# Treatment for superficial infusion thrombophlebitis of the upper extremity (Review)

**Di Nisio M, Peinemann F, Porreca E, Rutjes AWS**


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[Intervention Review]

# Treatment for superficial infusion thrombophlebitis of the upper extremity

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## ABSTRACT

### Background

Although superficial thrombophlebitis of the upper extremity represents a frequent complication of intravenous catheters inserted into the peripheral veins of the forearm or hand, no consensus exists on the optimal management of this condition in clinical practice.

### Objectives

To summarise the evidence from randomised clinical trials (RCTs) concerning the efficacy and safety of (topical, oral or parenteral) medical therapy of superficial thrombophlebitis of the upper extremity.

### Search methods

The Cochrane Vascular Group Trials Search Co-ordinator searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (2015, Issue 3). Clinical trials registries were searched up to April 2015.

### Selection criteria

RCTs comparing any (topical, oral or parenteral) medical treatment to no intervention or placebo, or comparing two different medical interventions (e.g. a different variant scheme or regimen of the same intervention or a different pharmacological type of treatment).

### Data collection and analysis

We extracted data on methodological quality, patient characteristics, interventions and outcomes, including improvement of signs and symptoms as the primary effectiveness outcome, and number of participants experiencing side effects of the study treatments as the primary safety outcome.

**Main results**

We identified 13 studies (917 participants). The evaluated treatment modalities consisted of a topical treatment (11 studies), an oral treatment (2 studies) and a parenteral treatment (2 studies). Seven studies used a placebo or no intervention control group, whereas all others also or solely compared active treatment groups. No study evaluated the effects of ice or the application of cold or hot bandages. Overall, the risk of bias in individual trials was moderate to high, although poor reporting hampered a full appreciation of the risk in most studies. The overall quality of the evidence for each of the outcomes varied from low to moderate mainly due to risk of bias and imprecision, with only single trials contributing to most comparisons. Data on primary outcomes improvement of signs and symptoms and side effects attributed to the study treatment could not be statistically pooled because of the between-study differences in comparisons, outcomes and type of instruments to measure outcomes.

An array of topical treatments, such as heparinoid or diclofenac gels, improved pain compared to placebo or no intervention. Compared to placebo, oral non-steroidal anti-inflammatory drugs reduced signs and symptoms intensity. Safety issues were reported sparsely and were not available for some interventions, such as notoginseny creams, parenteral low-molecular-weight heparin or defibrotide. Although several trials reported on adverse events with topical heparinoid creams, Essaven gel or phlebolan versus control, the trials were underpowered to adequately measure any differences between treatment modalities. Where reported, adverse events with topical treatments consisted mainly of local allergic reactions. Only one study of 15 participants assessed thrombus extension and symptomatic venous thromboembolism with either oral non-steroidal anti-inflammatory drugs or low-molecular-weight heparin, and it reported no cases of either. No study reported on the development of suppurative phlebitis, catheter-related bloodstream infections or quality of life.

**Authors' conclusions**

The evidence about the treatment of acute infusion superficial thrombophlebitis is limited and of low quality. Data appear too preliminary to assess the effectiveness and safety of topical treatments, systemic anticoagulation or oral non-steroidal anti-inflammatory drugs.

## PLAIN LANGUAGE SUMMARY

**Treatment for superficial infusion thrombophlebitis of the upper extremity**

**Background**

Superficial thrombophlebitis is an inflammatory condition of the veins just below the surface of the skin. The development of superficial thrombophlebitis frequently complicates the insertion of needles into the veins for catheters to give medication or fluids in hospitalised patients. The best treatment for these blood clots in the hands and arms remains unclear. While local treatment has the potential to improve the painful symptoms and patient discomfort, it may not prevent complications, including infection or the extension or transit of the clot into the deep vein system.

**Study characteristics and key results**

In the current review, which looked for studies up to April 2015, we identified 13 studies involving 917 participants. Eleven studies evaluated topical treatments (medication applied to the skin), two trials studied an oral treatment, and two studies assessed a parenteral treatment (via injection or infusion). Seven studies used a control group that received no treatment or a placebo, whereas all others also or solely compared two active treatment groups. No study evaluated the effects of ice or the application of cold or hot bandages. Overall, topical treatments resulted in a higher and faster improvement of the clinical signs and symptoms compared to placebo or no intervention. Reporting on safety data was limited, with no available information on some treatments (notoginseny creams, parenteral low-molecular-weight heparin or defibrotide). Although some studies reported on harmful side effects with topical heparinoid creams, Essaven gel or phlebolan, the trials were too small in size to adequately measure any differences between treatments. Reported side effects of topical treatments consisted mainly of local allergic reactions. Only one study with 15 participants assessed anything other than localised control of the condition. That study reported on extension of the clot or symptomatic venous thromboembolism (when the blood clot breaks loose and travels in the blood stream), observing no cases when treated orally with non-steroidal anti-inflammatory drugs or with low-molecular-weight heparin. None of the studies reported on the development of suppurative or septic phlebitis (when pus is formed inside the vein or around the vein wall or both), catheter-related bloodstream infections or quality of life.

**Quality of the evidence**

Some of the included studies may have been biased due to design limitations, but we could not always assess this risk because the original researchers did not always provide enough information to judge. The overall quality of the evidence for each of the outcomes varied from low to moderate, mainly because the studies had design flaws or were very small. We could not analyse data on primary outcomes together because the trials examined different treatments, in different ways, looking at different outcomes. In short, the evidence about the treatment of acute infusion superficial thrombophlebitis is limited and of low quality, and we do not have enough information to recommend the use of any of the treatments studied.

# BACKGROUND

## Description of the condition

Superficial thrombophlebitis of the upper extremity is a relatively frequent complication of intravenous catheters inserted into the peripheral veins of the upper extremity, usually in the forearm or hand, to administer fluids, nutrients, drugs and blood products in hospitalised patients (De la Sierra 1989; Maki 1991; Tagalakis 2002; Tager 1983). While there is no standard diagnostic criterion or group of diagnostic criteria, distinctive clinical findings for superficial thrombophlebitis of the upper extremity include pain, tenderness, warmth, erythema, swelling and a palpable cord on the cannulated vein. Depending on the definition used and the type of patients evaluated, the incidence of superficial thrombophlebitis of the upper extremity has varied broadly between 0.1% to 70% (Bregenzer 1998; Collin 1975; Maki 1991; Monreal 1999; Soifer 1998; Tagalakis 2002; Tager 1983). The condition usually appears 12 to 36 hours after cannulation, and peaks at 72 to 96 h although some patients have been diagnosed with thrombophlebitis more than 15 days after catheter placement, which may depend on the definition and diagnostic methods used (Collin 1975; Gaukroger 1988; Hershey 1984; Maki 1987; Tager 1983; Tomford 1984). The duration of superficial thrombophlebitis of the upper extremity lasts around 24 to 96 hours or longer depending on the severity, concomitant diseases and the provision of symptomatic treatment (Hershey 1984).

Superficial thrombophlebitis of the upper extremity is believed to result from the activation of the inflammatory and coagulation cascades by a variety of triggering factors that irritate and damage the vein wall, including mechanical factors such as traumatic injury of the vessel wall by the catheter, infective factors like the bacterial colonisation of the intravascular segment of the catheter, or damage to the vessel wall by chemicals. Preliminary data suggest that, as for deep vein thrombosis of the extremities, the formation of a thrombus within the vein accompanies and often precedes the development of the clinical signs and symptoms that characterise superficial thrombophlebitis (Everitt 1997). Different studies have described risk factors for superficial thrombophlebitis of the upper extremity, although results have not always been consistent (Maki 1991; Tagalakis 2002). Duration of the catheterisation, catheter material and size, type of infusion (e.g. hypertonic solutions, intravenous antibiotics, chemotherapeutic agents), and catheter-related infections were all associated with the risk and duration of superficial thrombophlebitis (Collin 1975; Fonkalsrud 1971; Gaukroger 1988; Hershey 1984; Maki 1987; Maki 1991; Monreal 1999; Tagalakis 2002; Tager 1983; Timmer 1991). Patient-related risk factors such as the 'quality' of the cannulated veins or underlying medical diseases (e.g. active cancer, immunodeficiencies, infections or skin diseases) also seem to influence the development of superficial thrombophlebitis (Gaukroger 1988; Hershey 1984; Tager 1983; Tomford 1984).

While superficial thrombophlebitis of the upper extremity is generally considered a trivial nosocomial complication, it can nonetheless cause substantial patient discomfort and require the removal of the catheter with insertion of a new cannulae at a different site. Repeated episodes of superficial thrombophlebitis can lead to venous access difficulties and placement of a central venous catheter with resulting delayed administration of parenteral medications and lengthened hospital stay. Occasionally, serious complications can occur; one of the most threatening local complications is a supervening infection with the development of suppurative superficial thrombophlebitis, which occurs in up to 2% of peripheral vein catheter insertions (Lee 2009; Stein 1970; Stratton 1982; Tomford 1984). Patients with superficial thrombophlebitis of the upper extremity also have an increased risk of catheter-related bloodstream infections, which occur in 0.1% of the cases (Maki 1973; Maki 2006).

## Description of the intervention

Superficial thrombophlebitis of the upper extremity can be prevented by intermittent heparin flushes or heparin continuous infusions, which Randolph 1998 reported as reducing the risk of superficial thrombophlebitis by 39% and 45%, respectively. Regular replacement of the catheter every 48 to 72 hours has been shown to be of no benefit compared with leaving the catheter in place for longer periods and changing it only if clinically indicated

(Smith 1990; Webster 2013). Once superficial thrombophlebitis has developed, the prompt removal of the catheter is generally associated with an improvement of the clinical signs and symptoms. In those with continued discomfort, treatment may be indicated to reduce pain and inflammation as well as to obtain the patency of the obstructed vein. There is no consensus on the optimal management of superficial thrombophlebitis of the upper extremity in clinical practice, although several therapies have been proposed in the literature, including topical and systemic medical treatments. The 2008 guidelines of the American College of Chest Physicians suggested treating patients experiencing symptomatic infusion superficial thrombophlebitis with an oral anti-inflammatory drug, topical diclofenac gel, or heparin gel until resolution of symptoms or for up to two weeks (Kearon 2008). These guidelines recommended against the use of systemic anticoagulation.

### Why it is important to do this review

Conservative management, such as the topical application of anti-inflammatory drugs, mainly focuses on relieving the painful symptoms of superficial thrombophlebitis, and it might be regarded as sufficient to improve the acute inflammatory state and patient discomfort. However, it is unclear whether such treatment is sufficient to prevent complications such as suppurative superficial thrombophlebitis or catheter-related bloodstream infections. Moreover, the effects of treatment on the underlying thrombosis and its potential extension into the deep vein system need to be evaluated. Lastly, a benefit-harm evaluation is indicated to evaluate if routine treatment of superficial thrombophlebitis is indicated.

## OBJECTIVES

To summarise the evidence from randomised clinical trials (RCTs) concerning the efficacy and safety of (topical, oral or parenteral) medical therapy of superficial thrombophlebitis of the upper extremity.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs or quasi-randomised RCTs.

#### Types of participants

Hospitalised or ambulatory patients of any age with a diagnosis of superficial thrombophlebitis of the upper extremity based on presentation of symptoms and signs, including pain, tenderness, induration or erythema in a superficial vein. Superficial thrombophlebitis could involve any of the following veins: cephalic vein, median cubital vein, basilic vein, median antebrachial vein, dorsal metacarpal veins or dorsal network veins. We did not consider superficial thrombophlebitis of the lower extremity as this is the subject of another Cochrane review (Di Nisio 2013).

#### Types of interventions

Interventions included any (topical, oral or parenteral) medical treatment to relieve the symptoms and signs or to prevent complications of superficial thrombophlebitis (e.g. non-steroidal anti-inflammatory drugs or anticoagulants such as fondaparinux or low-molecular-weight heparin).

Comparison included either an inactive control intervention (i.e. placebo, no treatment), or another active intervention (i.e. a different variant scheme or regimen of the same intervention, a different pharmacological type of treatment).

We planned to record the use of ice or the application of cold or hot bandages, but no trials reported this outcome.

#### Types of outcome measures

##### Primary outcomes

###### Effectiveness

- Reduction or resolution of symptoms (for example, pain)
- Reduction or resolution of clinical signs (for example, induration and erythema)

We used the measures for assessing resolution as reported by the trialists.

###### Safety

Number of participants experiencing one or more side effects attributed to study treatment (e.g. bleeding or allergic reactions)

##### Secondary outcomes

###### Effectiveness

- Extension of superficial thrombophlebitis
- Suppurative superficial thrombophlebitis
- Catheter-related bloodstream infections

- Symptomatic venous thromboembolism
- Quality of life (by any validated quality of life instrument)

Venous thromboembolism (VTE) comprised deep venous thrombosis, pulmonary embolism, or both.

#### Safety

Adverse events (drug-related and non drug-related, local and systemic).
We planned to address all outcomes in a 'Summary of findings' table.

## Search methods for identification of studies

### Electronic searches

The Cochrane Vascular Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched April 2015) and the Cochrane Register of Studies (CRS) http://www.metaxis.com/CRSWeb/Index.asp (2015, Issue 3). See Appendix 1 for details of the search strategy used to search the CRS. The Specialised Register is maintained by the TSC and is constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular Group module in the *Cochrane Library* (www.cochranelibrary.com).
The following trial databases were searched by the TSC for details of ongoing and unpublished studies using the terms 'thrombophlebitis' AND 'arm', or 'phlebitis' AND 'arm'.

- World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/
- ClinicalTrials.gov http://clinicaltrials.gov/
- ISRCTN register http://www.controlled-trials.com/isrctn/

### Searching other resources

We searched the reference lists of relevant papers and conference proceedings of the International Society for Thrombosis and Hemostasis (January 2003 to December 2013) and American Society of Hematology (January 2004 to December 2013).

## Data collection and analysis

### Selection of studies

Two review authors (MDN, FP) independently reviewed titles and abstracts from the database searches to determine whether the studies seemed to meet our inclusion criteria, retrieving the full text of all potentially relevant trials. In both title/abstract and full text screening, these two review authors (MDN, FP) independently made decisions regarding inclusion, resolving disagreements through discussion or involvement of a third review author (AWSR).
We were not blinded to the journal, institution or results of the study. Where necessary, we contacted the trial investigators for additional information to judge eligibility. We documented the reasons for excluding studies in the Characteristics of excluded studies table. One review author (MDN) screened conference proceedings and included them if adequate information could be obtained either from the abstract or from personal communication, also identifying potentially relevant articles from reference lists. Two review authors (MDN, FP) independently assessed eligibility.

