterial lines (Review)

Kulkarni 1994 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	No details were provided
--------------------------------------	--------------	--------------------------

Tuncali 2005

Methods	Randomized, double-blind
---------	--------------------------

Participants	200 (100/group) participants included in study for preoperative patients
--------------	--

- Heparin group: 61 males, 39 females
- Normal saline group: 72 males, 28 females

Mean age, years

Gp 1 Hep 1 IU: 61.5 (± 14.7)

Gp 2 N/saline: 65.6 (± 12.6)

Exclusion criteria

- History of heparin allergy
- Preoperative heparin
- Surgical procedures requiring systemic heparin
- Preop platelet or coag abnormalities
- Thrombotic risk
- Radial or ulnar blood flow abnormalities

Site of insertion

- Radial artery

Interventions	Gp 1 (n = 100): heparin 1 IU/mL Gp 2 (n = 100): N/saline • 300 mmHg continuous pressure/3 mL/h
---------------	--

Outcomes

Primary outcome of interest
Duration of catheter placement (minutes)

Mean duration of catheter placement was similar in the 2 groups

- Gp 1: 378 minutes (± 150 minutes)
- Gp 2: 332 minutes (± 154.6 minutes)

Mean number of times blood withdrawn

The mean number of times blood was withdrawn from the system was similar in the 2 groups

Mean number of corrective interventions

The mean number of corrective interventions due to dampening of the pressure wave, such as positional changes and manual flushes, was not significantly different in the 2 groups

- Gp 1: 1.4 (± 3.8)
- Gp 2: 1.5 (± 2.0)

Tuncali 2005 (Continued)

Incidence of haematoma post decannulation

The incidence of hematoma after decannulation and at 24 hours was similar in the 2 groups

Notes	The study authors concluded that there is no significant difference between heparinized and non-heparinized flush solutions in the maintenance of radial artery catheter patency
-------	--

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers sequence was placed in sealed envelopes and opened before each anaesthesia induction
Allocation concealment (selection bias)	Unclear risk	No details were provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Researcher and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data remained consistent and accounted for throughout analysis and reporting
Selective reporting (reporting bias)	Unclear risk	No details were provided

Whitta 2006

Methods	Randomized, double-blind
Participants	<p>65 adult patients from a mixed medical/surgical ICU</p> <ul style="list-style-type: none"> Gp 1: mean age, years: 58 Gp 2: mean age, years: 50 <p>Exclusion criteria</p> <ul style="list-style-type: none"> Preexisting coagulopathy precluding heparin use History of heparin-induced thrombocytopenia Heparin sensitivity Age younger than 16 years Requirements for therapeutic heparin <p>Site of insertion</p> <p>Radial, brachial or femoral artery</p>
Interventions	<ul style="list-style-type: none"> Gp 1 (n = 35): 1 IU heparin Gp 2 (n = 30): N/saline <p>Each participant's nurse was asked to score from 3-0, the function of the line at the end of each 8-hour shift</p> <ul style="list-style-type: none"> 3 functioning well for monitoring and blood sample-taking 2 functioning well most of the time, requiring some attention

Heparin versus normal saline for patency of arterial lines (Review)

Whitta 2006 (Continued)

- 1 functioning poorly
- 0 requiring changing

Participant removed from trial if score 0; however, result maintained for analysis purposes

Outcomes	Primary outcome of interest 1. Catheter patency and functionality as measured by: <ul style="list-style-type: none"> • Functional score as a mean percentage and compared with central limit theorem at 95% CI
Notes	Catheter function results Gp 1: 82% Gp 2: 83% Cathether function comparisons completed using central limits theorem CI (-6% to 10%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were provided
Allocation concealment (selection bias)	Unclear risk	No details were provided
Blinding (performance bias and detection bias) All outcomes	Low risk	It was reported that both the researcher and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data remained consistent and accounted for throughout analysis and reporting
Selective reporting (reporting bias)	Unclear risk	No details were provided

Abbreviations:

ASA = Acetylsalicylic acid.

BP = Blood pressure.

CI = Confidence interval.

Coag = Coagulation.

Gp = Group.

Hep = Heparin.

HITS = Heparin induced thrombocytopenia

ICU = Intensive care unit.

PT = Prothrombin time.

PTT = Partial thromboplastin time.

