Rutosides for treatment of post-thrombotic syndrome

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Rutosides for treatment of post-thrombotic syndrome (Review)

Morling JR, Broderick C, Yeoh SE, Kolbach DN

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[Intervention Review]

Rutosides for treatment of post-thrombotic syndrome

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ABSTRACT

Background

Post-thrombotic syndrome (PTS) is a long-term complication of deep venous thrombosis (DVT) that is characterised by pain, swelling, and skin changes in the affected limb. One in three patients with DVT will develop post-thrombotic sequelae within five years. Rutosides are a group of compounds derived from horse chestnut (Aesculus hippocastanum), a traditional herbal remedy for treating oedema formation in chronic venous insufficiency (CVI). However, it is not known whether rutosides are effective and safe in the treatment of PTS. This is the second update of the review first published in 2013.

Objectives

To determine the effectiveness (improvement or deterioration in symptoms) and safety of rutosides for treatment of post-thrombotic syndrome (PTS) in patients with DVT compared to placebo, no intervention, elastic compression stockings (ECS) or any other treatment.

Search methods

The Cochrane Vascular Information Specialist searched the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers to 21 August 2018.

Selection criteria

Two review authors independently assessed studies for inclusion. Studies were included to allow the comparison of rutosides versus placebo or no treatment, rutosides versus ECS, and rutosides versus any other treatment. Two review authors extracted information from the trials. Disagreements were resolved by discussion.

Data collection and analysis

Data were extracted using designated data extraction forms. The Cochrane 'Risk of bias' tool was used for all included studies to assist in the assessment of quality. Primary outcome measures were the occurrence of leg ulceration over time (yes or no) and any improvement or deterioration of post-thrombotic syndrome (yes or no). Secondary outcomes included reduction of oedema, pain, recurrence of DVT or pulmonary embolism, compliance with therapy, and adverse effects. All of the outcome measures were analysed using Mantel-Haenzel fixed-effect model odds ratios. The unit of analysis was the number of patients. We used GRADE to assess the quality of the evidence for each outcome.

Main results

Ten reports of nine studies were identified following searching and three studies with a total of 233 participants met the inclusion criteria. Overall quality of evidence using the GRADE approach was low, predominantly due to the lack of both participant and researcher blinding in the included studies. The quality of the evidence was further limited as only three small studies contributed to the review findings. A subjective scoring system was used to obtain the symptoms of PTS so it was important that the assessors were blinded to the intervention. One study compared rutosides with placebo, one study compared rutosides with ECS and rutosides plus ECS versus ECS alone, and one study compared rutosides with an alternative venoactive remedy. Occurrence of leg ulceration was not reported in any of the included studies. There was no clear evidence to support a difference in PTS improvement between the rutosides or placebo/no treatment groups (OR 1.29, 95% CI 0.69 to 2.41; 164 participants; 2 studies; low-quality evidence); or between the rutosides and ECS groups (OR 0.80, 95% CI 0.31 to 2.03; 80 participants; 1 study ; low-quality evidence). Results from one small study reported less PTS improvement in the rutosides group compared to an alternative venoactive remedy (OR 0.18, 95% CI 0.04 to 0.94; 29 participants; 1 study; low-quality evidence). There was no clear evidence to support a difference in PTS deterioration when comparing rutosides with placebo/no treatment (OR 0.61, 95% CI 0.19 to 1.90; 80 participants; 1 study); with ECS (OR 0.61, 95% CI 0.19 to 1.90; 80 participants; 1 study); or an alternative venoactive remedy (OR 0.19, 95% CI 0.01 to 4.24; 29 participants; 1 study). No clear evidence of a difference in adverse effects between the rutosides and placebo/no treatment groups was seen ('mild side effects' reported in 7/41 and 5/42 respectively). In the study comparing rutosides with ECS, 2/80 could not tolerate ECS and 6/80 stopped medication due to side effects. The study comparing rutosides with an alternative venoactive remedy did not comment on side effects

Authors' conclusions

There was no evidence that rutosides were superior to the use of placebo or ECS. Overall, there is currently limited low-quality evidence that 'venoactive' or 'phlebotonic' remedies such as rutosides reduce symptoms of PTS. Mild side effects were noted in one study. The three studies included in this review provide no evidence to support the use of rutosides in the treatment of PTS.

PLAIN LANGUAGE SUMMARY

Rutosides for treatment of post-thrombotic syndrome

Background

Blood clots in the veins of the leg are a common problem and are termed deep vein thrombosis (DVT). One in three patients with a DVT develops a complication known as post-thrombotic syndrome (PTS). This syndrome involves ongoing swelling of the affected leg, pain, cramps, burning or prickling, and itching. Darkening of the skin because of increased pigmentation and varicose veins, redness and skin irritation can also occur. At the current time the main way of treating PTS is to wear compression stockings. It is known however that patients frequently find the stocking uncomfortable and so they may prefer to take an oral medication to treat the problem. Rutosides are a herbal remedy which has been shown to be effective in other conditions affecting the veins (chronic venous insufficiency).

Study characteristics and key results

This review aimed to evaluate the existing literature to see if rutosides were useful for treating PTS. We also investigated whether there were any side effects from the treatment. We searched all existing databases for trials relating to the use of rutosides for the treatment of PTS following DVT (current until 21 August 2018). Two review authors independently assessed the trials for inclusion and extracted results in line with our prescribed criteria. We found three suitable trials, with a total of 233 patients, and six unsuitable trials that were not included in the review.

The studies were small and undertaken very differently meaning they could not be combined. The studies used different comparisons with rutosides (placebo (inactive product), compression stockings alone or combined with rutosides, or hidrosmina (a venoactive drug, which acts on the vascular system). They also used different doses of rutosides (900 mg/day to 2000 mg/day). We found no clear evidence from any of the trials that treatment with rutosides improved symptoms and signs of PTS; or that there was any difference in side effects. Occurrence of leg ulceration was not reported in any of the included studies.