### Data extraction and management

Two review authors (MDN, FP) independently extracted the data from the included trials using piloted extraction forms. We resolved any disagreements by discussion and, if necessary, by involving a third review author (AWSR). We extracted data from any trial published in more than one report from the most complete record, which was typically the most recent publication. However, we checked all related trial reports for additional outcome data or trial descriptions. Collected information included methodological quality, characteristics of participants, characteristics of the intervention and control treatment, and outcomes of interest. If reported, we described how clinicians diagnosed the superficial thrombophlebitis of the upper extremity. We describe the methodological quality features in Assessment of risk of bias in included studies. In addition, we extracted information on trial size, design (parallel, factorial, cross-over; single centre, multicentre), setting (hospital versus ambulatory), reported primary and secondary outcomes, sample size calculations, funding and potential conflicts of interest. We recorded participant characteristics (whether clinicians diagnosed the thrombus in the superficial vein by venography or venous ultrasonography and whether other factors, such as age, gender or the presence of cancer or diabetes came into play) as well as treatment characteristics (type of intervention (e.g. type of analgesic or anti-inflammatory drug, type of anticoagulant), dosing, route of administration (topical, oral, parenteral)) and type of standardised co-interventions (e.g. removal catheters).

### Assessment of risk of bias in included studies

Two review authors (MDN, FP or AWSR) independently assessed randomisation, blinding, selective outcome reporting and adequacy of analyses (Higgins 2011). We resolved disagreements by consensus and, if necessary, AWSR acted as arbitrator. We assessed two components of randomisation: generation of allocation sequences and allocation concealment.

We considered generation of allocation sequences to denote a randomised design if it resulted in an unpredictable allocation schedule. Adequate mechanisms included random-number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards and drawing lots. On the other hand, we considered trials using potentially predictable allocation mechanisms, such as alternation or the allocation of participants according to date of birth, to be quasi-randomised (Rutjes 2009). We considered allocation concealment adequate if participants and investigators responsible for participant selection were unable to predict, before allocation, which treatment was next. Methods considered adequate included central randomisation, pharmacy-controlled randomisation using identical pre-numbered containers, and sequentially numbered, sealed, opaque envelopes (Rutjes 2009).
We considered blinding of participants and therapists to be adequate if studies explicitly described experimental and control preparations as indistinguishable, if trialists used a double-dummy technique or if there was an attempt to blinding. For blinding of assessors, we considered the method adequate if investigators explicitly affirmed that the trial used blinding methods on assessors.
We judged analyses as adequate (i.e. absence of attrition bias) if trials included all or at least 95% of randomised participants in the analysis according to the intention-to-treat principle. We classified the item 'free of selective reporting' (reporting bias) as at 'high risk of bias' if a report did not present data on all outcomes reported in either the protocol or the Methods section. If studies presented results for outcomes that were not mentioned in the Methods section, we also scored them as having a 'high risk of bias'.
We planned to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to describe the quality of the overall body of evidence for the primary effectiveness outcomes (Guyatt 2008; Higgins 2011).

### Measures of treatment effect

We presented results as summary risk ratios (RRs) for dichotomous variables and mean differences (MDs) for all continuous variables. We determined 95% confidence intervals (CIs) for each estimate. For statistically significant results, we aimed to calculate the number needed to treat in order to benefit one patient (NNT) or the number needed to treat in order to harm one patient (NNH) to express the final results of the review.

### Assessment of heterogeneity

We measured heterogeneity of the treatment effect between trials with both the variance estimate $I^2$ and $Tau^2$. The $I^2$ values of 25%, 50% and 75% correspond to low, moderate and high between-trial heterogeneity, respectively (Higgins 2011). A $Tau^2$ of 0.04 is typically interpreted to indicate low heterogeneity, while 0.09 indicates moderate heterogeneity, and 0.16 indicates high heterogeneity across trials (Spiegelhalter 2004).

### Assessment of reporting biases

For the main outcomes, we planned to evaluate publication bias and other biases related to small study size using funnel plots, plotting the RRs on the vertical axis against their standard errors on the horizontal axis (Sterne 2001). Funnel plot symmetry would be expected in the absence of any bias related to small study size. We planned to use the Egger's test for continuous outcomes and the Harbord-Egger's test to assess symmetry for binary outcomes (Harbord 2006), exploring any anomalies in stratified analyses (see Data synthesis).

### Data synthesis

Our main analyses included all eligible trials. We analysed and presented data by stratifying for the type of intervention used. We used standard inverse-variance, random-effects meta-analysis to pool outcome data, and the fixed-effect model if only one study was available. We planned to explore between-trial heterogeneity by stratifying the main outcomes for the following trial characteristics.

- Allocation concealment (adequate versus inadequate or unclear).
- Blinding (adequate versus inadequate or unclear).
- Analysis in accordance with the intention-to-treat principle ('yes' versus 'no' or 'unclear').
- Trial size.

In addition, we planned to investigate the effects of the following treatment features.

- Type of treatment (e.g. antiinflammatory versus anticoagulant).
- Route of administration (e.g. topical versus parenteral or oral).
- Length of treatment (one week versus longer).
- Length of follow-up (48 h versus one week versus two weeks or longer).

Regarding patient characteristics, we planned to explore whether the setting (ambulatory or inpatient) or the presence of cancer caused an effect. For all categorical trial, patient and treatment characteristics, we planned to use univariate random-effects meta-regression models to determine whether these characteristics influenced treatment effects (Thompson 1999). We performed data analyses in Cochrane Review Manager software, RevMan 2014. For stratified analyses and funnel plot exploration, we planned to use Stata 2012.
We planned to use GRADEpro 2008 software to create a 'Summary of findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

### Subgroup analysis and investigation of heterogeneity

We planned no additional analyses other than those described in Data synthesis and Sensitivity analysis.

### Sensitivity analysis

If there were sufficient trials, we aimed to perform a sensitivity analyses to control for the methodological quality of the trials. We defined high-quality trials according to the results of the stratified analyses. For example, if trials with adequate allocation concealment and blinding of outcome assessors showed significantly different results than trials without these features, we restricted the sensitivity analysis to trials that were adequately concealed and used blinded outcome assessors.

## RESULTS

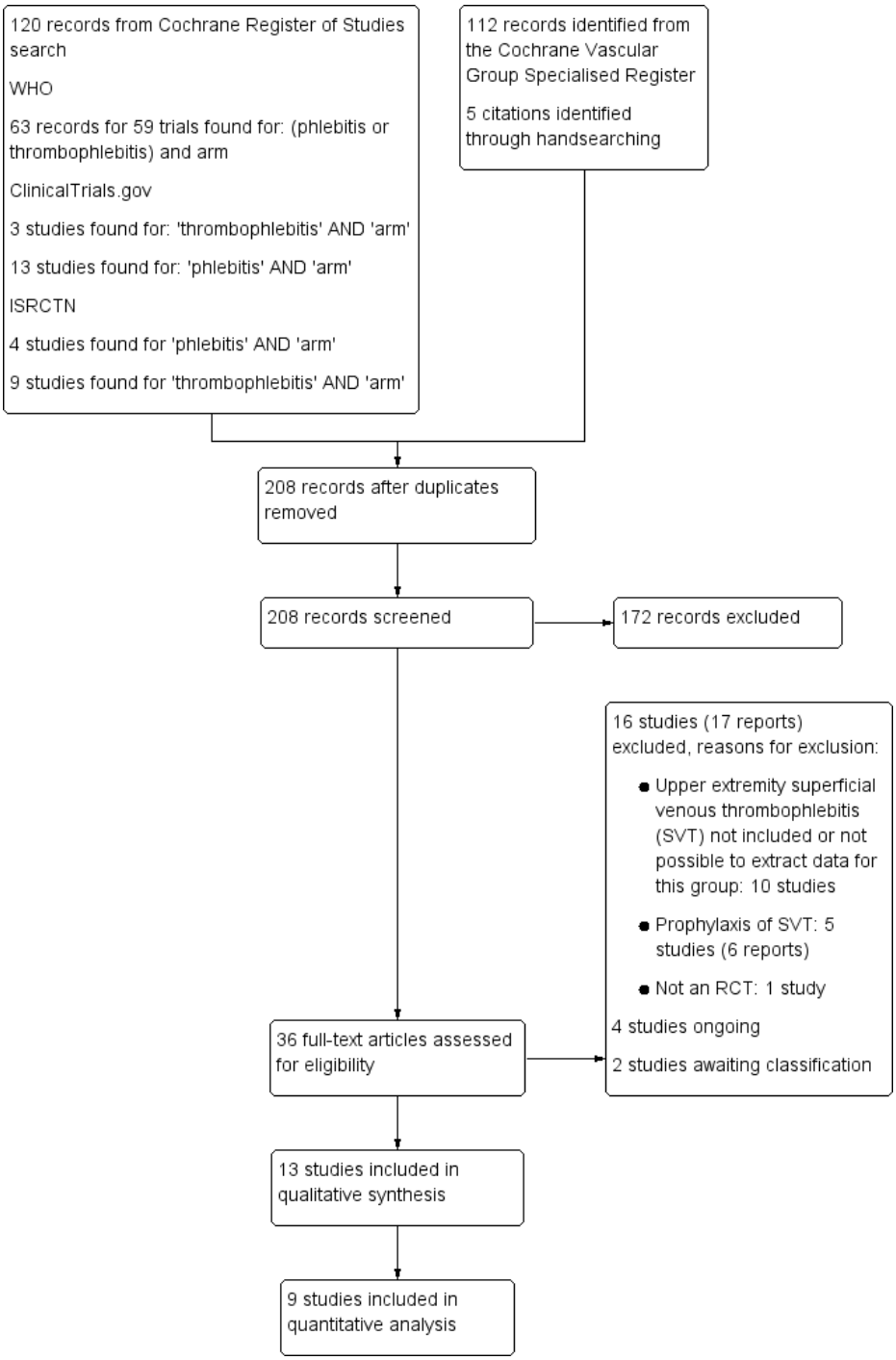
### Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

### Results of the search

See Figure 1.

**Figure 1. Study flow diagram**



Following title and abstract screening, we considered 36 reports to be potentially eligible.

We classified two studies as awaiting classification (Xiao 2004; Xu 2001) and four studies as ongoing (CTRI/2012/05/002629; CTRI/2013/12/004245; NCT01943006; NCT00377806).

## Included studies

Following full-text analysis, we included 13 studies (Almenar 1993; Becherucci 2000; Berrazueta 1993; De Sanctis 2001; Gouping 2003; Kowalsky 1978; Mehta 1975; Nachbur 1972; Rathbun 2012; Rozsos 1994; Schedel 1977; Seccia 1989; Vilardel 1999) with a total of 917 participants.

The characteristics of the included studies are detailed in the section Characteristics of included studies. Eleven studies evaluated topical treatments (Almenar 1993; Becherucci 2000; Berrazueta 1993; De Sanctis 2001; Gouping 2003; Kowalsky 1978; Mehta 1975; Nachbur 1972; Rozsos 1994; Schedel 1977; Vilardel 1999), two studied oral treatments (Becherucci 2000; Rathbun 2012) and two assessed parenteral treatments (Rathbun 2012; Seccia 1989). Six studies used a placebo control (De Sanctis 2001; Kowalsky 1978; Mehta 1975; Nachbur 1972; Schedel 1977; Vilardel 1999), while the control group in Becherucci 2000 received no intervention. All other studies also or solely compared different active treatment groups (Almenar 1993; Berrazueta 1993; Gouping 2003; Rathbun 2012; Rozsos 1994; Seccia 1989). None of the studies randomised participants to non-pharmacological prophylaxis.

Below we provide details on the comparisons available from the included studies. The numbering of the comparisons correspond to the numbering in the sections Effects of interventions and Data and analyses.

### Studies evaluating a topical treatment versus inactive control

#### 1. Heparin gel versus placebo

Kowalsky 1978 randomised participants (n = 102) with superficial thrombophlebitis of the upper extremity caused by endovenous catheters after gynaecological operation to organo-heparinoid ointment (Hirudoid 40,000 international units (IU) per 100 g topical application) or placebo during the 10-day study period.

Mehta 1975 randomised participants (n = 100) with infusion superficial thrombophlebitis caused by continuous intravenous infusion of normal saline, dextrose saline, blood or other fluids to heparinoid ointment (Hirudoid) or placebo cream. Study treatment was applied daily for at least five days and continued thereafter if symptoms persisted.

Schedel 1977 randomised participants (n = 40) with infusion superficial thrombophlebitis of the upper extremity to organo-heparinoid ointment (Hirudoid 40,000 topical application twice per day) or placebo during the 6-day study period.

Vilardel 1999 randomised inpatients (n = 132) with acute infusion superficial phlebitis secondary to indwelling intravenous catheter to receive topical sodium bovine heparin as gel preparation (containing 1000 IU/g of heparin) or placebo. Study treatment was applied three times a day until clinical healing or for a maximum of seven days.

#### 2. Essaven gel versus placebo

De Sanctis 2001 randomised participants (n = 23) with infusion superficial thrombophlebitis of the upper extremity to Essaven gel (5 $cm^2$ of gel corresponding to about 1 g of Essaven gel for each application) or placebo. All participants received low-molecular-weight heparin (enoxaparin sodium (Clexane) 0.1 mL/10 kg of body weight once daily) during the study period of four weeks.

#### 3. Phlebolan versus placebo

Nachbur 1972 randomised participants (n = 48) with infusion superficial thrombophlebitis of the upper extremity caused by endovenous catheters to phlebolan spray (diphenylbutazone 5%, prednisolone 0.5%, sodium rutin sulphate 0.2%, topical application three times per day) or placebo during the 5-day study period.

#### 4. Topical or oral diclofenac versus no intervention

Becherucci 2000 randomised hospitalised participants (n = 120) with infusion superficial thrombophlebitis to topical (gel 1% three times a day) or oral diclofenac (75 mg twice a day) for 48 h versus no intervention.

### Studies evaluating a topical treatment versus active control

#### 5 Transdermal nitroglycerine versus heparinoid gel

Almenar 1993 randomised inpatients and outpatients (n = 100) with superficial infusion phlebitis caused by endovenous catheters to receive six days of transdermal nitroglycerine gel 2% (2 $cm^2$ once daily) or heparinoid gel (sulphuric polyholoside ester sodium salt) applied three times daily. All participants had the catheter removed.

