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Rutosides for prevention of post-thrombotic syndrome (Review)

Morling JR, Yeoh SE, Kolbach DN

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[Intervention Review]

Rutosides for prevention 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. The current standard care for the prevention of PTS following DVT is elastic compression stockings. 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 prevention of PTS. This is the second update of the review first published in 2013.

Objectives

To determine the effectiveness and safety of rutosides for prevention of post-thrombotic syndrome (PTS) in patients with deep vein thrombosis (DVT), compared to placebo, no intervention, or reference medication.

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

We planned to include trials of rutosides versus any alternative (placebo, no intervention, or reference medication) in the prevention of PTS in patients with DVT.

Data collection and analysis

Two review authors independently assessed studies for inclusion and intended to extract information from the trials.

Main results

No studies were identified comparing rutosides versus any alternative in the prevention of PTS.

Authors' conclusions

As there were no studies identified in this review there is currently insufficient evidence to determine the effectiveness and safety of rutosides for prevention of PTS in patients with DVT. Some studies suggest that rutosides may provide short-term relief of PTS symptoms.

However, there is nothing published on their use as a preventative therapy for PTS. High quality randomised controlled trials of rutoside versus any alternative are required to build the evidence base in this area.

PLAIN LANGUAGE SUMMARY

Rutosides for prevention 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, and also skin changes. At the current time the main way of preventing PTS is to wear compression stockings. However, it is known that patients frequently find the stocking uncomfortable and would prefer to take an oral medication to prevent the problem.

Rutosides are a herbal remedy which have been shown to reduce swelling and skin changes in other conditions affecting the veins such as in chronic venous insufficiency. This review aimed to evaluate the existing literature to see if there was evidence from randomised controlled trials for the effectiveness of rutosides in preventing PTS following a DVT. We also aimed to investigate whether there were any side effects from the treatment.

Search methods and selection of studies

We searched existing databases (current until 21 August 2018) for trials relating to the use of rutosides for the prevention of PTS following DVT. Two authors independently reviewed trials for inclusion and intended to extract results in line with prescribed criteria.

Key results and conclusions

We did not find any trials of rutosides versus an alternative therapy for the prevention of PTS that were suitable for inclusion. We therefore have no evidence to support the use of rutosides in the prevention of PTS and high quality randomised controlled trials are required.

BACKGROUND

Description of the condition

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 every three patients with a DVT will develop post-thrombotic syndrome (PTS) within five years (Prandoni 1996). Symtoms vary from mild to significantly debilitating. In the acute phase of DVT, a fresh thrombus in the deep vein produces an obstruction. In the first few months following DVT recanalisation (a complex process involving fibrinolysis, thrombus organisation, and neovascularisation) occurs (Meissner 2002). This process can result in valve destruction. Damaged valves, insufficient closure or occlusion, or both, of the veins increase pressure in the veins (venous hypertension). It is suggested that this venous hypertension disturbs the normal flow in small capillaries resulting in increased capillary filtration, which leads to oedema in the lower leg and a number of skin changes (Widmer 1985). Whilst the anticoagulant treatment for DVT prevents clot extension and embolisation it does not break down the primary clot.

Description of the intervention

The standard therapy for both the prevention and treatment of PTS is elastic compression stocking (ECS) therapy of the legs. It is assumed to reduce oedema, accelerate venous blood flow, and improve venous pump function (Partsch 1991). However, compression treatment sometimes leads to discomfort and has associated poor compliance, which renders oral drug treatment an attractive option.

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 (CVI) (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 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 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 prevention of PTS.

OBJECTIVES

To determine the effectiveness and safety of rutosides for prevention of PTS in patients with DVT compared to placebo, no intervention, or reference medication.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs, also known as quasi-RCTs) evaluating rutosides in the prevention of 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 evaluates rutosides in the prevention of PTS. The effects of rutosides on treatment of PTS are reported in the Cochrane review Morling 2018.