Quality of the evidence

Overall quality of evidence, using the GRADE approach, was low mainly due to the lack of both participant and researcher blinding. This means both investigators and participants knew what drug they were getting and this can effect the results. The quality of the evidence was further limited as only three small studies contributed to the review findings. A subjective scoring system was used to obtain the symptoms of PTS so it was important that the assessors were blinded to the intervention.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Rutosides versus placebo (or no treatment) for the treatment of post-thrombotic syndrome

Comparison 1: Rutosides versus placebo or no treatment for the treatment of PTS

Patient or population: patients with PTS
Setting: outpatients
Intervention: rutosides
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no comparator	Risk with rutosides				
Occurrence of leg ulceration	See comment					This outcome was not reported by any included study
Improvement in PTS (8 weeks - 12 months)	Study population		OR 1.29 (0.69 to 2.41)	164 (2 RCTs)	⊕⊕⊖⊖ low[a]	De Jongste 1989 compared rutosides vs placebo, Prandoni 2005 vs no comparator
	554 per 1000	616 per 1000 (462 to 750)				
Deterioration in PTS (8 weeks - 12 months)	Study population		OR 0.61 (0.19 to 1.90)	80 (1 RCT)	⊕⊕⊖⊖ low[b]	
	150 per 1000	97 per 1000 (32 to 251)				
Adverse effects (8 weeks - 12 months)	See comment					De Jongste 1989 reported 'mild side effects' in 7/41 of the rutoside group and 5/42 of the placebo or no treatment group. Prandoni 2005 reported 6/80 stopped taking medication due to side effects

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **PTS**: post-thrombotic syndrome; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] We downgraded by two steps due to serious risk of bias (no information on outcome assessor blinding (De Jongste 1989) and non blinded comparator group (Prandoni 2005)); imprecision of the estimate and suspected publication bias
[b] We downgraded by two steps due to lack of blinding, imprecision of the estimate and possible risk of publication bias

Summary of findings 2. Rutosides versus elastic compression stockings for the treatment of post-thrombotic syndrome

Comparison 2: Rutosides versus ECS for the treatment of PTS

Patient or population: patients with PTS
Setting: outpatients
Intervention: rutosides
Comparison: ECS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with ECS	Risk with rutosides				
Occurrence of leg ulceration	See comment					This outcome was not reported by any included study
Improvement in PTS (12 months)	Study population		OR 0.80 (0.31 to 2.03)	80 (1 RCT)	⊕⊕⊖⊖ low[a]	
	700 per 1000	651 per 1000 (420 to 826)				
Deterioration in PTS (12 months)	Study population		OR 0.61 (0.19 to 1.90)	80 (1 RCT)	⊕⊕⊖⊖ low[b]	
	150 per 1000	97 per 1000 (32 to 251)				
Adverse effects (12 months)	See comment					Prandoni 2005 reported 2/80 participants not tolerating ECS and 6/80 stopping the medication due to side effects, described as mainly gastrointestinal

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **ECS**: elastic compression stockings; **OR:** odds ratio; **PTS**: post-thrombotic syndrome; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] We downgraded the quality of the evidence for this outcome by two steps as there was no blinding of treatment groups and publication bias was suspected
[b] We downgraded the quality of the evidence for this outcome by two steps as there was no blinding of treatment groups and publication bias was suspected

Summary of findings 3. Rutosides versus an alternative venoactive remedy (hidrosmina) for the treatment of post-thrombotic syndrome

Comparison 3: Rutosides versus hidrosmina for the treatment of PTS

Patient or population: patients with PTS

Settings: outpatients

Intervention: rutosides

Comparison: hidrosmina (venoactive remedy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with hidrosmina	Risk with rutosides				
Occurrence of leg ulceration	See comment					This outcome was not reported by any included study
Improvement in PTS (6 months)	Study population		OR 0.18 (0.04 to 0.94)	29 (1 RCT)	⊕⊕⊖⊖ low[a]	
	600 per 1000	213 per 1000 (57 to 585)				
Deterioration in PTS (6 months)	Study population		OR 0.19 (0.01 to 4.24)	29 (1 RCT)	⊕⊕⊖⊖ low[b]	
	133 per 1000	28 per 1000 (2 to 395)				

Adverse effects	See comment		This outcome was not reported by Monreal 1994

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **OR:** odds ratio; **PTS**: post-thrombotic syndrome; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] We downgraded the quality of the evidence for this outcome by two steps due to imprecision, suspected publication bias and lack of blinding
[b] We downgraded the quality of the evidence for this outcome by two steps due to imprecision, suspected publication bias and lack of blinding

BACKGROUND

Description of the condition

Post-thrombotic syndrome (PTS) is a long-term complication of deep venous thrombosis (DVT) that is characterised by chronic complaints, swelling, and skin changes in the affected limb. One in every three patients with DVT will develop post-thrombotic sequelae within five years (Prandoni 1996). Although there is no gold standard for the diagnosis of PTS, the presence of typical clinical features of venous insufficiency in a patient with previous DVT provides strong supporting evidence. The most commonly used diagnostic criterion for PTS is the Villalta Scale (Villalta 1994). This considers five symptoms (pain, cramps, heaviness, paraesthesias, and pruritus) and six signs (pre-tibial oedema, hyperpigmentation, venous ectasia, redness, skin irritation, and pain during calf compression) in the affected limb. Each element is scored on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) and the scores totaled. Total scores are then used to diagnose PTS: 0 to 4 no PTS, 5 to 9 mild PTS, 10 to 14 moderate PTS, and > 14 or ulceration = severe PTS.

Description of the intervention

The standard intervention for both the prevention and treatment of PTS is elastic compression stocking (ECS) therapy of the legs. Compression therapy of the legs is assumed to reduce oedema, accelerate venous blood flow, and improve venous pump function (Partsch 1991). It is the treatment of first choice for PTS (Partsch 1991). However, compression treatment sometimes leads to discomfort and has been associated with poor compliance, which renders oral drug treatment an attractive option. In addition, the benefits of ECS for PTS have not been fully proven, furthering the need to investigate alternative interventions.

Rutosides are a group of compounds derived from horse chestnut (Latin name: Aesculus hippocastanum), a traditional herbal remedy for treating oedema formation in chronic venous insufficiency (Bombardelli 1996). The active component of horse chestnut seed extract (HCSE) is escin (also spelled aescin) (Guillaume 1994; Lorenz 1960; Schrader 1995). Rutosides and escin are known as 'venoactive' or 'phlebotonic' remedies.