Berrazueta 1993 randomised participants (n = 47) with infusion thrombophlebitis of a superficial forearm vein to transdermal glyceryl trinitrate ointment (2% gel solution at a daily dose of 12 mg) or a heparinoid ointment (sulphuric polyholoside ester sodium salt).

**6. Notoginseny cream versus heparinoid cream**

Gouping 2003 included participants (n = 65) with postinfusion superficial thrombophlebitis of the forearm and randomised them to notoginseny cream (topical Chinese medicine containing safflower, notoginseng, shiny-leaf prickly ash and rhubarb) or heparinoid cream (Hirudoid cream). Both topical treatments were applied every 4 h until clinical resolution.

**7. Topical versus oral Diclofenac**

Becherucci 2000, described above.

**8. Pentosan polysulphate sodium ointment versus mucopolysaccharide ointment**

Rozsos 1994 randomised adult participants (n = 110) with acute infusion thrombophlebitis in one arm to pentosan polysulphate sodium ointment 0.5% or mucopolysaccharide ointment 0.445%. Participants received study treatments three times daily for seven days.

#### Studies evaluating an oral or parenteral treatment versus any control

Becherucci 2000 is described above.

**9. Defibrotide versus no intervention**

Seccia 1989 randomised outpatients and inpatients with superficial thrombophlebitis of the lower (n = 125) and upper (n = 15) extremities to four groups. We only included the participants with superficial thrombophlebitis of the upper extremities in this review. The patients with acute superficial thrombophlebitis of the upper extremity presented within 72 h of symptoms onset and were randomised to either defibrotide (800 mg/d intramuscular (IM) for four days followed by 400 mg/d IM until clinical resolution) plus standard treatment, or standard treatment alone until clinical resolution. Standard treatment consisted of antimicrobic therapy (bacampicillin 800 mg/d for 48 h), diclofenac 100 mg/d, topical desoxyribonuclease and elastic compression.

**10. Dalteparin versus ibuprofen**

Rathbun 2012 randomised consecutive inpatients and outpatients with superficial thrombophlebitis of the lower (n = 57) or upper (n = 15) extremities to dalteparin (200 IU/kg subcutaneously at presentation followed by 10,000 IU subcutaneously daily for an additional six days) plus placebo given orally three times daily for seven days versus ibuprofen (800 mg given orally three times daily for seven days) plus placebo injections given daily for seven days. In case symptoms of superficial thrombophlebitis were not resolved at day 7 to 9, the patient received an additional seven days of the blinded therapy provided there was no thrombus extension. This review only included the people with superficial thrombophlebitis of the upper extremities.

### Excluded studies

We excluded 16 studies (17 reports; see Characteristics of excluded studies). The reasons for exclusion were that participants with upper extremity superficial thrombophlebitis were not included or it was not possible to extract data for this group (Bergqvist 1990; Bruni 1979; D'Amico 1987; Nocker 1990; De Tullio 1989; Gorski 2005; Nocker 1991; Porters 1981; Pozza 1980; Stolle 1986), the study was about prophylaxis of superficial thrombophlebitis of the upper extremity (Cökmez 2003; Messing 1985; Nieto-Rodriguez 1992; Reid 1990; Wright 1985) or the study was not an RCT (Marrapodi 1986).

## Risk of bias in included studies

The risks of bias in the included studies is shown in Figure 2 and Figure 3.

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

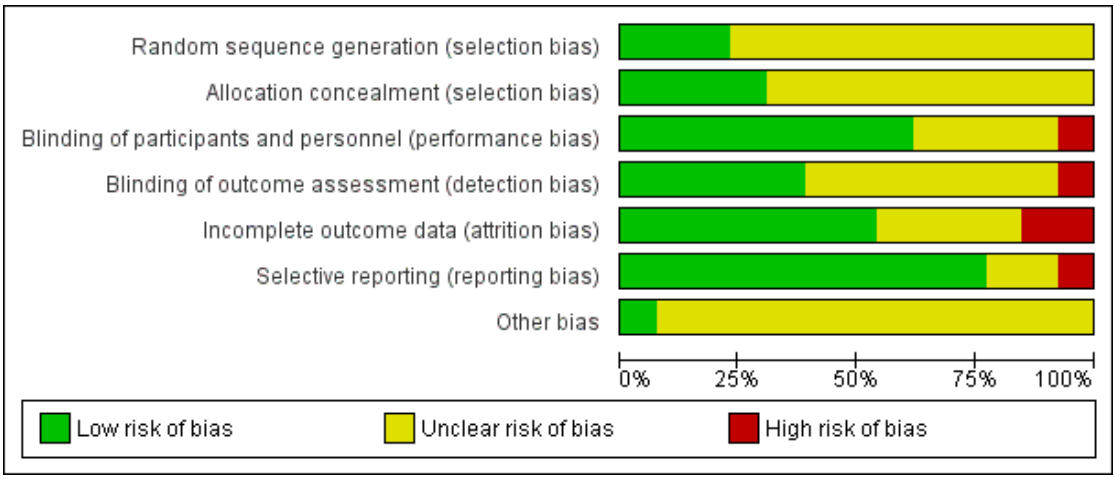
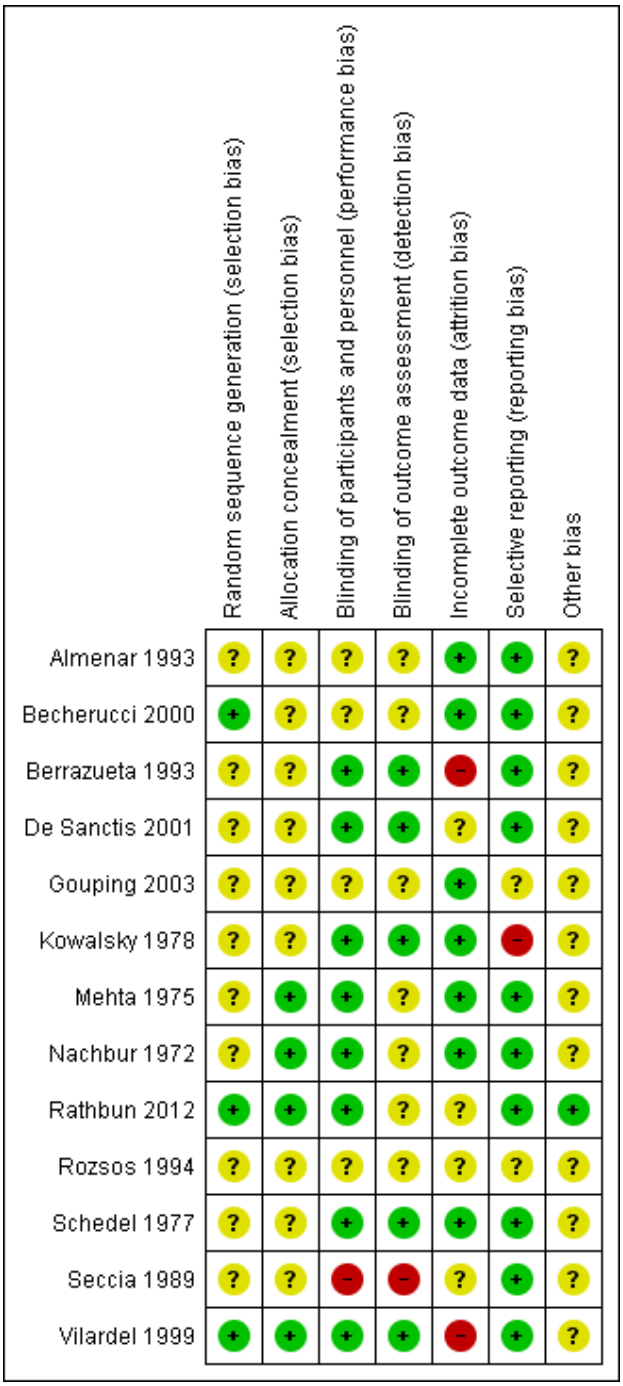


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study**



### Allocation

Three studies used adequate random sequence generation ( Becherucci 2000; Rathbun 2012; Vilardel 1999), but this aspect was unclear in the remaining studies due to poor reporting. Allocation concealment was appropriate in four studies (Mehta 1975; Nachbur 1972; Rathbun 2012; Vilardel 1999), but this was unclear in the remaining studies due to poor reporting.

### Blinding

Blinding of participants and personnel was adequate in eight studies (Berrazueta 1993; De Sanctis 2001; Kowalsky 1978; Mehta 1975; Nachbur 1972; Rathbun 2012; Schedel 1977; Vilardel 1999), as was blinding of outcome assessment in five (Berrazueta 1993; De Sanctis 2001; Kowalsky 1978; Schedel 1977; Vilardel 1999), whereas in the other studies these biases were unclear due to poor reporting. Seccia 1989 did not attempt blinding, so we judged it to be at high risk of bias.

### Incomplete outcome data

Five studies performed their analyses according to the intention-to-treat principle (Almenar 1993; Becherucci 2000; Gouping 2003; Kowalsky 1978; Mehta 1975) while in two additional studies we judged this domain to be at low risk of bias since the percentage of participants not analysed was lower than 5% and comparable between groups (Nachbur 1972; Schedel 1977). We considered the risk of attrition bias to be high in two studies (Berrazueta 1993; Vilardel 1999) and unclear in the remainder (Rathbun 2012; Rozsos 1994; Seccia 1989; see also Differences between protocol and review).

### Selective reporting

We deemed 10 studies to be free of selective reporting bias (Almenar 1993; Becherucci 2000; Berrazueta 1993; De Sanctis 2001; Mehta 1975; Nachbur 1972; Rathbun 2012; Schedel 1977; Seccia 1989; Vilardel 1999). In Gouping 2003, the authors did not explicitly predefine the outcomes, and there were inconsistencies between the Methods and the Results sections. Kowalsky 1978 planned to report on 'induration' but dropped it as an outcome during the trial (see Characteristics of included studies). These two studies were therefore considered to be at a high risk of reporting bias. In Rozsos 1994, which was only reported as an abstract, reporting bias was unclear.

### Other potential sources of bias

Only Rathbun 2012 included participants consecutively, whereas in all other studies it was unclear if participants were consecutively enrolled.

## Effects of interventions

No study reported on the secondary outcomes development of suppurative phlebitis, catheter-related bloodstream infections, or aspects related to quality of life through validated quality of life questionnaires. Only one study reported on thrombus extension and symptomatic VTE (Rathbun 2012).

Except for the secondary outcome local adverse events, we could not statistically pool data because of the between-study differences in comparisons, outcomes and type of measuring instruments. We therefore mainly describe the effects of interventions on a trial-by-trial basis, both below and in the Data and analyses section.

### Topical treatment versus inactive control

#### 1. Heparin gel versus placebo

Four studies compared a heparinoid gel versus placebo (Kowalsky 1978; Mehta 1975; Schedel 1977; Vilardel 1999). Although these studies evaluated the improvement of signs and symptoms with treatment, the heterogeneity in the measurement or reporting of the effects precluded any pooling of the results. For all outcomes depicted in Data and analyses related to this comparison, we graded the quality of the evidence as low. We downgraded because of the likely attrition bias in Vilardel 1999, the unclear allocation concealment in Kowalsky 1978 and Schedel 1977, and imprecision. We deemed imprecision to be a factor for all endpoints, as the 95% CIs contained either the 'no effect value' of one or values very close to one, so we could not rule out the possibility that topical treatment is associated with trivial effects.

In Vilardel 1999 signs and symptoms of superficial thrombophlebitis resolved at the end of follow-up (day 7) in 27 of 61 (44%) participants receiving heparin gel versus 17 of 65 (26%) of those receiving placebo (RR 1.69; 95% CI 1.03 to 2.78; Analysis 1.1). All 49 (39%) participants who were withdrawn from the study and did not receive any clinical assessment were considered as treatment failures. At the end of the follow-up period, phlebitis was rated by the investigator as 'severe' in 1 of 59 participants treated with the heparin gel and in 6 of 62 treated with placebo. The investigators judged efficacy as either 'good' or 'moderate' in 82% of the participants in the heparin group and in 86% of the placebo group, and tolerability as 'good' in 86.9% and 92.3%, re-

spectively. One participant treated with topical heparin developed mild urticaria.

Kowalsky 1978 reported the number of participants with a resolution of clinical signs and symptoms in the heparinoid arm versus the placebo arm. Pain resolved in 96.2% (50 of 52) versus 76.0% (38 of 50) (RR 1.27; 95% CI 1.07 to 1.49; Analysis 1.2), oedema in 98.1% (51 of 52) versus 90.0% (45 of 50) (RR 1.09; 95% CI 0.99 to 1.20; Analysis 1.3), and erythema in 82.7% (43 of 52) versus 64.0% (32 of 50) (RR 1.29; 95% CI 1.01 to 1.65; Analysis 1.4), respectively. There were no adverse events.

Mehta 1975 observed a faster relief of local symptoms and signs in participants receiving the heparinoid cream (58 h, range 36 to 102 h) compared to placebo (126 h, range 48 to 148 h). As we were unable to obtain or derive the standard deviation, we omit these results from the section Data and analyses. For the same reason, we were unable to grade the quality of evidence of this finding. The study authors reported no local or systemic side effects.

Schedel 1977 reported the mean percentages of residual clinical signs or symptoms at six days after start of treatment compared to the intensity at diagnosis, which was arbitrarily set at 100%. The pain score decreased from 100% at baseline to 3% in the organo-heparinoid group and to 80% in the placebo group. The oedema score decreased to 4% in the organo-heparinoid group and to 87% in the placebo group. The erythema score decreased to 18% in the organo-heparinoid group and did not change (100%) in the placebo group. The induration score decreased to 40% in the organo-heparinoid group and remained at 100% in the placebo group. There was no measurement of spread or statistics to evaluate differences between groups, so we omit these results from the section Data and analyses. One participant out of 20 (5%) suffered from a local allergic reaction to the organo-heparinoid ointment, leading to withdrawal from the trial (RR 3.00; 95% CI 0.13 to 69.52; Analysis 1.5).

Three studies contributed to the outcome local adverse events (Kowalsky 1978; Schedel 1977; Vilardel 1999), but they were too small to detect statistically significant differences (RR 3.09; 95% CI 0.33 to 28.95; Analysis 1.5).