SD = Standard deviation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
AACN 1993	Different protocol. Saline was not the only comparison: lactated Ringer's solution, glucose and others. In addition, no data were available regarding the dose of heparin administered
Alexander 2010	Methodological: systematic review
Barrett 1990	Methodological: non-randomized
Bolgiano 1990	Different protocol. Comparison of two strengths of heparin, not heparin versus normal saline
Branson 1993	Different protocol. Used sodium citrate in base solution for maintenance of arterial catheters
Carlson 1989	Methodological. Cost/benefit analysis
Hall 2006	Duplicate publication with Whitta's
Halm 2008	Methodological: review of available literature
Hamilton 1988	Different protocol. Intermittent infusion devices
Hook 1987	Different protocol: comparison between heparin and lactated Ringer's solution
Kaye 2001	Different protocol: randomized trial to review catheter patency; however, no comparison between heparin and saline, only use of normal saline to maintain catheter patency. No head-to-head comparison
Leighton 1994	Methodological: non-randomized
Ouellet 1992	Incomplete data. No participant data provided in published or non-published form
Randolph1998	Different protocol: used a range of comparative solutions with heparin
Vázquez-Calatayud 2010	Methodological: systematic review
Zevola 1997	Different protocol: pulmonary artery catheters

ADDITIONAL TABLES

Table 1. Duration of catheter functionality

Study	Number of participants	Heparin dose	Arterial insertion site	Duration of catheter functionality
Budz 1995	Gp 1: 10	Gp 1: 2 IU/mL	Radial	1 IU Hep: 36.10 hours
	Gp 2: 10	Gp 2: 1 IU/mL		2 IU Hep: 39.15 hours
	Gp 3: 10	Gp 3: N/saline		N/saline: 37 hours
Clifton 1991	Gp 1:15	Gp 1: N/saline	Radial	4 IU Hep: 100% @ 40 hours
	Gp 2:15	Gp 2: 4 IU/mL		N/saline: 52% @ 40 hours

Table 1. Duration of catheter functionality *(Continued)*

Del Cotillo 2008	Gp 1: 65	Gp 1: 1 IU/mL	<ul style="list-style-type: none"> Radial: 62% of Hep group; 57% saline Femoral: 38% Hep; 38% saline Pedal: 0% Hep; 3% saline Humeral: 0% Hep; 2% saline 	I IU Hep: 122.4 hours
	Gp 2: 68	Gp 2: N/saline		N/saline: 129.6 hours
Goh 2011	Gp 1: 34	Gp 1: 1 IU/mL	<ul style="list-style-type: none"> Radial: 28 in Gp 1 and 26 in Gp 2 Brachial: 10 in Gp 1 and 4 in Gp 2 Pedal: 0 in Gp 1 and 2 in Gp 2 	I IU Hep: 100% @ 72 hours
	Gp 2: 36	Gp 2: NS		N/saline: 97% @ 72 hours
Kulkarni 1994	Gp 1:40	Gp 1: 2 IU/mL	Radial	2 IU Hep: 93% @ 72 hours
	Gp 2:38	Gp 2: N/saline		N/saline: 82% @ 72 hours
Tuncali 2005	Gp 1: 100	Gp 1: 1 IU/mL	Radial	1 IU Hep: 6.3 hours
	Gp 2:100	Gp 2: N/saline		N/saline: 5.53 hours
Whitta 2006	Gp 1:35	Gp 1:1 IU/mL	Radial, brachial or femoral artery	1 IU Hep: 158.4 hours
	Gp 2:30	Gp 2: N/saline		N/saline: 132 hours

The last column is an adaptation of the primary study results into a single measurement: hours.

APPENDICES

Appendix 1. CENTRAL search strategy

```
#1 MeSH descriptor Heparin explode all trees
#2 heparin*
#3 MeSH descriptor Sodium Chloride explode all trees
#4 MeSH descriptor Saline Solution, Hypertonic explode all trees
#5 saline*:ti,ab
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 flush
#8 vascular patency
#9 Arterial Lines
#10 MeSH descriptor Catheters, Indwelling explode all trees
#11 MeSH descriptor Injections, Intra-Arterial explode all trees
#12 arterial catheter*
#13 arterial NEAR catheter*
#14 MeSH descriptor Catheterization, Peripheral explode all trees
#15 (catheterization or catheterisation):ti,ab
#16 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #15)
#17 (#6 AND #16)
```

Appendix 2. MEDLINE search strategy

```
1. exp Heparin/ or exp Sodium Chloride/ or exp Saline Solution, Hypertonic/ or (heparin* or saline*).ti,ab.
2. exp Catheters, Indwelling/ or exp Injections, Intra-Arterial/ or exp Catheterization, Peripheral/ or (flush or vascular patency or arterial line*).mp. or (arterial adj3 catheter*).mp. or catheteri?ation.ti,ab.
3. 1 and 2
```

4. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.