How the intervention might work

In chronic venous insufficiency (CVI) patients, white blood cells accumulate in the affected limbs (Moyses 1987; Thomas 1988) resulting in activation of enzymes which degrade the protein within the capillary walls (Sarin 1993). Studies have shown that escin inhibits these enzymes thereby preventing fluid leakage and swelling due to loss of capillary wall patency (Facino 1995).

Why it is important to do this review

There is evidence to support the use of rutosides for rapid relief of signs or symptoms in CVI and microangiopathy (Cesarone 2005). A Cochrane review of 17 trials comparing HCSE against placebo, ECS, or other medications concluded that HCSE is effective for short-term treatment of CVI symptoms such as leg pain and oedema, and that adverse events were mild and infrequent (Pittler 2012). However, it is not known whether rutosides are effective and safe in the treatment of post-thrombotic syndrome.

OBJECTIVES

To determine the effectiveness (improvement or deterioration in symptoms) and safety of rutosides for treatment of post-thrombotic syndrome (PTS) in patients with deep vein thrombosis (DVT) compared to placebo, no intervention, elastic compression stockings (ECS), or any other treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) evaluating rutosides in the treatment of post-thrombotic syndrome (PTS). Trials which use allocation processes that are transparent before assignment, such as open list of random numbers, case record, day of the week, surname, and so forth, are classified as CCTs.

This review evaluated rutosides in the treatment of PTS. The effects of rutosides on prevention of PTS are reported in the Cochrane review by Morling 2018.

Types of participants

Men and women of any age with complaints or clinical changes of the legs after a previous DVT, with PTS diagnosed by a recognised scoring system. Methods considered acceptable for diagnosis of DVT were ultrasound, venography, and impedance plethysmography.

Types of interventions

The primary intervention was rutosides (any formulation at any dose). Comparisons were with placebo or no intervention, ECS, and any other treatment (including an alternative type or dosage of rutosides and other venoactive remedies). Other kinds of concomitant treatment (including ECS) were equal in both groups, and they were not the comparator treatment.

Types of outcome measures

Primary outcomes

- Occurrence of leg ulceration over time (yes or no)
- Any improvement of PTS (yes or no)
- Any deterioration of PTS (yes or no)

The definitions used in each trial paper for PTS were accepted provided they included a systematic clinical history and scoring of physical examinations. Some trials may report only changes in complaints over time. These are less valid indicators of effectiveness as the complaints may vary.

Secondary outcomes

- Any reduction of oedema in PTS (yes or no)
- Any reduction of pain in PTS (yes or no)
- Any recurrence of DVT or pulmonary embolism (yes or no)
- Compliance
- Adverse effects after initiation of rutosides

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist conducted systematic searches of the following databases for randomised controlled trials and controlled clinical trials without language, publication year, or publication status restrictions.

- The Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web searched on 21 August 2018).
- The Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Register of Studies Online (CRSO 2018, issue 7).
- MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) (searched from 1 January 2017 to 21 August 2018).
- Embase Ovid (searched from 1 January 2017 to 21 August 2018).
- CINAHL Ebsco (searched from 1 January 2017 to 21 August 2018).
- AMED Ovid (searched from 1 January 2017 to 21 August 2018).

The Information Specialist modelled search strategies for other databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6, Lefebvre 2011). Search strategies for major databases are provided in Appendix 1.

The Information Specialist searched the following trials registries on 21 August 2018.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

Reference lists of identified studies were scrutinised in order to identify further citations.

Data collection and analysis

Selection of studies

Two review authors (JM, DNK) independently assessed studies for inclusion. JM and SEY independently extracted information from the trials. Disagreement was resolved by discussion.

Data extraction and management

Details of the studies were extracted and summarised using a data extraction sheet.

The following data items were collected, where available.

- Trial setting (country, and whether primary or secondary care).
- Method of randomisation.
- PTS diagnosis assessment method, and whether blinded.
- Length of follow-up.
- Number of patients randomised.
- Inclusion criteria.
- Exclusion criteria.
- Description of interventions and co-interventions.
- Baseline characteristics of groups for important variables (e.g. first DVT, recurrent DVT).
- Definition of PTS.
- Results.
- Compliance.
- Adverse events.
- Intention-to-treat analysis.
- Number and reasons for withdrawals.
- Source of funding.
- Use of an a priori sample size or power calculation.

Assessment of risk of bias in included studies

Two review authors (JM, SEY) independently assessed bias using the Cochrane 'Risk of bias' tool. Disagreement was resolved by discussion. Five key domains were examined for bias: selection bias; performance bias; attrition bias; detection bias; and reporting bias. These were assessed and classified as either at a low risk of bias or a high risk of bias. Where insufficient detail was reported in a study to assess the risk, this was reported as 'unclear'. In addition, any other form of bias noted in the study was reported.

Measures of treatment effect

All of the outcomes for this review were considered as dichotomous (present or absent). For dichotomous variables the odds ratio (OR) with 95% confidence intervals (CI) were reported. When it was not possible to combine patient data from different trials due to clinical heterogeneity, the results of individual trials are reported and discussed.

Unit of analysis issues

For all outcomes the unit of analysis was the number of patients. Cross-over trials were analysed examining the first treatment period only.

Dealing with missing data

Where outcome variables were not reported the available data were analysed. For missing data related to losses to follow-up the data were assumed to be missing at random. The potential impact of missing data was considered by the review authors when making their final conclusions. It was not necessary for the review authors to contact the original investigators to request missing data.

Assessment of heterogeneity

We planned to explore heterogeneity by examining factors that may be influential, such as the definition of PTS used by the trialists, care setting, time of follow-up, and incidence of recurrent DVT. In the absence of clinical heterogeneity we intended to test for statistical heterogeneity using the Chi^2 test, but insufficient numbers of studies were identified.

Assessment of reporting biases

Funnel plots were planned to consider reporting bias but insufficient numbers of studies were identified.