#### 2. Essaven gel versus placebo

In De Sanctis 2001, a composite score based on local pain, disability and swelling decreased with Essaven gel at the end of the 4-week treatment (MD − 9.00; 95% CI − 11.87 to − 6.13; Analysis 2.1). The authors reported the absence of treatment-related adverse events in both study arms. We graded the quality of these findings as moderate, due to unclear allocation concealment and unclear risk of attrition bias. We did not extract the average skin temperature, as the reported data were implausibly low (average skin temperature as low as 24°C).

#### 3. Phlebolan versus placebo

Nachbur 1972 reported the number of participants who responded to treatment, defining response as an evident improvement of clinical signs and symptoms, and non-response as no change or deterioration. Pain, oedema, erythema and induration improved in 70% (16 of 23) in the phlebolan arm versus 42% (10 of 24) in the placebo arm (RR 1.67; 95% CI 0.97 to 2.88; Analysis 3.1). There were no adverse events. We graded the quality of these findings as low, due to imprecision and unclear blinding of outcome assessors.

#### 4. Topical or oral diclofenac versus no intervention

Becherucci 2000 observed a reduction of signs and symptoms intensity in 60% (24 of 40) of participants of both diclofenac groups, compared to 20% (8 of 40) of those in the control group (for both diclofenac groups versus control: RR 3.00; 95% CI 1.54 to 5.86; Analysis 4.1). The MD in reduction from baseline was -5.58 (95% CI -7.38 to -3.78; Analysis 4.2) in the topical diclofenac versus no intervention and -4.70 (95% CI -6.50 to -2.90; Analysis 4.2) in the oral diclofenac versus no intervention. Considered individually, pain, oedema, erythema and skin temperature were all significantly reduced by topical and oral diclofenac compared to control group (Analysis 4.3; Analysis 4.4; Analysis 4.5; Analysis 4.6). We graded the quality of these findings as moderate, due to unclear allocation concealment and unclear blinding. Trialists reported adverse effects for the two diclofenac groups but not for the control group (see also comparison 7 below).

### Topical treatment versus active control

Four studies compared the effects of two topical treatments (Almenar 1993; Berrazueta 1993; Gouping 2003; Rozsos 1994), and one study compared topical treatment versus oral treatment (Becherucci 2000). For all outcomes listed in Data and analyses, we graded the evidence as low to moderate due to unclear allocation concealment in all studies and unclear blinding or imprecision in several others.

#### 5. Transdermal nitroglycerine versus heparinoid gel

Almenar 1993 observed a faster clinical improvement with transdermal nitroglycerin gel compared to heparinoid gel. Transdermal nitroglycerin gel was associated with a faster resolution of pain (50.2 h versus 72.0 h, MD -21.80 h; 95% CI -37.40 to -6.20; Analysis 5.2), a two-fold reduction of erythema (28.8 h versus 54.6 h, MD -25.80 h; 95% CI -37.48 to 14.12; Analysis 5.3) and of fibrous cord (58.3 h versus 84.5 h, MD -26.20 h; 95% CI -41.87 to -10.53; MD). There was no difference in how long it took to halve the oedema (31.2 h versus 33.0 h, MD -1.80 h; 95% CI -10.88 to 7.28; Analysis 5.5). The study authors reported no side effects with the heparinoid gel and two cases of headache

following the administration of transdermal nitroglycerin gel (RR 5.00; 95% CI 0.25 to 101.58; Analysis 5.6). There were no cases of symptomatic hypotension.

In Berrazueta 1993, signs of thrombophlebitis resolved at two days in 18 of 22 participants in the glyceryl trinitrate ointment group and 6 of 18 of the controls. The corresponding values were 22 of 22 versus 11 of 18 at four days, and 22 of 22 versus 16 of 18 at one week, respectively. At nine days signs of thrombophlebitis had disappeared in all participants of both groups. At two days, the reduction in pain was significantly higher in the glyceryl trinitrate ointment group with an analgesic index of 84.6 ± 18 (excellent) versus 49 ± 45% (reasonable) in the control group ($P < 0.01$). Two participants in the glyceryl trinitrate ointment group experienced headache as a side effect.

We could only pool adverse event data from Almenar 1993 and Berrazueta 1993. The studies were too small to show any difference in average effect (RR 4.54; 95% CI 0.55 to 37.68; 140 participants; Analysis 5.6). We graded the overall evidence as low due to imprecision, unclear allocation concealment and potential attrition bias. Although the individual study estimates were consistent with each other, data are insufficient to exclude that the direction of bias was the same in both studies.

#### 6. Notoginseny cream versus heparinoid cream

In Gouping 2003, clinical signs and symptoms had resolved after 48 h in all 34 participants treated with notoginseny cream compared to 26 of 31 of those on heparinoid cream (RR 0.08; 95% CI 0.00 to 1.44; Analysis 6.1). Notoginseny was associated with a significantly faster recovery time (MD to complete clinical resolution -10.71 h; 95% CI -16.01 to -5.41; Analysis 6.2).

#### 7. Topical versus oral Diclofenac

Becherucci 2000 is also partly described above in comparison 4. In this study, the authors observed a 60% (24 of 40) reduction of signs and symptoms intensity in participants from both the topical and oral diclofenac groups. There was no difference in mean reduction of overall symptom severity from baseline (RR -0.88; 95% CI -2.25 to 0.49; Analysis 7.2) nor in reduction of individual signs and symptoms such as in pain, oedema, erythema and skin temperature considered individually (see Analysis 7.3; Analysis 7.4; Analysis 7.5; Analysis 7.6). Reported adverse effects for topical and oral diclofenac groups included headache (9 and 5 participants, respectively), epigastralgia (4 and 17 participants), nausea (6 and 16 participants), and local pruritus (5 and 2 participants). As the studies did not report information at the patient level, we omit these results in the Data and analyses.

#### 8. Pentosan polysulphate sodium ointment versus mucopolysaccharide ointment

Rozsos 1994 reported that both polysulphate sodium ointment and mucopolysaccharide ointment had equivalent efficacy, with faster symptom reduction with the pentosan polysulphate sodium. Neither study reported adverse effects, and both topical treatments were well tolerated. None of these results are depicted in the section Data and analyses.

### Oral or parenteral treatment versus any control

See description of Becherucci 2000, which evaluated oral diclofenac, in comparisons 4 and 7 above.

#### 9. Defibrotide versus no intervention

In Seccia 1989, clinical signs and symptoms of inflammation resolved completely within 4.8 days in the group receiving defibrotide versus 10.5 days in the control group. We omitted these results from Data and analyses because we were unable to obtain or derive the standard deviation for these results. The studies did not report changes in other clinical signs and symptoms separately for participants with acute thrombophlebitis of the upper extremities.

#### 10. Dalteparin versus ibuprofen

Rathbun 2012 reported no thrombus extension or symptomatic VTE in any participant randomised to dalteparin or ibuprofen. There were no cases of clinically overt bleeding. We graded the evidence to be of low quality due to imprecision. The improvement of pain or adverse effects were not reported separately for the group of participants with superficial thrombophlebitis of the upper extremities. None of these results are depicted in the section Data and analyses.

## DISCUSSION

### Summary of main results

A number of topical treatments, including heparinoid or diclofenac gels, appeared to significantly reduce the intensity of clinical signs and symptoms and achieve higher complete resolution relative to placebo or no intervention. In one study, both topical and oral diclofenac were more effective than no intervention in improving the clinical signs and symptoms, whereas there was no apparent difference between the topical and oral application (Becherucci 2000). No thrombus extension or symptomatic VTE were observed with oral non-steroidal anti-inflammatory drugs or low-molecular-weight heparin, but the low number of participants

included limits any conclusion (Rathbun 2012). Defibrotide was associated with a faster recovery of inflammatory signs relative to no defibrotide, although these findings come from only 15 participants receiving extensive background therapy, which included antimicrobial, anti-inflammatory and mechanical treatments (Seccia 1989). No study evaluated the use of ice or the application of cold or hot bandages, and none reported on the development of suppurative phlebitis, catheter-related bloodstream infections, or aspects related to quality of life through validated questionnaires. Although several trials reported on adverse events in topical heparinoid creams, Essaven gel or phlebolan versus control, the trials were underpowered to adequately measure any differences across treatment modalities (Almenar 1993; Berrazueta 1993; De Sanctis 2001; Kowalsky 1978; Nachbur 1972; Schedel 1977; Vilardel 1999). While no data were available to evaluate the risk of adverse events in participants on either topical or oral diclofenac relative to no treatment, the local and systemic side effects appeared to occur at a high rate in the diclofenac groups (Becherucci 2000). No safety data were available for notoginseny creams nor for the parenteral low-molecular-weight heparin or defibrotide.

## Quality of the evidence

### Risk of bias assessment of individual trials

The methodological quality of the included studies was generally low, although a proper assessment was hampered by poor reporting (Figure 3). As an example, bias related to the random sequence generation or allocation concealment were unclear in most of the studies. Although we considered the risk of selective reporting bias adequate in 10 (77%) studies, the included trials rarely addressed relevant outcomes such as thrombus extension or symptomatic VTE, and only about half considered adverse effects. We could not evaluate bias related to small study size, such as publication biases. Overall data came from 13 studies for a total of 917 participants, where half of them had less than 50 participants and the number per arm ranged from fewer than 10 to no more than 60. Therefore, both the effects observed and the lack of difference between the groups may represent a true effect or simply chance given the small number of RCTs, participants and events as reflected by the very wide confidence intervals around the observed measures of effect. Due to the scarce evidence and poor reporting, no sensitivity analyses according to the methodological quality of the trials could be conducted.

### Grading of the overall body of evidence

We graded the overall body of evidence as low to moderate, due to the unclear allocation concealment, unclear blinding or imprecision. Due to the absence of negative results in placebo- or no intervention-controlled studies and the unclear or high risk of bias observed in individual trials, we judged the overall evidence for effectiveness as low (at best), meaning that 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.

## Potential biases in the review process

We followed a systematic approach to searching, study selection and data extraction as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). It is unlikely that we failed to identify relevant trials, but we acknowledge that we were unable to fully evaluate two studies awaiting classification because of language issues and the lack of author contact details (Xiao 2004; Xu 2001). It is unlikely that the general conclusions of the review would be influenced by the findings of these two relatively small studies.

The fact that two independent assessors (MDN, FP or AWSR) performed the data extraction minimised possible mistakes in this process. As previously noted, quality assessment may be relatively subjective and open for different interpretations, especially where the quality of reporting is poor (Di Nisio 2013). To help readers formulate their own judgments over the bias items, we inserted quotations and the arguments on which we based our decisions, as suggested by Cochrane (Higgins 2011).

## Agreements and disagreements with other studies or reviews

The 2008 guidelines of the American College of Chest Physicians summarised the evidence about the treatment of superficial thrombophlebitis of the upper extremities (Kearon 2008). The guideline authors suggested treatment with either an oral anti-inflammatory drug, topical diclofenac gel, or heparin gel until resolution of symptoms or for up to two weeks. Kearon 2008 included only 3 of the 13 RCTs considered in the present review (Becherucci 2000; De Sanctis 2001; Vilardel 1999), although they also included a fourth study that covered superficial thrombophlebitis of both lower and upper extremities (Bergqvist 1990). Even though the present work has data available from 10 additional RCTs, the evidence is still insufficient to draw conclusions regarding the efficacy and safety of topical, oral or parenteral)medical therapy for superficial thrombophlebitis of the upper extremity.

# AUTHORS' CONCLUSIONS

## Implications for practice

The evidence about the treatment of acute infusion superficial thrombophlebitis is limited and of low quality. Data appear too

preliminary to assess the effectiveness and safety of topical treatments, systemic anticoagulation or oral non-steroidal anti-inflammatory drugs.

### Implications for research

The effect of treatment in preventing complications such as suppurative superficial thrombophlebitis, catheter-related bloodstream infections, and the effects, if any, on the underlying thrombosis remain unknown. To demonstrate benefit of any of the evaluated treatments, future trials should best prespecify subgroups or define a more homogeneous patient population, and consider stratifying participants based on relevant risk factors such as type of catheters or duration of catheter use. Standardisation of background therapy and definitions of critical and patient-relevant endpoints are additional points of attention. For the latter, it will be important to involve patient representatives. Such studies may evaluate whether the addition of systemic anticoagulation to topical treatment may confer protection against the thrombotic complications without increasing the rate of bleeding. Whether lower doses or different types of non-steroidal anti-inflammatory drugs can achieve clinical improvements while maintaining a safe profile requires further evaluation.

## ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

**Almenar 1993**

| | |
|---|---|
| Methods | Prospective, randomised study<br>**Setting**: hospital |
| Participants | Inpatients (n = 100) with superficial phlebitis caused by endovenous catheters. Phlebitis was "diagnosed [clinically] by the presence of pain, erythema, oedema, and fibrous cord in area around the catheter." Trialists did not report whether ultrasonography was used to confirm the presence of vein thrombosis<br>**Sex**: 73/100 (73%) males<br>**Mean age**: 67.3 years (range 28 to 89 years) |
| Interventions | **Intervention A**: transdermal nitroglycerine gel 2% (2 $cm^2$ once daily)<br>**Intervention B**: heparinoid gel (sulphuric polyholoside ester sodium salt) applied tree times a day<br>Study treatment was given for 6 d<br>The catheter was removed in all participants |
| Outcomes | • Time for the disappearance of pain<br>• Time to reduction of erythema by half<br>• Time to reduction of oedema by half<br>• Time to reduction of induration (fibrous cord) by half<br>Clinical evaluation was performed every 4 h for 6 d |
| Notes | **Funding**: not reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation only reported as occurring "according to a randomisation order" (our translation) |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported |

**Almenar 1993** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | There were apparently no participants lost to follow-up, as Table 1 in Almenar 1993 reports outcome for all participants initially included |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion section |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Becherucci 2000**

| | |
|---|---|
| Methods | Randomised, 3-arm controlled study<br>**Setting**: hospital |
| Participants | Inpatients (n = 120) with superficial infusion thrombophlebitis defined clinically as the presence of signs and symptoms of inflammation on and around the cannulated vein<br>**Sex**: 70/120 (58%) males<br>**Mean age**: 66.8 ± 13.5 years in the control group; 57.6 ± 17.2 years in the topical diclofenac group; 51.9 ± 17.3 years in the oral diclofenac group |
| Interventions | **Intervention A**: diclofenac topical gel 1% applied three times daily for 48 h<br>**Intervention B**: diclofenac: 75 mg twice a day orally for 48 h<br>**Control**: no intervention |
| Outcomes | • Pain measured on a 10 cm VAS scale; erythema, oedema and warmth evaluated through a seemingly self constructed scale ranging from 2 to 10. Measurements at entry and 48 h later. These were totaled in the Results section as well, where we assumed that the range of the combined scale was from 6 to 30. Treatment response defined as a reduction of the intensity of clinical signs and symptoms by at least 30%<br>• Adverse effects |
| Notes | Funding: not reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Sequence of random numbers. Quote: "una secuencia de 120 dígitos generados al azar." |
| Allocation concealment (selection bias) | Unclear risk | Not reported |

**Becherucci 2000** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported. Quote: "Las variables intensidad de la TFSI, rubor, tumor, calor y dolor fueron comparadas en función de los promedios de las diferencias registradas entre T2 y T0." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | No participants lost to follow-up. Quote: "No se registraron pérdidas de pacientes debido al corto período de observación de cada caso" |
| Selective reporting (reporting bias) | Low risk | Trialists reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Berrazueta 1993**

| | |
|---|---|
| Methods | Prospective, double blind, randomised study<br>**Setting**: hospital |
| Participants | Patients (n = 40) with thrombophlebitis of a superficial forearm vein developed during a therapeutic venous infusion. Quote: "Thrombophlebitis was defined as the presence of two or more of the following signs: pain, local warmth, erythema, local oedema and/or palpable venous cord . . . The severity of signs allowed thrombophlebitis to be graded into five stages as follows:<br>• Grade I: pain, without other inflammatory signs<br>• Grade II: pain with erythema or swelling<br>• Grade III: pain, erythema, oedema and a palpable venous cord extending less than 5 cm<br>• Grade IV, all signs of Grade III in a extension of more than 5 cm with perivein induration<br>• Grade V adds frank vein thrombosis with or without suppuration<br>Grade I thrombophlebitis was rejected for study."<br>Trialist do not report the use of ultrasonography to confirm the presence of vein thrombosis<br>**Sex**: 20/40 (50%) males<br>**Mean age**: 60.5 ± 19.4 years |
| Interventions | **Intervention A**: transdermal glyceryl trinitrate (GTN) ointment 2% gel solution at a daily dose of 12 mg (2 $cm^2$), applied gently without massage along the surface of the swelling |

| | |
|---|---|
| | **Intervention B**: ointment of heparinoid substance (sulphuric polyholoside ester (SPE) sodium salt)<br>Treatment duration not reported |
| Outcomes | • Pain assessed with an analogue scale. The authors calculated an analgesic index and results were considered 'excellent' when the index was over 75%, 'good' between 75 and 50%, 'reasonable' between 49 and 25%, and 'bad' when lower than 25%<br>• Signs of erythema, swelling, palpable venous cord, and perivein induration graded into 5 stages<br>• Number of days required for complete disappearance of symptoms<br>Outcomes assessed every 24 hours until complete healing of thrombophlebitis |
| Notes | Funding: This study was supported by a grant of the R Areces Foundation, Madrid, Spain<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation not reported. Quote: "randomised study" |
| Allocation concealment (selection bias) | Unclear risk | Method of allocation concealment not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | "Double blind study". Quote: "The control group was treated with SPE ointment of identical physical characteristics to those of the GTN ointment." Blinding of treating personnel not explicitly reported |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The assessment was made blindly by the same clinical investigator in each case every 24 hours after ointment application. " |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 7 of the 47 (15%) participants initially admitted to the study were excluded. Thus, the study population consisted of 40 participants. Quote: "Forty-seven patients were admitted to this study. Of these, seven patients were excluded, three because they were discharged from the hospital before the last evaluation and four because the protocol was not completed." |

**Berrazueta 1993** (*Continued*)

| | | |
|---|---|---|
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**De Sanctis 2001**

| | |
|---|---|
| Methods | Randomised, placebo-controlled study<br>**Setting**: hospital |
| Participants | Patients (n = 23) with superficial thrombophlebitis of the upper extremity (distally to the shoulder level) developed after infusion treatment with an intravenous catheter. Limbs evaluated by colour duplex, but it is unclear whether the superficial thrombophlebitis was defined by the presence of thrombosis<br>**Sex**: 6/12 (50%) males in the treatment arm; 6/11 (54%) males in the placebo arm<br>**Mean age**: 58 ± 7 years in the treatment arm; 59 ± 6 years in the placebo arm |
| Interventions | **Intervention**: Essaven gel (5 $cm^2$ of gel corresponding to about 1 g of Essaven gel for each application); number of applications per day not reported<br>**Control**: placebo<br>Participants received low-molecular-weight heparin (enoxaparin sodium 0.1 mL/10 kg of body weight once daily) for 4 weeks |
| Outcomes | Average decrease in skin temperature of the affected area after 4 weeks of treatment<br>Analogue symptomatic score (ranging from 0 to 30) based on 3 signs/symptoms: pain, disability and swelling, each graded from 0 (normal) to 10 (unbearable symptom/sign)<br>Outcomes assessed after 4 weeks |
| Notes | Funding: none reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available<br>Gianni Belcaro was erased from the UK medical register in June 2007 for 'misconduct', which seems to have been that he included as co-authors on his papers people who were not involved in the research. The GMC report did not suggest that data were falsified ( http://webcache.gmc-uk.org/minutesfiles/3313.HTML). |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of sequence generation not reported. Quote: "The randomization process was controlled by an external statistician" |

**De Sanctis 2001** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Quote: "Sealed envelopes were opened at the end of evaluation of all subjects". Not clear if the envelopes were consecutively numbered and opaque and whether these were actually used to assign the treatment, as they were opened at the end of evaluation rather than at the time of randomisation. The use of an external statistician likely refers to central randomisation, but the applied methods remain unclear |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study. Quote: "Operators were unaware of the content of the tube" and "Placebo comparable to EG was used (Aventis Pharma, Milan, Italy)" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Not explicitly reported, but likely blinded as treatment assignment was revealed after outcome assessment. Quote: "Sealed envelopes were opened at the end of evaluation of all subjects" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | The number of randomised participants is not explicitly reported. It remains unclear if all participants randomised were evaluated and included in the analysis |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Gouping 2003**

| | |
|---|---|
| Methods | Randomised study<br>**Setting**: hospital |
| Participants | Patients (n = 65) with postinfusion superficial thrombophlebitis of the forearm, diagnosed clinically by trained nurses; trialists did not report on use of ultrasonography to verify presence of the thrombus<br>**Sex**: 32/65 (49%) males<br>**Age range**: 4 to 90 years |
| Interventions | **Intervention A**: notoginseny cream, a topical Chinese medicine containing safflower, notoginseng, shiny-leaf prickly ash, and rhubarb<br>**Intervention B**: heparinoid cream (Hirudoid Cream, Luitpold Pharma, Munich, Ger- |

**Gouping 2003** (*Continued*)

| | |
|---|---|
| | many)<br>Both topical study treatments were applied every 4 h starting as soon as the phlebitis was diagnosed and continued until the signs and symptoms had disappeared |
| Outcomes | Participants' conditions and level of pain. Quote: "The four infusion nurses trained in phlebitis assessment monitored the participants' conditions and obtained feedback on their level of pain"<br>The Methods section does not describe how these outcomes were evaluated |
| Notes | Funding: none reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of sequence generation not reported. Quote: "The 65 patients were divided randomly into two groups." |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | It is likely an open study. Study personnel was not blinded as different dressing procedures were used for the two topical study treatments. Quote: "In cases where Hirudoid cream was applied, a cotton swab was used after the cannula had been removed, but no dressing was applied to the site after the cream was applied". It is unclear if participants were blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | It is not reported whether the outcome assessment was blinded. Quote: "The four infusion nurses trained in phlebitis assessment monitored the patients' conditions and obtained feedback on their level of pain" |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All participants randomised were analysed |
| Selective reporting (reporting bias) | Unclear risk | Neither the Abstract, Introduction nor the Methods sections describe outcomes explicitly, and the focus of the report is unclear; no protocol or trial registration was available |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Kowalsky 1978**

| | |
|---|---|
| Methods | Prospective double blind randomised study<br>**Setting**: hospital |
| Participants | Female inpatients (n = 102) with superficial thrombophlebitis after gynaecological operation caused by endovenous catheters. The diagnosis of phlebitis was clinical. 52 participants were allocated to the intervention and 50 participants were allocated to the control<br>**Sex**: 0 males<br>**Mean age**: 48.9 years (range 22 to 79) in the intervention group; 48.2 (15 to 77) in the control group |
| Interventions | **Intervention**: 40,000 IU organo-heparinoid per 100 g ointment (Hirudoid 40,000), topical application<br>**Control**: topical placebo ointment<br>Study treatments were given for 10 d |
| Outcomes | Proportion of the decrease of pressure pain, oedema and erythema after 10 d; severity of symptoms was graded from 0 to 3, with 0 standing for no symptoms and 3 for severe irritation; clinical evaluation was performed twice per day for 10 d |
| Notes | Funding: not reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Use of 440 numbered tubes, 220 with active and 220 with placebo ointment. As each patient received 4 tubes, there were 110 unique numbers provided to the 440 tubes. The randomisation code was opened after the end of trial. It was not reported who allocated the packages to the participants, nor was it clear if the coding was consecutive. As it was not reported whether the tubes were identical in appearance, we judged unclear risk of bias |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study. Participants were explicitly reported to be blinded to study treatment. The active and placebo ointments were reported to be identical in colour and consistency. It was not reported if the tubes were identical as well. Blinding of treating personnel was not explicitly reported |

**Kowalsky 1978** (*Continued*)

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Outcomes were assessed jointly by the participant and the physician assessing the outcome, who were both explicitly reported to be blinded to study treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | It appears that the study included all randomised participants in the data analyses |
| Selective reporting (reporting bias) | High risk | Induration was planned as an outcome but not reported. The authors assumed that the follow-up duration of 10 d was too short to observe a decrease of induration as a response to the therapy. At the trial level, we judge this as high risk of bias. For the outcomes pain, swelling and redness, it likely does not introduce any bias |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Mehta 1975**

| | |
|---|---|
| Methods | Prospective, double blind, randomised trial<br>**Setting**: hospital |
| Participants | Inpatients (n = 100) in surgical wards who developed superficial thrombophlebitis after continuous intravenous infusion of normal saline, dextrose saline, blood, or other fluids. Thrombophlebitis was diagnosed clinically "when a tender palpable cord or a red flare developed over the vein after stopping the infusion." $^{125}$I-labelled fibrinogen test used for detecting the presence of thrombi. Quote: "The original difference in radioactivity between this site and the corresponding area on the opposite (unaffected) limb was assumed to represent the total radioactivity contained in the thrombus and locally accumulated inflammatory exudate."<br>**Sex**: 39/50 (78%) males in the treatment arm; 34/50 (68%) males in the placebo arm<br>**Mean age**: 44.9 years (range 17 to 72) in the treatment arm; 56.3 years (range 35 to 83) in the placebo arm |
| Interventions | **Intervention**: heparinoid ointment (Hirudoid)<br>**Control**: placebo cream<br>Study treatment was applied to the area of redness and tenderness, and this was followed by firm bandaging. Treatment was repeated daily for at least 5 d and continued thereafter if symptoms persisted |
| Outcomes | Time to relief of local symptoms and signs and the rate of local decline in radioactivity (not extracted)<br>Outcomes assessed every every day for 5 days. |

| | |
|---|---|
| Notes | Funding: financial support from the King's College Hospital Research Trust; Luitpold-Werk (Munich) supplied Hirudoid and placebo cream<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of sequence generation not reported. Quote: "treatment schedules distributed in random order" |
| Allocation concealment (selection bias) | Low risk | Quote: "One hundred envelopes were prepared, sealed, and numbered in sequence, each containing one of two treatment schedules distributed in random order. As each patient was admitted to the trial his treatment was selected by opening the next envelope, which indicated whether the patient was to receive the contents of a green or a red tube." Opacity of envelopes not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study with colour-coded tubes. Quote: "After completion of the trial the red tubes were found to contain the active, heparinoid compound and the green tubes the placebo cream." We judged low risk of bias as an attempt to blinding was made (see review protocol), but acknowledge that the blinding is suboptimal, as the evident difference in colour enhances the chance that personnel and even participants understand which product is the active ointment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Blinding of outcome assessment not reported explicitly, but this was likely given that treatment assignment was blinded and disclosed at the end of the study. Quote: "After completion of the trial the red tubes were found to contain the active, heparinoid compound and the green tubes the placebo cream." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised participants evaluated and included in the analysis. Quote: "All patients successfully completed a full course of treatment and no local or systemic side |

**Mehta 1975** (*Continued*)

| | | |
|---|---|---|
| | | effects were observed." |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Nachbur 1972**

| | |
|---|---|
| Methods | Prospective double blind randomised study<br>**Setting**: hospital |
| Participants | Inpatients (n = 48) with superficial thrombophlebitis caused by endovenous catheters. The diagnosis of phlebitis was clinical. 24 participants were allocated to the intervention and 24 participants were allocated to the control<br>Age and sex not reported |
| Interventions | **Intervention**: phlebolan spray containing diphenylbutazone 5%, prednisolone 0.5%, sodium rutin sulphate 0.2%, topical application three times per day<br>**Control**: placebo spray, topical application three times per day<br>Study treatment was given for 5 d |
| Outcomes | Proportion of treatment responders with evident improvement of skin temperature, erythema, induration, pain and oedema after 5 d; severity of symptoms was graded from for pain and oedema as follows: 0 standing for no symptoms, + for light and ++ for strong irritation |
| Notes | Funding: not reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation not reported |
| Allocation concealment (selection bias) | Low risk | Use of coded packages that were identical in appearance. Trialists did not report who allocated the packages to the participants, nor was it clear if the coding was consecutive. As the packages were identical in appearance, we judged low risk of bias |