Types of participants

- Men and women of any age
- Deep venous thrombosis (DVT) that has been objectively diagnosed within the year prior to the study. Methods considered acceptable for diagnosis were ultrasound, venography, and impedance plethysmography

Types of interventions

- Primary intervention: rutosides in the first year after the diagnosis of a DVT
- Comparator groups: no intervention, different dosages of rutosides, or any other treatments (for example elastic compression stockings (ECS)) in the first year after a diagnosis of DVT

Where rutosides were being compared to a non-ECS alternative, ECS therapy was allowed if equal in all patient groups in the trial.

Types of outcome measures

Primary outcomes

- Development of post-thrombotic syndrome (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.

Secondary outcomes

- Any reduction in oedema (yes or no)
- Any development of pain (yes or no)
- Recurrence of DVT or pulmonary embolism (yes or no)
- Compliance with therapy
- Adverse effects

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.

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

Searching other resources

We intended to scrutinise the reference lists of identified studies, if found, in order to identify further relevant citations.

Data collection and analysis

Selection of studies

Two authors (JM, DNK) independently assessed studies for inclusion and if studies were identified, would have extracted information from the trials. Disagreement was resolved by discussion.

Data extraction and management

It was intended that the following data be extracted.

- 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 (or limbs) 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 effects.
- 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

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

Measures of treatment effect

We intended for dichotomous variables to be reported as the odds ratio (OR) with 95% confidence intervals. All of the intended outcomes for this review were considered as dichotomous (present or absent).

Unit of analysis issues

The unit of analysis was intended to be the number of patients.

Dealing with missing data

Where outcome variables were not reported, we intended to analyse the available data. For missing data related to losses to follow-up the data were assumed to be missing at random.

If necessary, we intended to contact the original investigators to request missing data.

The potential impact of missing data was to be considered by the authors when making their final conclusions.

Assessment of heterogeneity

We planned to explore heterogeneity by examining factors that may be influential, such as definition of PTS used, 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 I^2 statistic.

Assessment of reporting biases

Funnel plots were planned to consider reporting bias.

Data synthesis

Mantel-Haenzel fixed-effect model analyses were planned.

'Summary of findings' table

Should relevant studies have been identified, we intended to present the evidence found for rutosides for prevention of PTS by creating a 'Summary of findings' table according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADE profiler software (GRADEpro GDT 2015). We intended to use the GRADE system to assess the quality of the body of evidence associated with each outcome described in Types of outcome measures. Using the GRADE approach, we would have assessed the quality of the body of evidence for each outcome as

high, moderate, low, or very low based on the criteria for risk of bias, inconsistency, indirectness, imprecision, and publication bias (Atkins 2004; Guyatt 2011).

Subgroup analysis and investigation of heterogeneity

No subgroup analyses planned.