Data synthesis

Data were synthesised using the RevMan software. When possible, meta-analysis was carried out using a fixed-effect model where heterogeneity was low (determined by the I^2 statistic). If substantial

heterogeneity was present (I^2 statistic > 50%), we planned to use a random-effects model. As only three studies investigating different comparisons were included, it was not possible to pool all data. When data could not be combined results were discussed textually.

Subgroup analysis and investigation of heterogeneity

Where sufficient numbers of studies were identified, subgroup analyses would have been undertaken for the differing comparator groups (versus placebo or no treatment, versus ECS, and versus alternative venoactive remedies).

Sensitivity analysis

If applicable, RCTs and CCTs were analysed separately to access the efficacy of the effect estimation, calculated with the Mantel-Haenszel test. Where sufficient trials were available we re-analysed the data excluding low-quality trials. Due to the small number of trials in each comparison this was not possible.

'Summary of findings' table

A table compiling and summarising the best evidence of relevant outcomes was constructed for comparisons of rutosides with the three comparator groups i) placebo or no treatment, ii) ECS and iii) hidrosmina). Study populations consisting of patients with PTS were considered. The most important and clinically relevant outcomes (both desirable and undesirable) that were thought to be essential for decision-making were occurrence of leg ulceration over time, any improvement of PTS, any deterioration of PTS and adverse effects. These are reported within Summary of findings for the main comparison, Summary of findings 2 and Summary of findings 3. Assumed control intervention risks were calculated by the mean number of events in the control groups of the selected studies for each outcome. The system developed by the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE working group) was used for grading the quality of evidence as high, moderate, low and very low, based on within-study risk of bias, directness of evidence, heterogeneity, precision of effects estimates, and risk of population bias (GRADE 2004).

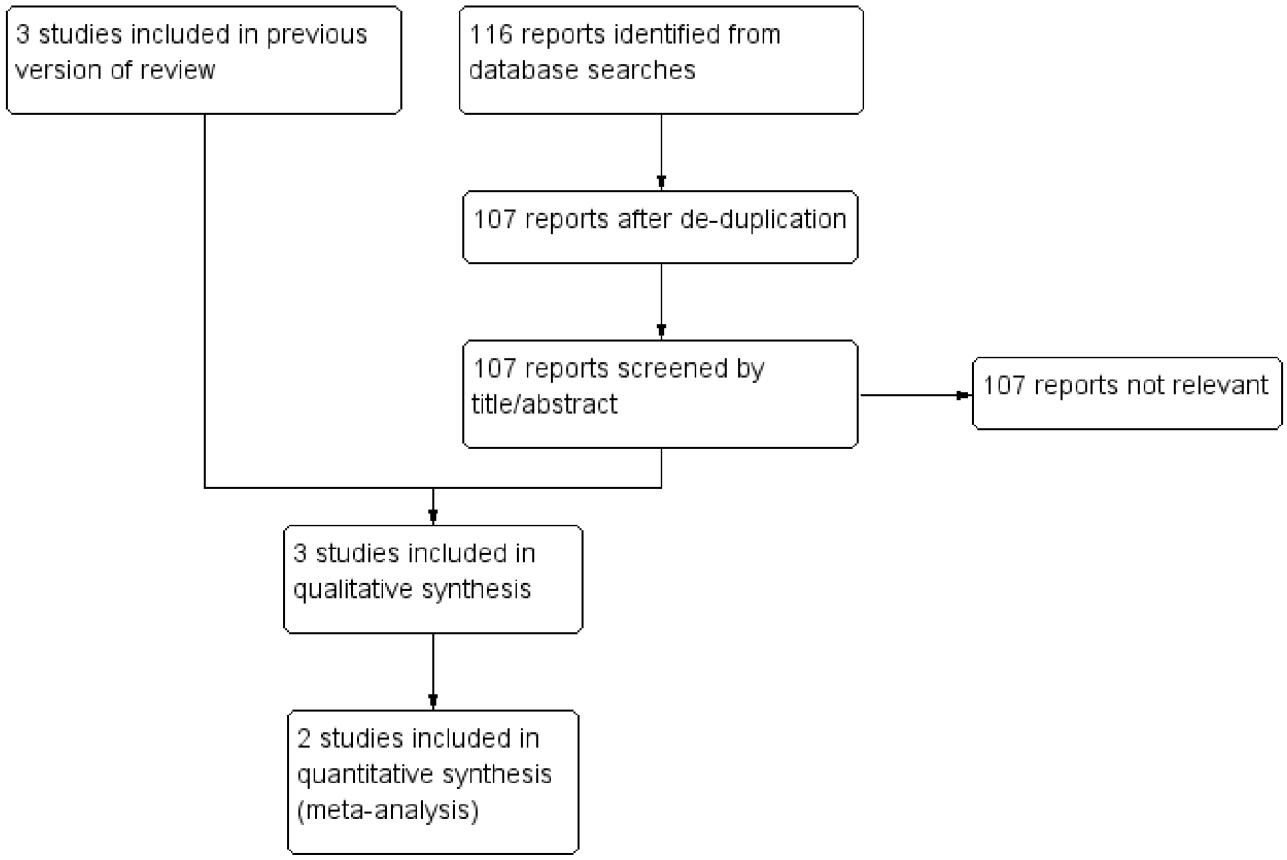
RESULTS

Description of studies

Results of the search

See Figure 1. No additional studies were identified for this update.

Figure 1. Study flow diagram.



Following consideration of the inclusion and exclusion criteria, three studies (four reports) were suitable for inclusion with six studies excluded. Briefly, these were two RCTs and an open cross-over study. The included studies allowed three comparisons to be examined: rutosides versus placebo or no treatment (De Jongste 1989; Prandoni 2005), rutosides versus ECS (Prandoni 2005), and rutosides versus an alternative venoactive remedy (Monreal 1994). See Included studies and Excluded studies for further details of each study.

Included studies

De Jongste 1989

This was a multi-centre, double blind, RCT to assess the use of 0-(β-hydroxyethyl)-rutosides (1200 mg/day) in 84 patients with unilateral PTS of at least six months duration and a venography proven DVT in the affected leg. Consenting ambulant outpatients (referred by their general practitioner (GP)) were randomised by a computer system to receive either rutosides or placebo for eight weeks. There were 48 male and 35 female participants (mean age 53 to 54 years). Each patient was followed up at four weeks and eight weeks. At each visit a standard questionnaire recorded tiredness, pain, heaviness, feeling of swelling, restless legs, cramps, presence of pitting oedema on a scale of: 0 = absent, 1 = mild, 2 = moderate, 3 = severe. In addition, minimum ankle circumferences were recorded as well as both the patients' and the (blinded) doctors' opinion of the efficacy of the treatment.