**Nachbur 1972** (*Continued*)

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study using coded packages. Trialists did not explicitly report who was blind or whether the substances were identical in appearance |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Double blind study, but outcome assessors were not explicitly reported to be blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The data of one patient from the intervention group (1 out of 24; 4%) was not analysed because the mode of application did not comply with the protocol |
| Selective reporting (reporting bias) | Low risk | The single outcome reported in the Methods section was addressed in the Results section |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Rathbun 2012**

| | |
|---|---|
| Methods | Randomised, controlled, double blind, double dummy trial<br>**Setting**: inpatients and outpatients |
| Participants | Consecutive inpatients and outpatients with superficial thrombophlebitis of the lower (n = 57) or upper (n = 15) extremities in the absence of a current intravenous (IV) catheter. Presence of the thrombus was objectively tested using ultrasonography. Only the participants with superficial thrombophlebitis of the upper extremity were included in this review<br>Sex and age are not reported separately for the group with superficial thrombophlebitis of the upper extremity |
| Interventions | **Intervention A**: Dalteparin (200 IU/kg sc at presentation followed by 10,000 IU sc daily for<br>an additional 6 d) plus placebo given orally three times daily for 7 d<br>**Intervention B**: Ibuprofen 800 mg given orally three times daily for 7 d plus placebo injections given daily for 7 d<br>In case the symptoms of superficial thrombophlebitis were not resolved at days 7-9, the patient received an additional 7 d of the blinded therapy provided there was no thrombus extension |
| Outcomes | **Primary outcome**: extension of thrombus or new symptomatic VTE during the 14-day and 3-month follow-up period<br>**Secondary outcomes**: reduction in pain; major, minor and trivial bleeding; thrombocytopenia<br>Pain severity was evaluated at presentation and during the 14-day treatment period using |

| | |
|---|---|
| | the 11-point Box Pain scale<br>Follow-up visits were scheduled at days 7-9, 14-16 and at 1 and 3 months. Ultrasonography was repeated on days 7-9 and 14-16 to verify thrombus extension |
| Notes | Funding: The authors acknowledged the support of the University of Oklahoma General Clinical Research Center grant M01 RR14467 from the National Center for Research Resources, National Institutes of Health, and Pzer Inc. for provision of dalteparin sodium, ibuprofen and nurse personnel salary support<br>Disclosure of potential conflicts of interest: The authors stated that they had no conflict of interest |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "Randomization was performed using balanced randomization blocks of four each consisting of equal numbers" |
| Allocation concealment (selection bias) | Low risk | Quote: "Randomization was performed using balanced randomization blocks of four each consisting of equal numbers" and "Randomization of patient to treatment group was performed by the investigational medication pharmacist within 24 h of presenting with a confirmed diagnosis of supercial thrombophlebitis." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study. Quote: "The patient, research assistant and principal investigator were blinded to the treatment group." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Trialists do not report if outcome assessment was blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Trialists do not report if all participants included were followed up to 3 months and included in the analysis |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Low risk | No apparent other sources of bias. Participants consecutively included |

**Rozsos 1994**

| | |
|---|---|
| Methods | Randomised double blind trial<br>**Setting**: hospital |
| Participants | Adult patients (n = 110) with acute infusion thrombophlebitis in one arm. Age and sex not reported. It is not reported whether thrombophlebitis was defined by the presence of a thrombus nor if ultrasonography was performed |
| Interventions | **Intervention A**: pentosan polysulphate sodium ointment 0.5%<br>**Intervention B**: mucopolysaccharide ointment 0.445%<br>Study medication was applied three times daily |
| Outcomes | • Symptoms (induration, swelling, erythema, temperature, pain) severity combined into a score with a 5-stage scale; symptoms assessed daily<br>• Radioactivity over the inflamed veins on day 1, 3 and 7 of the treatment period measured by $^{125}$I-fibrinogen test |
| Notes | Funding: none reported.<br>Disclosure of potential conflicts of interest: not reported and no COI forms available<br>Study reported in abstract form only. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported. |
| Allocation concealment (selection bias) | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Trialists report the study to be double blind, but not the method of blinding nor who was blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear whether all participants randomised were included in the analysis; study only available as an abstract |
| Selective reporting (reporting bias) | Unclear risk | Unclear whether all outcomes were presented; no protocol or Methods section available |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Schedel 1977**

| | |
|---|---|
| Methods | Prospective double blind randomised study<br>**Setting**: hospital |
| Participants | Inpatients (n = 40) with superficial thrombophlebitis after various operations. The diagnosis of phlebitis was clinical. 20 participants were allocated to the intervention and 20 participants were allocated to the control<br>**Sex**: 8/20 (40%) males in the treatment arm; 7/20 (35%) males in the placebo arm<br>**Mean age**: 59.7 years (range 34 to 90) in the intervention group; 60.6 years (18 to 90) in the control group |
| Interventions | **Intervention**: organo-heparinoid, topical application twice per day<br>**Control**: placebo ointment, topical application twice per day<br>Study treatment was given for 6 d |
| Outcomes | • Primary outcome: result of a $^{125}$I fibrinogen scan of the affected side compared to the unaffected side (not extracted)<br>• Secondary outcomes: proportion of the remaining pain, oedema, induration and erythema after 6 d. Severity of symptoms was graded from 0 to 4: 0 standing for no symptoms, 1 for light, 2 for medium, 3 for strong, and 4 for very strong irritation<br>Outcomes assessed at 6 days |
| Notes | Funding: not reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation not reported |
| Allocation concealment (selection bias) | Unclear risk | Use of colour-coded ointment described; method of allocation concealment not reported in sufficient detail to allow a judgment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study with colour-coded ointment. In line with our protocol we judged low risk of bias as there was an attempt to blind. We acknowledge that colour coding may have increased the awareness of personnel and even participants to distinguish the active and placebo ointments |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double blind study; although it is not explicitly reported if outcome assessors (the physician for oedema, induration and erythema; the participant for pain) were |

**Schedel 1977** (*Continued*)

| | | |
|---|---|---|
| | | blinded, we deduce that they were, as the treatment assignment was reported to be disclosed at the end of the study. Quote: "After completion of the outcome assessments, the code was opened" (our translation) |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | 19 out of 20 (95%) randomised participants were analysed in the experimental group, 20 out of 20 (100%) were analysed in the control group |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Seccia 1989**

| | |
|---|---|
| Methods | Randomised, two-arm open study<br>**Setting**: inpatients and outpatients |
| Participants | Outpatients and inpatients with superficial thrombophlebitis of the lower (n = 125) and upper extremities (n = 15). Trialists did not report whether thrombophlebitis was defined by the presence of a thrombus<br>Sex and age not reported |
| Interventions | Within 72 h of symptoms onset:<br>**Intervention A** (n = 7): standard treatment B plus defibrotide 800 mg/d IM for 4 d followed by 400 mg/d IM until clinical resolution<br>**Intervention B** (n = 8): standard treatment consisting of antimicrobic therapy (bacampicillin 800 mg/d for 48 h) plus diclofenac 100 mg/d, topical desoxyribonuclease and elastic compression until clinical resolution |
| Outcomes | • Variation of signs (body and local temperature, redness, oedema, satellite adenopathy)<br>• Pain<br>• Laboratory parameters (leucocytosis)<br>Indicators evaluated before treatment start and subsequently every 3 d by the medical study personnel and recorded daily by the patient<br>Periodic checks performed by Doppler ultrasonography to exclude the extension into the deep vein system |
| Notes | Funding: none reported<br>Disclosure of potential conflicts of interest: not reported and no COI forms available<br>The original study relates to 140 participants. We did not report the study details relating to the 125 participant with lower extremity phlebitis. The study stratified by the time |

**Seccia 1989** (*Continued*)

| | |
|---|---|
| | to onset of symptoms, but this related to those with lower extremity phlebitis only |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of random sequence generation not reported. Participants were first divided based on the time elapsed from onset of symptoms and subsequently randomised to study treatment |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Participants and personnel were not blinded to study treatment. Quote: "La rilevazione è stata effettuata da personale medico a intervalli di 3 giorni e registrata quotidianamente da parte del paziente stesso" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Outcomes were assessed by participants and personnel who were not blinded to study treatment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 3 participants within the defibrotide group were excluded from the study after they had developed allergic reactions to the drug in the first 24-48 h of treatment. It is not reported if these 3 participants belonged to the group of 15 participants with thrombophlebitis of the upper extremity (percentage of participants analysed from the upper extremity subgroup may be between 80% and 100% of the total). Quote: "3 casi di pazienti tolti dallo studio in fase del tutto precoce" |
| Selective reporting (reporting bias) | Low risk | For the entire group including lower extremity phlebitis, authors reported all outcomes from the Methods section in the Results or Discussion section. As lower extremity was not the focus of the study, we judged that there was no indication for high risk of bias |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**Vilardel 1999**

| | |
|---|---|
| Methods | Randomised, placebo-controlled, double blind study<br>**Setting**: hospital |
| Participants | Inpatients (n = 132) over 18 years with acute superficial phlebitis secondary to indwelling IV catheter<br>**Sex**: 24/61 (39%) males in the treatment arm; 26/65 (40%) males in the placebo arm<br>Age not reported<br>Not reported whether thrombophlebitis was defined by the presence of a thrombus nor if ultrasonography was performed |
| Interventions | **Intervention**: topical sodium bovine heparin as gel preparation (containing 1000 IU/g of heparin)<br>**Control**: placebo<br>Topical heparin or placebo applied three times daily until clinical healing or for a maximum of 7 d<br>Application of other anti-inflammatory topical preparations not allowed during the study. Anticoagulants were administered to 6 participants in the intervention group and 1 in the control group |
| Outcomes | • Disappearance of the symptoms and signs of superficial phlebitis<br>• Investigator's global impression<br>• Adverse events<br>Clinical evaluation of the superficial phlebitis was done by the nurse personnel every 24 h until healing or for a maximum follow-up of 7 d |
| Notes | Funding: Laboratorios Menarini, S.A. (Barcelona) provided the product samples and financial support for the conduct of the study<br>Disclosure of potential conflicts of interest: not reported and no COI forms available |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: "The assignment schedule was generated at Institut Català de Farmacologia by a computer random number generator" |
| Allocation concealment (selection bias) | Low risk | Quote: "[S]tudy medication was supplied to the hospital pharmacy" and "[L]abelling was neutral and identified with the patient inclusion number . . . For each patient, two tubes were available . . . For each patient the investigator received an opaque envelope with the inclusion number and the identification of the sample; codes could only be disclosed in the case of severe adverse events and at the end of the statistical evaluation." The authors also report that the "inclusion sequence followed the ran- |

| | | |
|---|---|---|
| | | domisation plan with two exceptions: one in the intervention group and another one in the control group." Although it was not reported whether randomisation envelopes were sealed, we judged low risk of bias for the overall procedure |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double blind study. Quote: "[L]abelling was neutral and identified with the patient inclusion number . . . For each patient, two tubes were available . . . For each patient the investigator received an opaque envelope with the inclusion number and the identification of the sample; codes could only be disclosed in the case of severe adverse events and at the end of the statistical evaluation" |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "[C]odes could only be disclosed in the case of severe adverse events and at the end of the statistical evaluation" |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | 6 (4.5%) participants with protocol deviations (5 in the heparin and 1 in the placebo) were excluded from the analysis. Quote: "There were five protocol deviations in the intervention group and one in the control group. In the intervention group, three cases were included in the study for a second time; additionally, in this group two cases were identified as the same patient treated for a few days simultaneously for two concomitant episodes of phlebitis. In the control group, one case corresponded to a second superficial phlebitis in a patient previously included in the study"<br>There were 49 (39%) withdrawals, 24 in the intervention group (36.4%) and 25 in the control group (37.9%). All these participants were considered as treatment failures<br>Quote: "Sixteen patients in the intervention group and 18 in the control group were discharged before phlebitis had healed. Five patients in the intervention group and four in the control group decided to withdraw from the study. One patient in the intervention group and two in the control group developed concomitant illnesses and application of the study preparation was discontin- |

| | | |
|---|---|---|
| | | ued. One patient in the intervention group died of liver cirrhosis, and another one developed contact urticaria. In one patient of the control group, study medication was insufficient due to the size of the phlebitis lesion (29 cm). For the intention-to-treat analysis all these cases were considered as failures" |
| Selective reporting (reporting bias) | Low risk | Authors reported all outcomes from the Methods section in the Results or Discussion sections |
| Other bias | Unclear risk | Unclear if participants were consecutively included |

**COI**: conflict of interest; **EG**: Esseven gel; **G MC**: General Medical Council (UK); **IM**: intramuscular; **IV**: intravenous(ly); **sc**: subcutaneously; **VAS**: visual analogue scale; **VTE**: venous thromboembolism.