Sensitivity analysis

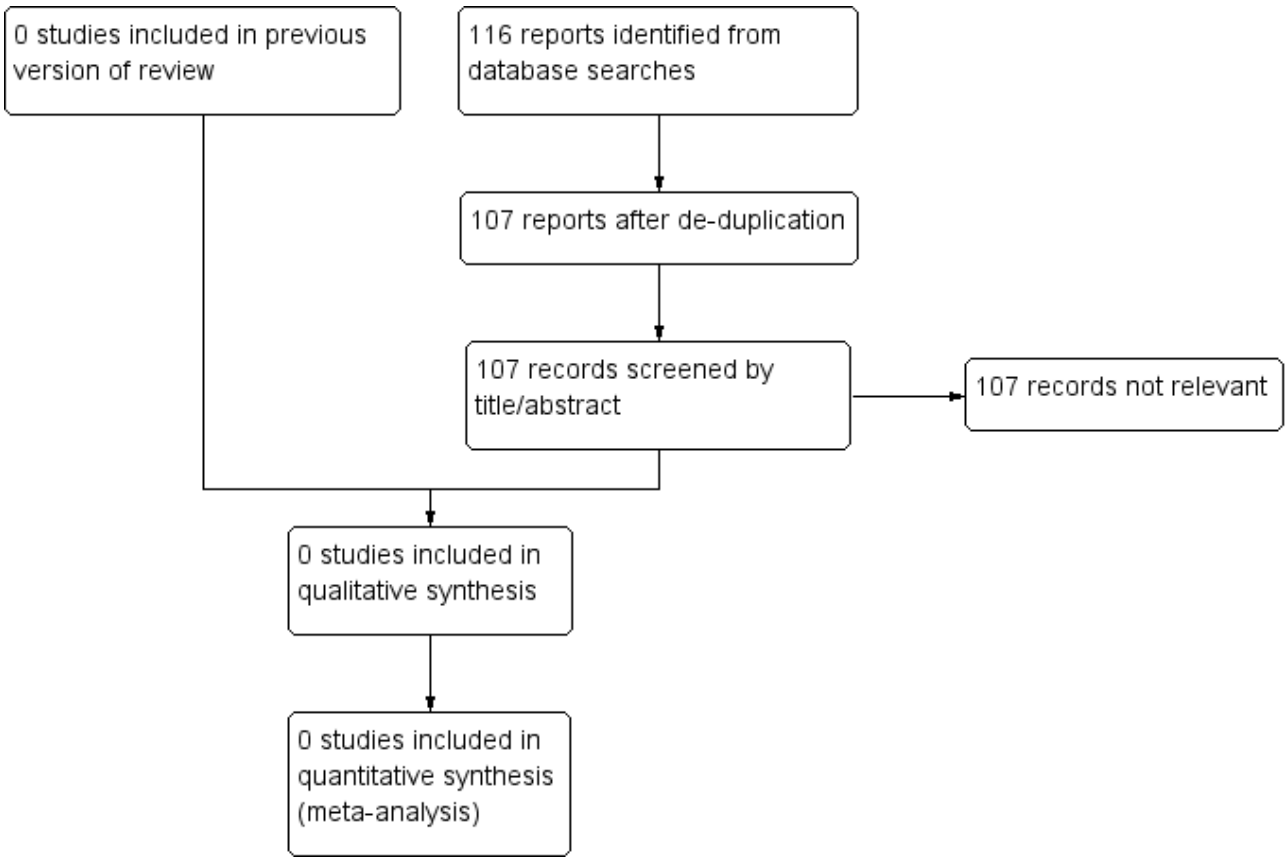
If applicable, RCTs and CCTs were analysed separately to access the efficacy of the effect estimation, calculated with the Mantel-Haenszel test. Where sufficient trials were available we re-analysed the data excluding low quality trials.

RESULTS

Description of studies

See Figure 1.

Figure 1. Study flow diagram.



Results of the search

We did not identify any trials for this, or previous versions of the review, of rutosides versus alternative treatment for the prevention of PTS. Searching identified only one study, an open randomised pilot study of hidrosmina (an alternative venoactive remedy) versus no treatment for prevention of PTS (Monreal 1997).

Included studies

There were no studies identified for inclusion.

Excluded studies

Monreal 1997 was an open, randomised, pilot study to assess the use of hidrosmina (600 mg daily) compared with no treatment for prevention of PTS. One hundred consecutive patients with objectively confirmed DVT were randomly allocated using a randomisation schedule to receive either the intervention (n = 52) or no additional treatment (n = 48), at the point of hospital discharge. There were 49 male and 51 female participants (aged 17 to 76 years). In total, 89 patients had a unilateral lower limb DVT and 11 had bilateral events. Each patient was followed up at 4-month intervals for three years. At each follow-up appointment the participants were questioned regarding PTS symptoms in both the affected and unaffected leg (or both affected limbs for bilateral disease). Clinical examination was undertaken and PTS scored using the Society of Vascular Surgery/International Society for Cardiovascular Surgery scoring system (Iafrati 1994). The funding source was not declared. This study was excluded because hidrosmina is not a rutoside but an alternative venoactive remedy.