This study provided data for the comparison: rutosides versus placebo or no treatment.

Monreal 1994

This was an open cross-over study of 0-(β-hydroxyethyl)-rutosides (900 mg/day) versus hidrosmina (600 mg/day), each for six months. Hidrosmina is an alternative venoactive remedy. Twenty-nine outpatients with unilateral PTS of at least 12 months duration following a venography proven lower limb DVT were randomised. The Kakkar and Lawrence scoring system was used to record the severity of symptoms and signs. The initial drug was taken for six months. The drug was then discontinued and the alternative taken for a further six months. Following discontinuation of both drugs, patients were examined at three and six months. For this review only the first treatment period was considered.

This study provided data for the comparison: rutosides versus hidrosmina (an alternative venoactive remedy).

Prandoni 2005

This was a randomised controlled pilot study comparing the efficacy of elastic compression stockings (ECS), hydroxyethylrutosides (HR) (2000 mg/day), or both in the treatment of PTS in ultrasound proven lower limb DVT. A total of 120 consecutive patients were randomised by a computer system, with 40 patients in each of the three groups. They received treatment for 12 months. In order to assess the efficacy of HR, this Cochrane review compared the use of HR and ECS with elastic compression stockings alone. There were 36 male and 84 female participants (aged 24 to 91 years). Each patient was followed up at three months, six months, and 12 months. At each visit an investigator blind to the participant's treatment scored the presence and severity of PTS according to the Villalta scale. Those whose scores fell to below five or that had a 30% reduction were considered to have a PTS improvement, those that had an increase by at least 30% were considered to have a PTS deterioration. Compliance with treatment was also recorded.

This study provided data for the comparisons: rutosides versus placebo or no treatment, and rutosides versus ECS.

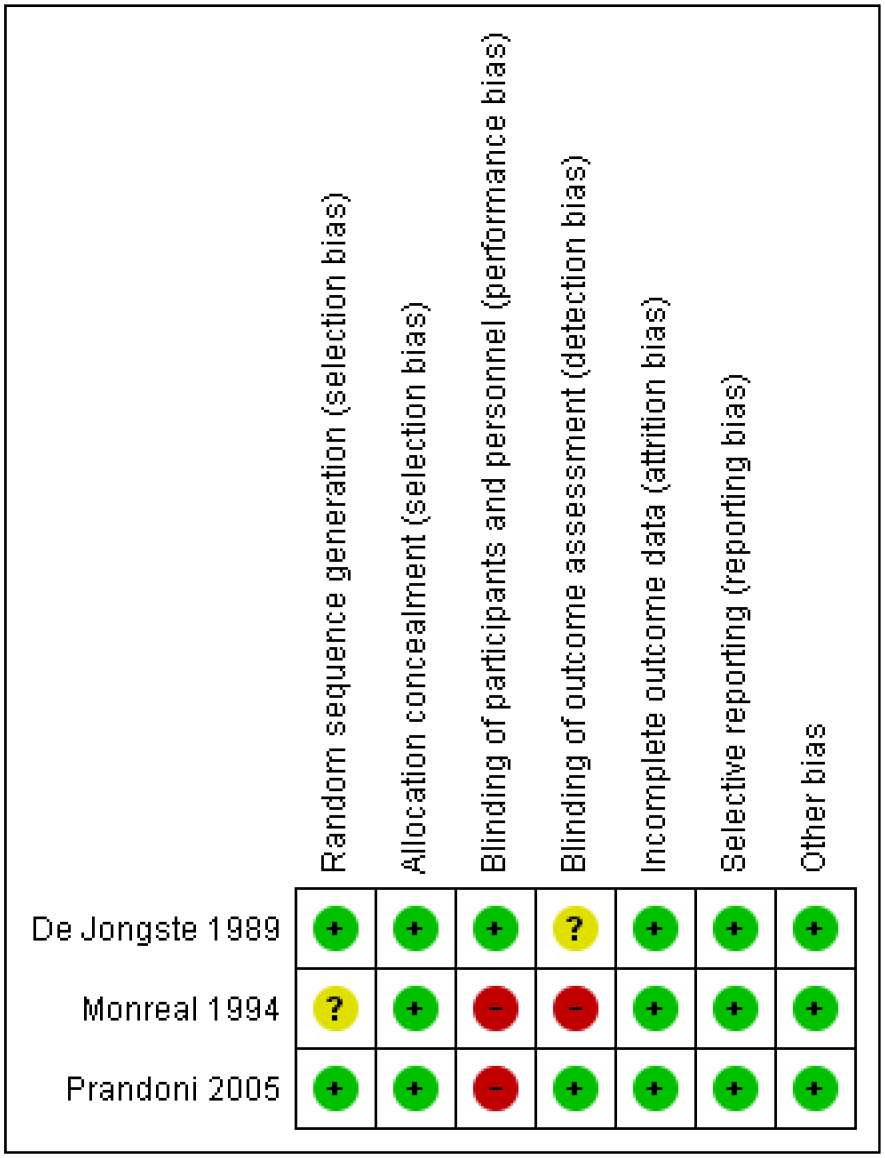
Excluded studies

Following application of the inclusion and exclusion criteria, six studies were excluded. Four of the studies investigated the effect of rutosides on the treatment of deep venous insufficiency with a mixed causality, not PTS (Cospite 1986; Diebschlag 1994; Incandela 2002; Rose 1970). Two studies either presented no results or it was not possible to extract the results related to PTS (De Jongste 1986; Nill 1970).

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias assessment.

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



Allocation

All three studies used random assignment of participants to each of the study groups. Both De Jongste 1989 and Prandoni 2005 specified computer randomisation schedules. Monreal 1994 did not specify the randomisation schedule.