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

| Study | Reason for exclusion |
|---|---|
| Bergqvist 1990 | The study includes participants with superficial thrombophlebitis of the lower extremities and upper extremities and it is not possible to extract data separately for latter |
| Bruni 1979 | The study includes participants with superficial thrombophlebitis of the lower extremities and upper extremities and it is not possible to extract data separately for latter |
| Cökmez 2003 | Study on the prevention of superficial thrombophlebitis |
| D'Amico 1987 | The study includes participants with vein insufficiency, post-thrombotic syndrome, and superficial thrombophlebitis of the lower extremities |
| De Tullio 1989 | Participants with superficial thrombophlebitis or deep vein thrombosis of the lower extremities |
| Gorski 2005 | Participants with superficial thrombophlebitis of the lower extremities |
| Marrapodi 1986 | Not an RCT |
| Messing 1985 | Study on the prevention of superficial thrombophlebitis |
| Nieto-Rodriguez 1992 | Study on the prevention of superficial thrombophlebitis |

(*Continued*)

| | |
|---|---|
| Nocker 1990 | Participants with superficial thrombophlebitis of the lower extremities |
| Nocker 1991 | Participants with superficial thrombophlebitis of the lower extremities |
| Porters 1981 | The study includes participants with superficial thrombophlebitis of the lower extremities and upper extremities and it is not possible to extract data separately for latter |
| Pozza 1980 | The study includes participants with superficial thrombophlebitis of the lower extremities and upper extremities and it is not possible to extract data separately for latter |
| Reid 1990 | Study on the prevention of superficial thrombophlebitis |
| Stolle 1986 | Participants with superficial thrombophlebitis of the lower extremities and only two of the upper extremities |
| Wright 1985 | Study on the prevention of superficial thrombophlebitis |

**RCT**: randomised controlled trial

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Xiao 2004**

| | |
|---|---|
| Methods | Randomised study |
| Participants | Chronic hepatopathy patients (n = 102) with peripheral phlebitis induced by fluid infusion |
| Interventions | Intervention: Notoginseng alcohol for external application<br>Control: magnesium sulphate solution for external application |
| Outcomes | Recovery of impaired vein |
| Notes | Study available in Chinese. It is currently not possible to extract data from the study |

**Xu 2001**

| | |
|---|---|
| Methods | Not reported |
| Participants | Not reported |
| Interventions | Not reported |
| Outcomes | Not reported |
| Notes | Study available in Chinese. It is currently not possible to extract data from the study |

## Characteristics of ongoing studies *[ordered by study ID]*

**CTRI/2012/05/002629**

| | |
|---|---|
| Trial name or title | Prevalence of infusion related inflammation of the vein and the comparison of the effectiveness of heparinoid application and ichthammol glycerin application on the reduction of infusion related inflammation of the vein |
| Methods | Unclear method of random sequence generation: "Method of generating randomization sequence: Coin toss, Lottery, toss of dice, shuffling cards et". Likely an open study with no allocation concealment: "Method of allocation concealment: Not Applicable. Blinding and masking: Not Applicable" |
| Participants | All adult patients admitted in selected adult wards who develop phlebitis of the upper limb with a visual infusion phlebitis score of two or more as the result of intravenous therapy |
| Interventions | **Intervention A**: heparinoid ointment applied in a thin layer to the skin of the affected part and its surrounding area two times per day for 48 h<br>**Intervention B**: 30-50 mL of ichthammol glycerine applied while doing dressing on the affected site 2 times daily for 48 h |
| Outcomes | Efficacy of intervention at 6 weeks |
| Starting date | 11 June 2012 |
| Contact information | Dr Punitha Ezhilarasu: punitha@cmcvellore.ac.in |
| Notes | CTRI: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2012/05/002629 |

**CTRI/2013/12/004245**

| | |
|---|---|
| Trial name or title | Comparison of the effectiveness of Ichthammol glycerine, heparinoid application and Magsulph glycerine application on the reduction of infusion related inflammation of the vein |
| Methods | "Method of generating randomisation sequence: computer generated randomisation; method of allocation concealment: open list of random numbers. Blinding and masking: participant and outcome assessor blinded" |
| Participants | All patients admitted in Advanced Cardiac Centre, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, who developed phlebitis with visual infusion phlebitis score of $\geq 2$ as the result of intravenous therapy |
| Interventions | **Intervention A**: 3-5 mL of ichthammol glycerine used for doing dressing on the affected site two times daily for 72 h<br>**Intervention B**: heparinoid ointment applied in a thin layer to the skin of the affected part and its surrounding two times per day for 72 h.<br>I**ntervention C**: magsulph glycerine applied in a thin layer to the skin of the affected part and its surrounding area two times per day for 72 h |
| Outcomes | **Primary**: efficacy of intervention at 6 weeks<br>**Secondary**: pharmacoeconomics of intervention at 6 weeks |

**CTRI/2013/12/004245** (*Continued*)

| | |
|---|---|
| Starting date | 15 July 2013 |
| Contact information | Dr Bikash Medhi: drbikashus@yahoo.com |
| Notes | CTRI: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2013/12/004245 |

**NCT00377806**

| | |
|---|---|
| Trial name or title | Topical diclofenac gel in patients with superficial inflammation of the veins |
| Methods | Randomised, double blind |
| Participants | Patients with spontaneous or iatrogenic superficial thrombophlebitis of the upper limb |
| Interventions | **Intervention**: diclofenac gel |
| Outcomes | **Primary outcome**: area under the curve (AUC) of the symptom score (pain, temperature and size of erythema along the superficial vein)<br>**Secondary outcomes**<br>• Patient's global assessment of drug effect at each visit<br>• AUC of assessment of temperature of inflammatory area around superficial thrombophlebitis between treatment day 1 and 5<br>• AUC of assessment of inflammatory area of the superficial thrombophlebitis between treatment day 1 and 5<br>• AUC of assessment of pain (visual analogue scale) between treatment day 1 and day 5<br>• Physician's global assessment of drug effect at each visit |
| Starting date | January 2003 |
| Contact information | Novartis Pharmaceuticals |
| Notes | ClinicalTrials.gov identifier: NCT00377806 |

**NCT01943006**

| | |
|---|---|
| Trial name or title | Efficacy and tolerability of Hirudoid cream in prophylaxis and treatment infusion phlebitis |
| Methods | Randomised, placebo-controlled study |
| Participants | Inpatients receiving infusion of a complete nutritional emulsion for 3 d (Kabiven Peripheral, 1400 kcal, 1920 mL, 750 mOsmol/L, pH 5.6) |
| Interventions | **Intervention**: Hirudoid cream 0.3% mucopolysaccharide polysulphate twice daily<br>**Control**: placebo<br>The treatment will be continued after the end of infusion for at least 7 d |

**NCT01943006** (*Continued*)

| | |
|---|---|
| Outcomes | **Primary outcome measures**: number of patient developing superficial thrombophlebitis<br>**Secondary outcome measures**<br>• Time to develop infusion related superficial thrombophlebitis<br>• Change of clinical symptoms in participants who developed superficial thrombophlebitis<br>• Time to complete resolution of signs and symptoms in participants who developed superficial thrombophlebitis<br>• Investigators' and participants' satisfaction<br>• Adverse events<br>• Global tolerability |
| Starting date | This study is not yet open for participant recruitment. Verified: September 2013 by Medinova AG |
| Contact information | Contact: Tun Myint Win, MD +66 8 1847 5696 tun.myint.win@dksh.com<br>Contact: Philipp Grob, PhD +41 792910960 grob.philipp@medinova.ch |
| Notes | Sponsor: Medinova AG<br>ClinicalTrials.gov Identifier: NCT01943006 |

## DATA AND ANALYSES

### Comparison 1. Topical treatment versus inactive control: heparin gel versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Disappearance of signs and symptoms | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Pain resolution | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 3 Oedema resolution | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 4 Erythema resolution | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 5 Local adverse events | 3 | 268 | Risk Ratio (IV, Random, 95% CI) | 3.09 [0.33, 28.95] |
| 5.1 Organo-heparinoid | 2 | 142 | Risk Ratio (IV, Random, 95% CI) | 3.00 [0.13, 69.52] |
| 5.2 Heparin gel | 1 | 126 | Risk Ratio (IV, Random, 95% CI) | 3.19 [0.13, 76.93] |

### Comparison 2. Topical treatment versus inactive control: Essaven gel versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Combined score of persisting signs/symptoms | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2 Treatment related adverse events | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |

### Comparison 3. Topical treatment versus inactive control: Phlebolan versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical response | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Adverse events | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |

**Comparison 4. Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical response | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Reduction in symptom severity | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2.1 Topical diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 2.2 Oral diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Pain reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3.1 Topical diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3.2 Oral diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4 Oedema reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4.1 Topical diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 4.2 Oral diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5 Erythema reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5.1 Topical diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 5.2 Oral diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Skin temperature reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6.1 Topical diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6.2 Oral diclofenac | 1 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |

**Comparison 5. Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Disappearance of signs and symptoms | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Time (h) to pain disappearance | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 Time (h) to halving of erythema | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Time (h) to halving of fibrous cord | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Time (h) to halving of oedema | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6 Adverse events | 2 | 140 | Risk Ratio (IV, Random, 95% CI) | 4.54 [0.55, 37.68] |

**Comparison 6. Topical treatment versus active control: notoginseny cream versus heparinoid cream**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Persistence of signs and symptoms at 48 h | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Mean time (h) for clinical resolution | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

**Comparison 7. Topical treatment versus active control: topical versus oral diclofenac**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical response | 1 | | Risk Ratio (IV, Fixed, 95% CI) | Totals not selected |
| 2 Reduction in symptom severity | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 3 Pain reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 4 Oedema reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 5 Erythema reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 6 Skin temperature reduction | 1 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |

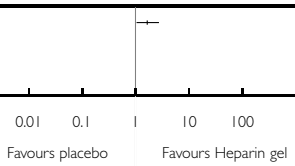
**Analysis 1.1. Comparison 1 Topical treatment versus inactive control: heparin gel versus placebo, Outcome 1 Disappearance of signs and symptoms.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 1 Topical treatment versus inactive control: heparin gel versus placebo

Outcome: 1 Disappearance of signs and symptoms

| Study or subgroup | Heparin gel n/N | Placebo n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Vilardel 1999 | 27/61 | 17/65 | | 1.69 [ 1.03, 2.78 ] |

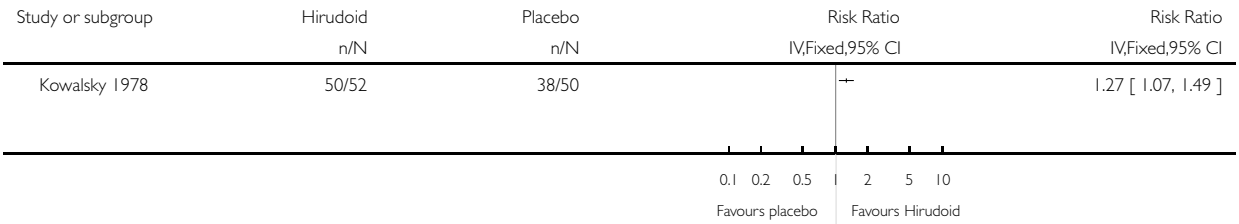


**Analysis 1.2. Comparison 1 Topical treatment versus inactive control: heparin gel versus placebo, Outcome 2 Pain resolution.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 1 Topical treatment versus inactive control: heparin gel versus placebo

Outcome: 2 Pain resolution

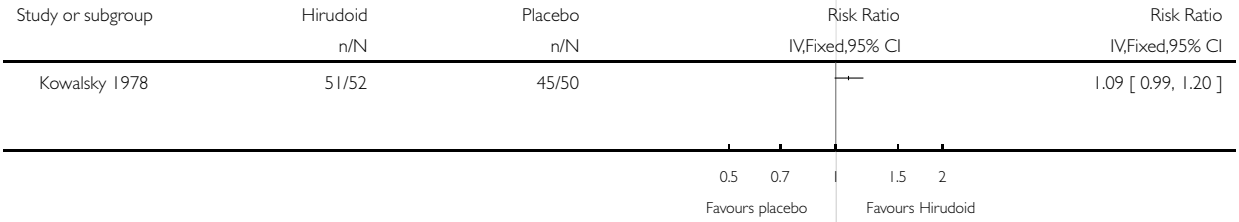



**Analysis 1.3. Comparison 1 Topical treatment versus inactive control: heparin gel versus placebo, Outcome 3 Oedema resolution.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 1 Topical treatment versus inactive control: heparin gel versus placebo

Outcome: 3 Oedema resolution



### Analysis 1.4. Comparison 1 Topical treatment versus inactive control: heparin gel versus placebo, Outcome 4 Erythema resolution.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 1 Topical treatment versus inactive control: heparin gel versus placebo

Outcome: 4 Erythema resolution

| Study or subgroup | Hirudoid n/N | Placebo n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Kowalsky 1978 | 43/52 | 32/50 | | 1.29 [ 1.01, 1.65 ] |

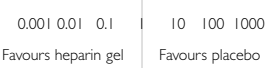

### Analysis 1.5. Comparison 1 Topical treatment versus inactive control: heparin gel versus placebo, Outcome 5 Local adverse events.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 1 Topical treatment versus inactive control: heparin gel versus placebo

Outcome: 5 Local adverse events

| Study or subgroup | Favours heparin gel n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Organo-heparinoid | | | | | |
| Kowalsky 1978 | 0/52 | 0/50 | | | Not estimable |
| Schedel 1977 | 1/20 | 0/20 | | 50.6 % | 3.00 [ 0.13, 69.52 ] |
| **Subtotal (95% CI)** | **72** | **70** | | **50.6 %** | **3.00 [ 0.13, 69.52 ]** |
| Total events: 1 (Favours heparin gel), 0 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | | |
| 2 Heparin gel | | | | | |
| Vilardel 1999 | 1/61 | 0/65 | | 49.4 % | 3.19 [ 0.13, 76.93 ] |
| **Subtotal (95% CI)** | **61** | **65** | | **49.4 %** | **3.19 [ 0.13, 76.93 ]** |
| Total events: 1 (Favours heparin gel), 0 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |

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(. . . *Continued*)

| Study or subgroup | Favours heparin gel n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Test for overall effect: Z = 0.72 (P = 0.47) | | | | | |
| **Total (95% CI)** | **133** | **135** | | **100.0 %** | **3.09 [ 0.33, 28.95 ]** |
| Total events: 2 (Favours heparin gel), 0 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.00, df = 1 (P = 0.98); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.99 (P = 0.32) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.00, df = 1 (P = 0.98), $I^2$ =0.0% | | | | | |


**Analysis 2.1. Comparison 2 Topical treatment versus inactive control: Essaven gel versus placebo, Outcome 1 Combined score of persisting signs/symptoms.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 2 Topical treatment versus inactive control: Essaven gel versus placebo

Outcome: 1 Combined score of persisting signs/symptoms

| Study or subgroup | Essaven N | Mean(SD) | Placebo N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| De Sanctis 2001 | 12 | 7 (4) | 11 | 16 (3) | | -9.00 [ -11.87, -6.13 ] |

**Analysis 2.2. Comparison 2 Topical treatment versus inactive control: Essaven gel versus placebo, Outcome 2 Treatment related adverse events.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 2 Topical treatment versus inactive control: Essaven gel versus placebo

Outcome: 2 Treatment related adverse events

| Study or subgroup | Essaven n/N | Placebo n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| De Sanctis 2001 | 0/12 | 0/11 | | Not estimable |


**Analysis 3.1. Comparison 3 Topical treatment versus inactive control: Phlebolan versus placebo, Outcome 1 Clinical response.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 3 Topical treatment versus inactive control: Phlebolan versus placebo

Outcome: 1 Clinical response

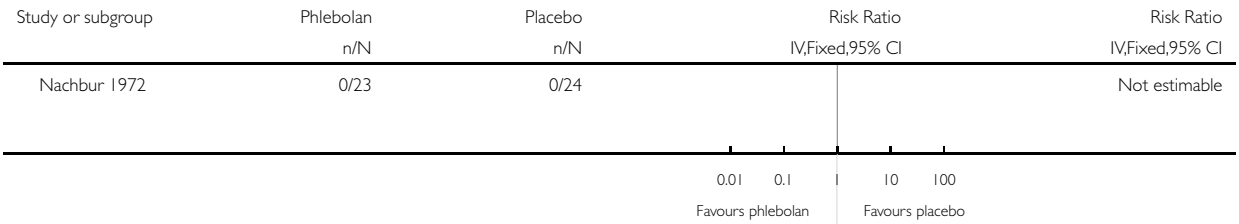
| Study or subgroup | Phlebolan n/N | Placebo n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Nachbur 1972 | 16/23 | 10/24 | | 1.67 [ 0.97, 2.88 ] |