Risk of bias in included studies

There were no studies identified for inclusion.

Effects of interventions

There were no studies identified for inclusion.

DISCUSSION

Summary of main results

We did not identify any studies comparing the use of rutosides versus any alternative intervention in the prevention of post-thrombotic syndrome (PTS) therefore there is currently insufficient evidence to determine the effectiveness and safety of rutosides for prevention of PTS in patients with deep vein thrombosis (DVT).

Overall completeness and applicability of evidence

We did not identify any evidence to support or oppose the use of rutosides for the prevention of PTS.

Quality of the evidence

With no identified evidence it is clear that there is a need for high quality studies in this area if the potential for rutosides to be used as a preventative intervention for PTS is to be pursued.

Potential biases in the review process

There are no included or excluded studies, therefore we were unable to assess the potential bias of the review process beyond the stage of trial selection.

We believe that all trials with the potential for inclusion will 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. The search criteria only identified one potentially relevant study, which was ultimately excluded because the treatment was not a rutoside but an alternative venoactive remedy. After reference list scrutiny no additional potentially relevant trials were identified and we remain confident in our study identification process.

Agreements and disagreements with other studies or reviews

It was not possible to assess agreement or disagreement with other studies as no studies on the prevention of PTS using rutosides were identified. Similarly, limited evidence is available regarding the treatment of PTS using rutosides (Morling 2018).

AUTHORS' CONCLUSIONS

Implications for practice

As there were no studies identified in this review there is currently insufficient evidence to determine the effectiveness and safety of rutosides for prevention of PTS in patients with DVT. Some studies suggest that rutosides may provide short-term relief of PTS symptoms (Morling 2018). However, there is nothing published on their use as a preventative therapy for PTS. High quality randomised controlled trials of rutoside versus any alternative intervention are required to build the evidence base in this area. Elastic compression stockings remain the gold standard for the prevention of PTS in proximal DVT (Appelen 2017).

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. Rutosides may be a viable option for PTS prevention, and their use would benefit from a large blinded RCT using an agreed standard definition for PTS (the Villalta Scale) and against the current gold standard intervention (ECS).

ACKNOWLEDGEMENTS

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The review authors would like to thank the Cochrane Vascular editorial base for their assistance.

REFERENCES

References to studies excluded from this review

Monreal 1997 *{published data only}*

Monreal M, Callejas JM, Martorell A, Sahuquillo JC, Contel E. Prevention of post-thrombotic syndrome with hidrosmina: a prospective pilot study. *Phlebology* 1997;**12**(1):21-4.

Additional references

Appelen 2017

Appelen D, van Loo E, Prins MH, Neumann MHAM, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database of Systematic Reviews* 2017, Issue 9. [DOI: 10.1002/14651858.CD004174.pub3]

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *British Medical Journal* 2004;**328**(7454):1490-4.

Bombardelli 1996

Bombardelli E, Morazzoni P, Griffini A. Aesculus hippocastanum L. *Fitoterapia* 1996;**67**(6):483-511.

Cesarone 2005

Cesarone MR, Belcaro G, Pellegrini L, Ledda A, Vinciguerra G, Ricci A, et al. HR, 0-(beta-hydroxyethyl)-rutosides; (Venoruton): rapid relief of signs/symptoms in chronic venous insufficiency and microangiopathy: a prospective, controlled study. *Angiology* 2005;**56**(2):165-72.