Blinding

The three studies included in this review all used slightly different trial methodologies, making the blinding process slightly different for each. De Jongste's traditional RCT (intervention versus placebo) stated double blinding, suggesting that both participants and study personnel were unaware of which treatment the individual was receiving (De Jongste 1989).

Prandoni 2005 had three trial arms. Participants were not blinded as patients received either elastic stockings, oral HR treatment, or both and it is difficult to use a placebo for the patients in the non-elastic stockings groups although sham devices are available. Some of the measured outcomes in this study were mostly based on severity of clinical symptoms, which could potentially be influenced by patients' perspectives. Other measured outcomes were based on clinical signs, which are unlikely to be influenced by patients' perspectives. There was no placebo in the ECS alone group so participants would be aware of whether they were receiving the trial medication. Study personnel recording outcome data were unaware of the treatment allocation and the results of previous measurements.

In the Monreal 1994 open cross-over trial it was not stated if patients were blinded to the treatment allocation. In addition, some of the measured outcomes in this study were based on the subjective severity of clinical symptoms and might potentially be influenced by patients' perspectives. All patients were examined by the same physician to increase the standardisation of measurement. It was not stated if the study personnel were blinded.

Incomplete outcome data

All excluded patients were accounted for and satisfactory reasons for exclusion given in all three included studies.

Selective reporting

In all included studies the pre-specified outcomes of interest in this review were reported.

Other potential sources of bias

There were no additional significant bias concerns.

Effects of interventions

See: **Summary of findings for the main comparison** Rutosides versus placebo (or no treatment) for the treatment of post-thrombotic syndrome; **Summary of findings 2** Rutosides versus elastic compression stockings for the treatment of post-thrombotic syndrome; **Summary of findings 3** Rutosides versus an alternative venoactive remedy (hidrosmina) for the treatment of post-thrombotic syndrome

Key effects of the intervention are shown in the data analysis table below. For each of the studies the final time point outcome was reported. It should be noted that the duration of each study differed. The results reported from the three studies allowed three comparisons to be made.

- Rutosides versus placebo or no treatment.
- Rutosides versus ECS.
- Rutosides versus hidrosmina (an alternative venoactive remedy).

Occurrence of leg ulceration over time

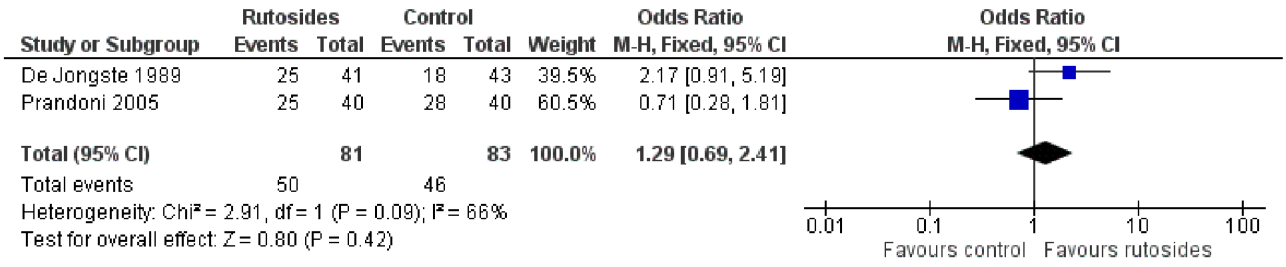
None of the studies reported on the development of ulceration. Monreal 1994 noted ulcer healing in the rutoside group (2/15) compared with hidrosmina (1/14) (P = 0.59).

Improvement of PTS

Different reporting methods were used by each study. Whilst not measured in identical ways these were comparable.

For this outcome we were able to pool data from two of the three treatment groups in Prandoni 2005 with those of De Jongste 1989 which showed a combined OR of 1.29 (95% CI 0.69 to 2.41; P = 0.42; 164 participants; 2 studies; low-quality evidence) for rutosides versus placebo or no treatment (Analysis 1.1) (Figure 3). This was supplemented by De Jongste 1989 reporting on the improvement of each component of PTS: tiredness (rutosides 46%, placebo 26%); heaviness (rutosides 41%, placebo 29%); restless legs (rutosides 17%, placebo 14%); and cramps (rutosides 34%, placebo 36%).

Figure 3. Forest plot of comparison: 1 Rutosides for the treatment of PTS, outcome: 1.1 Improvement in PTS.



For rutosides versus ECS, Prandoni 2005 reported PTS improvement in 26/40 participants in the rutosides group compared to 28/40 in the ECS group (OR 0.80, 95% CI 0.31 to 2.03; 80 participants; 1 study; low-quality evidence). (Analysis 2.1).

For rutosides versus hidrosmina, Monreal 1994 reported 9/15 participants with improvement of PTS in the hidrosmina treated group compared to 3/14 in the rutosides group (OR 0.18, 95% CI 0.04 to 0.94; 29 participants; 1 study; low-quality evidence) (Analysis 3.1).

Deterioration of PTS

Different reporting methods were used by each study. Whilst not measured in identical ways these were comparable.

Prandoni 2005 reported higher rates of PTS deterioration in the rutosides group (9/40) compared with the placebo or no treatment group (6/40) (OR 0.61, 95% CI 0.19 to 1.90; 80 participants; 1 study; low-quality evidence) (Analysis 1.2).

In Prandoni 2005, for rutosides versus ECS, there was more deterioration in the rutosides group (9/40) compared to the ECS group (6/40)(OR 0.61, 95% CI 0.19 to 1.90; 80 participants; 1 study; low-quality evidence) (Analysis 2.2).

For rutosides versus hidrosmina, Monreal 1994 reported deterioration of PTS in 0/14 patients in the rutoside group and deterioration in 2/15 patients in the hidrosmina group (OR 0.19, 95% CI 0.01 to 4.24; 29 participants; 1 study; low-quality evidence) (Analysis 3.2).

Reduction of oedema or swelling

Only De Jongste 1989 reported on improvement in swelling, with 20/41 participants in the rutosides group showing improvement compared to 18/42 participants in the placebo/no treatment group (OR 1.27, 95% CI 0.53 to 3.02; 83 participants; 1 study). (Analysis 1.3).