**Analysis 3.2. Comparison 3 Topical treatment versus inactive control: Phlebolan versus placebo, Outcome 2 Adverse events.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 3 Topical treatment versus inactive control: Phlebolan versus placebo

Outcome: 2 Adverse events

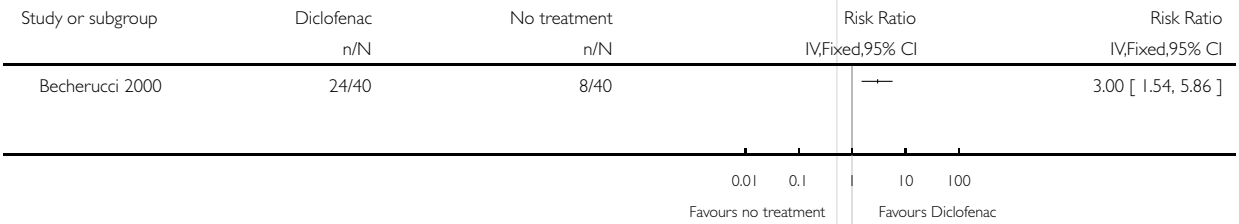



**Analysis 4.1. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 1 Clinical response.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 1 Clinical response



### Analysis 4.2. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 2 Reduction in symptom severity.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 2 Reduction in symptom severity

| Study or subgroup | Diclofenac N | Mean(SD) | No treatment N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Topical diclofenac | | | | | | |
| Becherucci 2000 | 40 | -5.7 (3.13) | 40 | -0.12 (4.89) | | -5.58 [ -7.38, -3.78 ] |
| 2 Oral diclofenac | | | | | | |
| Becherucci 2000 | 40 | -4.82 (3.14) | 40 | -0.12 (4.89) | | -4.70 [ -6.50, -2.90 ] |

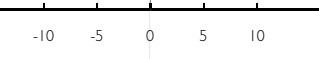

### Analysis 4.3. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 3 Pain reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 3 Pain reduction

| Study or subgroup | Diclofenac N | Mean(SD) | No treatment N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Topical diclofenac | | | | | | |
| Becherucci 2000 | 40 | -2.25 (1.58) | 40 | 0.07 (1.99) | | -2.32 [ -3.11, -1.53 ] |
| 2 Oral diclofenac | | | | | | |
| Becherucci 2000 | 40 | -2 (1.6) | 40 | 0.07 (1.99) | | -2.07 [ -2.86, -1.28 ] |



### Analysis 4.4. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 4 Oedema reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 4 Oedema reduction

| Study or subgroup | Diclofenac N | Mean(SD) | No treatment N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Topical diclofenac | | | | | | |
| Becherucci 2000 | 40 | -2.05 (1.23) | 40 | 0.01 (1.87) | | -2.06 [ -2.75, -1.37 ] |
| 2 Oral diclofenac | | | | | | |
| Becherucci 2000 | 40 | -1.72 (1.48) | 40 | 0.01 (1.87) | | -1.73 [ -2.47, -0.99 ] |

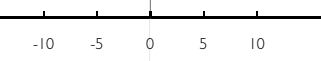

### Analysis 4.5. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 5 Erythema reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 5 Erythema reduction

| Study or subgroup | Diclofenac N | Mean(SD) | No treatment N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Topical diclofenac | | | | | | |
| Becherucci 2000 | 40 | -2.77 (1.84) | 40 | 0.16 (2.5) | | -2.93 [ -3.89, -1.97 ] |
| 2 Oral diclofenac | | | | | | |
| Becherucci 2000 | 40 | -2.2 (1.36) | 40 | 0.16 (2.5) | | -2.36 [ -3.24, -1.48 ] |



### Analysis 4.6. Comparison 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention, Outcome 6 Skin temperature reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 4 Topical or oral treatment versus inactive control: topical or oral diclofenac versus no intervention

Outcome: 6 Skin temperature reduction

| Study or subgroup | Diclofenac N | Mean(SD) | No treatment N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| 1 Topical diclofenac | | | | | | |
| Becherucci 2000 | 40 | -0.33 (0.32) | 40 | 0 (0.54) | | -0.33 [ -0.52, -0.14 ] |
| 2 Oral diclofenac | | | | | | |
| Becherucci 2000 | 40 | -0.27 (0.35) | 40 | 0 (0.54) | | -0.27 [ -0.47, -0.07 ] |

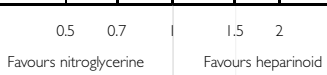

### Analysis 5.1. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 1 Disappearance of signs and symptoms.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 1 Disappearance of signs and symptoms

| Study or subgroup | Transderm nitroglycerine n/N | Heparinoid n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Berrazueta 1993 | 22/22 | 18/18 | | 1.00 [ 0.91, 1.10 ] |



### Analysis 5.2. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 2 Time (h) to pain disappearance.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 2 Time (h) to pain disappearance

| Study or subgroup | Transderm nitroglycer-ine N | Mean(SD) | Heparinoid N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Almenar 1993 | 50 | 50.2 (39.7) | 50 | 72 (39.9) | | -21.80 [ -37.40, -6.20 ] |


### Analysis 5.3. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 3 Time (h) to halving of erythema.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 3 Time (h) to halving of erythema

| Study or subgroup | Transderm nitroglycer-ine N | Mean(SD) | Heparinoid N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Almenar 1993 | 50 | 28.8 (24.2) | 50 | 54.6 (34.5) | | -25.80 [ -37.48, -14.12 ] |

### Analysis 5.4. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 4 Time (h) to halving of fibrous cord.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 4 Time (h) to halving of fibrous cord

| Study or subgroup | Transderm nitroglycer-ine N | Mean(SD) | Heparinoid N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Almenar 1993 | 50 | 58.3 (38.4) | 50 | 84.5 (41.5) | | -26.20 [ -41.87, -10.53 ] |


### Analysis 5.5. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 5 Time (h) to halving of oedema.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 5 Time (h) to halving of oedema

| Study or subgroup | Transderm nitroglycer-ine N | Mean(SD) | Heparinoid N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Almenar 1993 | 50 | 31.2 (20.3) | 50 | 33 (25.7) | | -1.80 [ -10.88, 7.28 ] |

### Analysis 5.6. Comparison 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel, Outcome 6 Adverse events.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 5 Topical treatment versus active control: transdermal nitroglycerine versus heparinoid gel

Outcome: 6 Adverse events

| Study or subgroup | Favours nitroglyc-erine n/N | Heparinoid n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Almenar 1993 | 2/50 | 0/50 | | 49.4 % | 5.00 [ 0.25, 101.58 ] |
| Berrazueta 1993 | 2/22 | 0/18 | | 50.6 % | 4.13 [ 0.21, 80.91 ] |
| **Total (95% CI)** | **72** | **68** | | **100.0 %** | **4.54 [ 0.55, 37.68 ]** |

Total events: 4 (Favours nitroglycerine), 0 (Heparinoid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0.0\%$

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable


### Analysis 6.1. Comparison 6 Topical treatment versus active control: notoginseny cream versus heparinoid cream, Outcome 1 Persistence of signs and symptoms at 48 h.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 6 Topical treatment versus active control: notoginseny cream versus heparinoid cream

Outcome: 1 Persistence of signs and symptoms at 48 h

| Study or subgroup | Notoginseny n/N | Hirudoid n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Gouping 2003 | 0/34 | 5/31 | | 0.08 [ 0.00, 1.44 ] |

## Analysis 6.2. Comparison 6 Topical treatment versus active control: notoginseny cream versus heparinoid cream, Outcome 2 Mean time (h) for clinical resolution.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 6 Topical treatment versus active control: notoginseny cream versus heparinoid cream

Outcome: 2 Mean time (h) for clinical resolution

| Study or subgroup | Notoginseny N | Mean(SD) | Hirudoid N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Gouping 2003 | 34 | 14.71 (7.55) | 31 | 25.42 (13.21) | | -10.71 [ -16.01, -5.41 ] |


## Analysis 7.1. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 1 Clinical response.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 1 Clinical response

| Study or subgroup | Topical Diclofenac n/N | Oral Diclofenac n/N | Risk Ratio IV,Fixed,95% CI | Risk Ratio IV,Fixed,95% CI |
|---|---|---|---|---|
| Becherucci 2000 | 24/40 | 24/40 | | 1.00 [ 0.70, 1.43 ] |

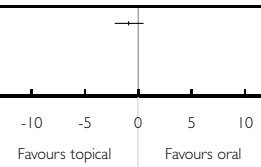
### Analysis 7.2. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 2 Reduction in symptom severity.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 2 Reduction in symptom severity

| Study or subgroup | Topical N | Mean(SD) | Oral N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Becherucci 2000 | 40 | -5.7 (3.13) | 40 | -4.82 (3.14) | | -0.88 [ -2.25, 0.49 ] |



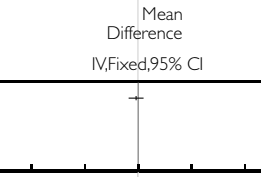

### Analysis 7.3. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 3 Pain reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 3 Pain reduction

| Study or subgroup | Topical N | Mean(SD) | Oral N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Becherucci 2000 | 40 | -2.25 (1.58) | 40 | -2 (1.6) | | -0.25 [ -0.95, 0.45 ] |



### Analysis 7.4. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 4 Oedema reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 4 Oedema reduction

| Study or subgroup | Topical N | Mean(SD) | Oral N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Becherucci 2000 | 40 | -2.05 (1.23) | 40 | -1.72 (1.48) | | -0.33 [ -0.93, 0.27 ] |


### Analysis 7.5. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 5 Erythema reduction.

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 5 Erythema reduction

| Study or subgroup | Topical N | Mean(SD) | Oral N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|
| Becherucci 2000 | 40 | -2.77 (1.84) | 40 | -2.2 (1.36) | | -0.57 [ -1.28, 0.14 ] |

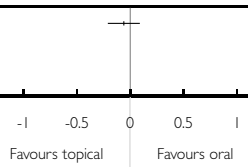
**Analysis 7.6. Comparison 7 Topical treatment versus active control: topical versus oral diclofenac, Outcome 6 Skin temperature reduction.**

Review: Treatment for superficial infusion thrombophlebitis of the upper extremity

Comparison: 7 Topical treatment versus active control: topical versus oral diclofenac

Outcome: 6 Skin temperature reduction

| Study or subgroup | Topical | | Oral | | Mean Difference | Mean Difference |
|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | IV,Fixed,95% CI | IV,Fixed,95% CI |
| Becherucci 2000 | 40 | -0.33 (0.32) | 40 | -0.27 (0.35) | | -0.06 [ -0.21, 0.09 ] |




# APPENDICES

## Appendix 1. CRS search strategy

| | | |
|---|---|---|
| #1 | MESH DESCRIPTOR Thrombophlebitis EXPLODE ALL TREES | 1045 |
| #2 | MESH DESCRIPTOR Administration, Intravenous EXPLODE ALL TREES WITH QUALIFIERS AE | 228 |
| #3 | MESH DESCRIPTOR Catheterization, Central Venous EXPLODE ALL TREES WITH QUALIFIERS AE | 344 |
| #4 | phlebitis:TI,AB,KY | 466 |
| #5 | thrombophlebitis:TI,AB,KY | 1308 |
| #6 | thrombo-phlebitis:TI,AB,KY | 3 |
| #7 | (vein near3 (pain* or tender* or induration or erythema)):TI,AB,KY | 42 |
| #8 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 | 2294 |

(*Continued*)

| | | |
|---|---|---|
| #9 | MESH DESCRIPTOR Upper Extremity EXPLODE ALL TREES | 5286 |
| #10 | arm:TI,AB,KY | 23977 |
| #11 | arms:TI,AB,KY | 12796 |
| #12 | ((upper near2 extremit*)):TI,AB,KY | 1565 |
| #13 | #9 OR #10 OR #11 OR #12 | 33831 |
| #14 | #8 AND #13 | 120 |

## CONTRIBUTIONS OF AUTHORS

Study conception: Di Nisio.

Protocol development: Di Nisio, Rutjes, Porreca.

Search development: The Cochrane Vascular Group Trials Search Co-ordinator

Screening and acquisition of data: Di Nisio, Peinemann, Rutjes.

Analysis and interpretation of data: Di Nisio, Peinemann, Porreca, Rutjes.

Statistical analysis: Di Nisio, Rutjes.

Drafting of the manuscript: Di Nisio, Rutjes.

Critical revision of the manuscript for important intellectual content: Di Nisio, Rutjes, Peinemann, Porreca, Rutjes.

Obtained funding: not applicable, no funding available

Supervision: Rutjes.

## DECLARATIONS OF INTEREST

MDN, EP, and AWSR performed the review as part of their routine research activities, without dedicated internal or external funding. FP received no internal or external funding.

MDN: Dr Di Nisio declares he received consulting fees from Bayer Health Care and Grifols outside the submitted work.

FP: none known

EP: none known

AWSR: none known

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## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to use random-effects meta-analyses to summarise outcome data across studies. For outcomes where only a single study was available, we used the fixed-effect option in RevMan (RevMan 2014).

We planned to explore between-trial heterogeneity by stratifying the main outcomes for trial characteristics, treatment and patient-related features; however, these exploratory analyses turned out not to be feasible due to the limited number of RCTs and the heterogeneity of study interventions and outcomes. For the same reasons, it was not possible to prepare a 'Summary of findings' table nor the GRADE assessment.

For the assessment of the risk of attrition bias we applied a conservative cut-off of 5% of participants randomised that we allowed to be excluded from analyses. If the analyses was according to the intention-to-treat principle, but the number of participants with missing data exceeded 20% per group or was differential between groups, we judged high risk of bias independent of the imputation methods.

## NOTES

We followed an in-house generated standard protocol, for the definition of outcomes, searches, risk of bias assessments, data-collection and statistical analyses, The description of the methods therefore (partly) overlaps with our previous reviews in this field (Di Nisio 2012; Di Nisio 2014).