5. 3 and 4

Appendix 3. EMBASE search strategy

1. heparin/ or sodium chloride/ or (heparin* or saline*).ti,ab.

2. indwelling catheter/ or intraarterial drug administration/ or catheterization/ or (flush or vascular patency or arterial line*).ti,ab. or (arterial adj3 catheter*).ti,ab. or catheteri?ation.ti,ab.

3. 1 and 2

4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.

5. 3 and 4

Appendix 4. Study retrieval form

Study characteristics	Eligibility criteria	Yes	No	Unclear	Location in text
	<i>(Insert eligibility criteria for each characteristic as defined in the protocol)</i>				<i>(pg & ¶/fig/table)</i>
Type of study	Randomized controlled trial				
	Controlled clinical trial				
	<i>(quasi-randomized trial)</i>				
Participants					
Types of interventions					
Types of outcome measures					
INCLUDE	EXCLUDE				
Reason for exclusion					
Notes:					

Appendix 5. Data extraction and quality appraisal form

1. General information

Date form completed (dd/mm/yyyy)

Name/ID of person extracting data

Report title

(title of paper/abstract/report from which data are extracted)

Report ID

(ID for this paper/abstract/report)

Reference details

Report author contact details

Publication type

(e.g. full report, abstract, letter)

Study funding sources

(including role of funders)

Possible conflicts of interest

(for study authors)

Notes:

2. Population and setting

	Description	Location in text
	Include comparative information for each group (i.e. intervention and controls) if available	(pg & ¶/fig/table)

Population description

(from which study participants are drawn)

Setting

(including location and social context)

(Continued)

Inclusion criteria
Exclusion criteria
Method/s of recruitment of participants
Informed consent obtained

Yes No Unclear

Notes:
3. Methods

	Descriptions as stated in report/paper	Location in text (pg & ¶/fig/table)
Aim of study		
Design (e.g. parallel, cross-over, cluster)		
Unit of allocation (by individuals, clusters/groups or body parts)		
Start date		
End date		
Total study duration		
Ethical approval needed/obtained for study		
	Yes No Unclear	
Notes:		

4. Risk of bias assessment

Domain	Risk of bias			Support for judgement	Location in text (pg & ¶/fig/table)
	Low risk	High risk	Unclear risk		

(Continued)

Random sequence generation

(selection bias)

Allocation concealment

(selection bias)

Blinding of participants and personnel

(performance bias)

Outcome group:
all/

(if required)

Outcome group:
Blinding of outcome assessment

(detection bias)

Outcome group:
all/

(if required)

Outcome group:
Incomplete outcome data

(attrition bias)

Selective outcome reporting?

(reporting bias)

Other bias
Notes:
5. Participants
**Description as stated
in report/paper**
Location in text
(pg & ¶/fig/table)

Total no. randomly assigned

(or total population at start of study for non-randomized controlled trials
(NRCTs))

Clusters

(Continued)

(if applicable, no., type, no. people per cluster)

Baseline imbalances

Withdrawals and exclusions

(if not provided below by outcome)

Age

Sex

Race/Ethnicity

Severity of illness

Co-morbidities

Other treatment received (additional to study intervention)

Other relevant sociodemographics

Subgroups measured

Subgroups reported

Notes:

6. Intervention groups
Intervention group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
<hr/>		
Group name		
<hr/>		
No. randomly assigned to group		
(specify whether no. people or clusters)		
<hr/>		
Theoretical basis (include key references)		
<hr/>		
Description (include sufficient detail for replication, e.g. content, dose, components)		
<hr/>		
Duration of treatment period		
<hr/>		

(Continued)

Timing (e.g. frequency, duration of each episode)

Delivery (e.g. mechanism, medium, intensity, fidelity)

Providers

(e.g. no., profession, training, ethnicity etc., if relevant)