Monreal 1994 reported mean ankle and calf circumferences at six, 12, and 18 month intervals. During treatment with both rutosides and hidrosmina Monreal 1994 reported a gradual reduction in mean values, however this was not sustained following withdrawal of treatment.

Reduction of pain

De Jongste 1989 reported 16/41 participants in the rutosides group compared to 14/42 participants in the placebo/no treatment group had a reduction of pain (OR 1.28, 95% CI 0.52 to 3.14; 83 participants; 1 study). (Analysis 1.4).

Recurrence of DVT or pulmonary embolism

Prandoni 2005 was the only study to report reoccurrence of DVT or pulmonary embolism (PE). This event occurred once in each of the rutosides, ECS, and placebo or no treatment groups. Each group had a total of 40 participants. (Analysis 1.5; Analysis 2.3).

Compliance

Prandoni 2005 was the only study to report on compliance, with 70/80 wearing stockings for ≥ 80% of the study and 64/80 taking ≥ 80% of the study medication. Note the numbers included all three groups (rutosides versus ECS versus rutosides plus ECS) as it was not possible to separate them.

Adverse effects after initiation of rutosides

De Jongste 1989 reported 'mild side effects' in 7/41 of the rutoside group and 5/42 of the placebo or no treatment group (OR 0.66, 95% CI 0.19 to 2.26; 83 participants 1 study) (Analysis 1.6). As above, Prandoni 2005 did not separate the outcomes fully with 2/80 not tolerating ECS and 6/80 stopping the medication due to side effects, described as mainly gastrointestinal. Monreal 1994 did not comment on side effects.

Because of the limited number of included studies we were unable to undertake heterogeneity, subgroup, reporting bias, and sensitivity analyses.

DISCUSSION

Summary of main results

Only three small studies, which were clinically heterogenous, were included in this review. For the majority of outcomes, data was available from only one study, limiting the evidence available.

This review shows that there is little or no difference in improvement or deterioration of post-thrombotic syndrome (PTS) (low-quality evidence) when comparing rutosides with placebo or no treatment (See Summary of findings for the main comparison); or when rutosides were compared to elastic compression stockings (ECS) (See Summary of findings 2).

There is low-quality evidence of less PTS improvement in the rutosides group compared to an alternative venoactive remedy (hidrosmina), and little or no difference in deterioration of PTS was detected (See Summary of findings 3).

There was little reported on compliance and adverse effects, with no clear differences between groups identified.

Overall completeness and applicability of evidence

This review considered DVT at any site without separate analysis of upper and lower limbs. A separate analysis would have been limited in this review given the inclusion of only three studies but should be considered for future updates.

Quality of the evidence

Overall, all of the evidence presented was considered to be of low-quality using GRADE (See Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3). This was predominantly due to the lack of both participant and researcher blinding in the included studies. With further downgrading due to this risk of bias and possible publication bias. The quality of the evidence was further limited by the small number of studies contributing to this review. The data were generated using a subjective scoring system for PTS, however this is unavoidable. The alternative would be repeated invasive pressure measures, which would be unacceptable to participants and potentially less useful than clinical symptom outcomes. Scoring systems differed across the studies but were all similar. Another notable difference in the included studies was the varied dosage of rutosides used (900 mg/day to 2000 mg/day).

Potential biases in the review process

We believe that all trials with the potential for inclusion have been identified via our searches of the Cochrane Vascular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL databases and World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov trials registers. It was not possible to contact any PTS specialists to recover any additional unpublished or ongoing studies. We remain confident in our study identification. Data collection and analysis methods were robust.

Agreements and disagreements with other studies or reviews

Six studies were excluded following the searches and of these only one referred to PTS. This double blind randomised placebo controlled study (De Jongste 1986) reported its data in a way which made it impossible to extract for inclusion in this review. However, in summary, a greater reduction in oedema and greater patient reported improvement of symptoms were noted in the rutoside treated group. This is in keeping with the findings of this Cochrane review. It was not possible to identify any additional studies to assess agreement or disagreement with.

Our study agrees with the findings of a recent meta-analysis by Cohen 2012 for the outcomes we included. In addition, Cohen 2012 chose to analyse the risk of adverse effects, combining De Jongste 1989 and Prandoni 2005, and reported a non-significant increased risk with rutoside use (RR 2.04, 95% CI 0.76 to 5.51). Cohen 2012 did not identify any studies additional to those we identified that compared the effects of rutosides versus placebo, no intervention, ECS, or any other treatment.

AUTHORS' CONCLUSIONS

Implications for practice

There was no evidence that rutosides were superior to the use of placebo or ECS. Overall, currently there is limited low-quality evidence that 'venoactive' or 'phlebotonic' remedies such as rutosides reduce symptoms of post-thrombotic syndrome (PTS). Mild side effects were noted in one study. The three studies included in this review provide no evidence to support the use of rutosides in the treatment of PTS.

Implications for research

Numerous in vitro studies conclude that rutosides reduce microvascular permeability both in healthy vessels and vessels showing signs of inflammation hence decreasing capillary flux or filtration, leakage, and swelling, with a potential improvement in signs and symptoms of PTS. Since PTS is not only dependent on platelets but also coagulation, fibrinolysis, and flow, studies have also shown that rutosides inhibit the aggregation of human red cells and platelets in vitro. Despite these in vitro research findings the effects have yet to be fully translated into human clinical trials. Also, not all studies have yet adopted the standardised Villalta Scale for the diagnosis and monitoring of PTS symptoms (Kahn 2009), which is essential in future work. Larger, longer duration RCTs are required to confirm the effectiveness of rutosides for treating PTS and also to examine their long-term benefits and any benefits over the current standard therapy of ECS.

ACKNOWLEDGEMENTS

The review authors would like to thank Dr Martin Prins for his work on the study protocol.
The review authors would like to thank the Cochrane Vascular editorial base for their assistance.

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CHARACTERISTICS OF STUDIES

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

De Jongste 1989

Methods	Randomised, double blind, placebo controlled trial Treatment period: eight weeks
Participants	Conducted in outpatient department of three Dutch hospitals Total number randomised: 84 (males 48, female 36) Mean age: intervention 53 (SD 12), placebo 54 (SD 13) years
Interventions	Arm 1: HR 1200 mg daily (in four divided doses) Arm 2: placebo
Outcomes	Deterioration of PTS

De Jongste 1989 *(Continued)*

	Presence of pain Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned ..... with the use of a computerised random assignment method". Comment: The randomisation schedule was specified.
Allocation concealment (selection bias)	Low risk	Quote: "A series of coded sealed envelopes for decoding any particular case was supplied to the local hospital pharmacy". Comment: Unlikely patients and personnel were aware of the randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind". Comment: Suggesting both participants and study personnel were unaware of which treatment the individual was receiving.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind", "All the assessments were performed by the same investigators at each center..." Comment: Not reported if investigators were aware of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All excluded patients were accounted for and satisfactory reasons for exclusion given.
Selective reporting (reporting bias)	Low risk	Comment: The study's pre-specified outcomes that are of interest to this review have been reported.
Other bias	Low risk	No additional significant bias concerns.

Monreal 1994

Methods	Randomised, open, cross-over trial Phase 1: first treatment period, six months Phase 2: second treatment period, six months Phase 3: washout period, four weeks
Participants	Conducted in single centre, outpatient department, Spain Total number randomised 29 (males 21, female 8) Mean age: 60 years (range 39 to 80)
Interventions	Arm 1: HR 900 mg daily (in three divided doses) Arm 2: HR 600 mg daily (in three divided doses)

Monreal 1994 *(Continued)*

Outcomes	Presence of pain (Kakkar and Lawrence Scoring System)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned". Comment: The randomisation schedule was not specified.
Allocation concealment (selection bias)	Low risk	Comment: Unlikely patients were aware of the randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open cross-over pilot study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open cross-over pilot study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All excluded patients were accounted for and satisfactory reasons for exclusion given.
Selective reporting (reporting bias)	Low risk	Comment: The study's pre-specified outcomes that are of interest to this review have been reported.
Other bias	Low risk	No additional significant bias concerns.

Prandoni 2005

Methods	Randomised, single blind, controlled trial Treament period: 12 months
Participants	Single centre Italian study Total number randomised 120 (males 33, female 87) Age range: 24 to 91 years
Interventions	Arm 1: HR 2000 mg daily (in two divided doses) Arm 2: ECS (below knee, 30 to 40 mmHg at ankle) Arm 3: HR 2000 mg daily (in two divided doses) and ECS (below knee, 30 to 40 mmHg at ankle)
Outcomes	Deterioration of PTS (Villalta Scale) Improvement of PTS (Villalta Scale) Compliance with therapy

Prandoni 2005 *(Continued)*

	Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "consenting patients were randomly allocated ..... according to a computer generated list". Comment: The randomisation schedule was specified.
Allocation concealment (selection bias)	Low risk	Comment: Unlikely patients were aware of the randomisation schedule.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded as patients received either ECS, oral HR treatment or both and it is difficult to use a placebo for the patients in the non-ECS groups although sham devices are available. Some of the measured outcomes in this study are mostly based on severity of clinical symptoms which could potentially be influenced by patients' perspectives. Other measured outcomes were based on clinical signs which are unlikely to be influenced by patients' perspectives.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment was carried out by an investigator who was aware as to the side of the index DVT but was unaware of the treatment allocation and the results of previous measurements.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: All excluded patients were accounted for and satisfactory reasons for exclusion given.
Selective reporting (reporting bias)	Low risk	Comment: The study's pre-specified outcomes that are of interest to this review have been reported.
Other bias	Low risk	No additional significant bias concerns.

DVT: deep vein thrombosis
ECS: elastic compression stockings
HR: 0-(β-hydroxyethyl)-rutosides
mg: milligram
PTS: post-thrombotic syndrome
SD: standard deviation

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

Study	Reason for exclusion
Cospite 1986	Not post-thrombotic syndrome
De Jongste 1986	No results presented suitable for data extraction or consistent with review outcomes
Diebschlag 1994	Not post-thrombotic syndrome
Incandela 2002	Not post-thrombotic syndrome

Study	Reason for exclusion
Nill 1970	Not possible to extract post-thrombotic syndrome data alone, and the outcome reported is not relevant for this review
Rose 1970	Not post-thrombotic syndrome

WHAT'S NEW

Date	Event	Description
21 August 2018	New citation required but conclusions have not changed	Search updated. No new included or excluded studies identified. Review text updated with no change to conclusions.
21 August 2018	New search has been performed	Search updated. No new included or excluded studies identified.

HISTORY

Protocol first published: Issue 1, 2006
Review first published: Issue 4, 2013

Date	Event	Description
2 September 2015	New citation required but conclusions have not changed	New search run. No studies identified. Minor text changes made, summary of findings table added. No change to conclusions.
2 September 2015	New search has been performed	New search run. No studies identified.
3 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JM: selected trials, developed data extraction tool, extracted data, assessed risk of bias, undertook analyses, wrote the review and update
CB: updated text for update
SEY: extracted data, assessed risk of bias, wrote the review
DK: wrote the protocol, checked the review

DECLARATIONS OF INTEREST

JM: declared that she is currently receiving a MRC Clinicial Scientist Fellowship grant which does not conflict with this review
CB: works within the Cochrane Vascular editorial base. Where necessary, editorial tasks were carried out by other members of the group
SEY: none known
DK: none known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Chief Scientist Office, Scottish Government Health Directorates, The Scottish Government, UK.

The Cochrane Vascular editorial base is supported by the Chief Scientist Office.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

According to Cochrane guidelines the quality of the trials was assessed using the Cochrane 'Risk of bias' tool (Higgins 2011).

The original protocol listed only negative primary outcomes regarding PTS. In order to present a balanced view we added a third primary outcome: 'any improvement in PTS (yes or no)'.

INDEX TERMS

Medical Subject Headings (MeSH)

Aesculus [*chemistry]; Phytotherapy [*methods]; Placebos [therapeutic use]; Plant Extracts [*therapeutic use]; Postthrombotic Syndrome [*drug therapy] [etiology] [therapy]; Randomized Controlled Trials as Topic; Rutin [*therapeutic use]; Stockings, Compression; Venous Thrombosis [complications]; Watchful Waiting

MeSH check words

Humans