Co-interventions

Economic variables

(i.e. intervention cost, changes in other costs as result of intervention)

Resource requirements to replicate intervention

(e.g. staff numbers, cold chain, equipment)

Notes:

7. Outcomes

Outcome 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	Yes No Unclear	
Imputation of missing data (e.g. assumptions made for intention-to-treat (ITT) analysis)		

(Continued)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:
8. Results
Dichotomous outcome

Description as stated in report/paper		Location in text	
		(pg & ¶/fig/table)	
Comparison			
Outcome			
Subgroup			
Time point (specify whether from start or end of intervention)			
Results	Intervention		Comparison
	No. events	No. participants	No. events No. participants
No. missing participants and reasons			
No. participants moved from other group and reasons			
Any other results reported			
Unit of analysis (by individuals, cluster/groups or body parts)			
Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation)			

(Continued)

Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results

Notes:

Continuous outcome

Description as stated in report/paper				Location in text (pg & ¶/fig/table)		
Comparison						
Outcome						
Subgroup						
Time point (specify whether from start or end of intervention)						
Post intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis (individuals, clusters/groups or body parts)						
Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation)						
Reanalysis required? (specify)						
Yes No Unclear						
Reanalysis possible?						

Yes No Unclear

(Continued)

Reanalysed results

Other outcome

Description as stated in report/paper					Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Time point (specify whether from start or end of intervention)					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (by individuals, clusters/groups or body parts)					
Statistical methods used and appropriateness of these methods					
Reanalysis required? (specify)					
	Yes	No	Unclear		
Reanalysis possible?					
	Yes	No	Unclear		
Reanalysed results					
Notes:					

9. Applicability

Have important populations been excluded from the study? (*consider disadvantaged populations and possible differences in the intervention effect*)

Yes No Unclear

Is the intervention likely to be aimed at disadvantaged groups? (*e.g. lower socioeconomic groups*)

Yes No Unclear

Does the study directly address the review question?

(*any issues of partial or indirect applicability*)

Yes No Unclear

Notes:

10. Other information

**Description as stated
in report/paper**

Location in text
(*pg & ¶/fig/table*)

Key conclusions of study authors

References to other relevant studies

Correspondence required for further study information (*from whom, what and when*)

Notes:

WHAT'S NEW

Date	Event	Description
14 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 5, 2014

Date	Event	Description
14 May 2014	Amended	Typo corrected

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Suzi Robertson-Malt (SRM).
 Co-ordinating the review: SRM, Greg Malt (GM).
 Undertaking manual searches: SRM, GM, Vincent Farquhar (VF).
 Screening search results: GM, VF.
 Organizing retrieval of papers: GM, VF.
 Screening retrieved papers against inclusion criteria: GM, VF.
 Appraising quality of papers: SRM, GM, VF.
 Abstracting data from papers: SRM, GM, VF.
 Writing to authors of papers to ask for additional information: GM, VF.
 Providing additional data about papers: SRM, GM.
 Obtaining and screening data on unpublished studies: SRM, GM.
 Managing data for the review: SRM, GM.
 Entering data into Review Manager ([RevMan 5.1](#)): SRM, GM.
 Handling RevMan statistical data: SRM, GM, William Greer (WG).
 Performing other statistical analyses not using RevMan: WG.
 Performing double entry of data (data entered by person one: SRM; data entered by person two: GM).
 Interpreting data: SRM, WG.
 Making statistical inferences: WG.
 Writing the review: SRM, GM, VF, WG.
 Securing funding for the review: not applicable.
 Performing previous work that served as the foundation of the present study: SRM.
 Serving as guarantor for the review (one review author): SRM.
 Taking responsibility for reading and checking the review before submission: SRM.

DECLARATIONS OF INTEREST

Suzanne Robertson-Malt: none known.

Greg N Malt: none known.

Vincent Farquhar: none known.

William Greer: none known.

SOURCES OF SUPPORT

Internal sources

- New source of support, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes were made to the published protocol ([Robertson-Malt 2008](#)).

1. We reworded the review objective statement.
2. We made 'all-cause mortality' a discreet secondary outcome measure.
3. We aligned the risk of bias with five of the domains outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

*Catheter Obstruction; Anticoagulants [*administration & dosage]; Heparin [*administration & dosage]; Randomized Controlled Trials as Topic; Sodium Chloride [*administration & dosage]

MeSH check words

Humans