Facino 1995

Facino RM, Carini M, Stefani R, Aldini G, Saibene L. Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from Hedera helix, Aesculus hippocastanum, and Ruscus aculeatus: factors contributing to their efficacy in the treatment of venous insufficiency. *Archiv der Pharmazie* 1995;**328**(10):720-4.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 10 October 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guillaume 1994

Guillaume M, Padioleau F. Veinotonic effect, vascular protection, anti-inflammatory and free radical scavenging properties of horse chestnut extract. *Arzneimittelforschung* 1994;**44**(1):25-35.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**:383-94.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Iafrati 1994

Iafrati MD, Welch H, O'Donnell TF, Belkin M, Umphrey S, McLaughlin R. Correlation of venous noninvasive tests with the Society of Vascular Surgery/International Society for Cardiovascular Surgery clinical classification of chronic venous insufficiency. *Journal of Vascular Surgery* 1994;**19**(6):1001-7.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lorenz 1960

Lorenz D, Marek ML. Das therapeutische wirksame Prinzip der Rosskastanie (Aesculus hippocastanum). *Arzneimittelforschung* 1960;**10**:263-72.

Meissner 2002

Meissner MH, Zierler BK, Bergelin RO, Chandler WL, Strandness DE Jr. Coagulation, fibrinolysis, and recanalization after acute deep venous thrombosis. *Journal of Vascular Surgery* 2002;**35**(2):278-85.

Morling 2018

Morling JR, Yeoh SE, Kolbach DN. Rutosides for treatment of post-thrombotic syndrome. *Cochrane Database of Systematic Reviews* 2018, Issue 11. [DOI: 10.1002/14651858.CD005625.pub4]

Moyses 1987

Moyses C, Cederholm-Williams SA, Michel CC. Haemoconcentration and accumulation of white cells in the feet during venous stasis. *International Journal of Microcirculation: Clinical and Experimental* 1987;**5**(4):311-20.

Partsch 1991

Partsch H. Compression therapy of the legs. A review. *Journal of Dermatologic Surgery and Oncology* 1991;**17**(10):799-805.

Pittler 2012

Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD003230.pub4]

Prandoni 1996

Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. *Annals of Internal Medicine* 1996;**125**(1):1-7.

Sarin 1993

Sarin S, Andaz A, Shields DA, Scurr JH, Coleridge Smith PD. Neutrophil activation in venous disease. *Journal of Vascular Surgery* 1993;**17**:444.

Schrader 1995

Schrader E, Schwankl W, Sieder C, Christoffel V. Comparison of the bioavailability of beta-aescin after single oral administration of two different drug formulations containing an extract of horse-chestnut seeds [Vergleichende Untersuchung zur Bioverfügbarkeit von ß-Aescin nach oraler Einmalverabreichung zweier Rosskastaniensamenextrakt enthaltender, galenisch unterschiedlicher Darreichungsformen]. *Pharmazie* 1995;**50**(9):623-7.

Thomas 1988

Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. *British Medical Journal* 1988;**296**(6638):1693-5.

Widmer 1985

Widmer LK, Zemp E, Widmer TM, Schmitt HE, Brandenberg E, Voelin R, et al. Late results in deep vein thrombosis of the lower extremity. *Vasa* 1985;**14**(3):264-8.

REFERENCES TO OTHER PUBLISHED VERSIONS OF THIS REVIEW

Kolbach 2006

Kolbach DN, Prins MH. Rutosides for prevention of post thrombotic syndrome. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: 10.1002/14651858.CD005626]

Morling 2013

Morling JR, Yeoh SE, Kolbach DN. Rutosides for prevention of post-thrombotic syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD005626.pub2]

Morling 2015

Morling JR, Yeoh SE, Kolbach DN. Rutosides for prevention of post-thrombotic syndrome. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD005626.pub3]

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Monreal 1997	This study did not investigate the use of rutosides; it compared the use of hidrosmina (an alternative venoactive remedy) versus no treatment in the prevention of PTS

APPENDICES

Appendix 1. Database search strategies

Source	Search strategy	Hits retrieved
CENTRAL	#1 MESH DESCRIPTOR Postthrombotic Syndrome EXPLODE ALL TREES 74	107
	#2 postthrombotic:TI,AB,KY 121	
	#3 (post near3 thrombot*):TI,AB,KY 191	
	#4 PTS:TI,AB,KY 10620	
	#5 MESH DESCRIPTOR Postphlebitic Syndrome EXPLODE ALL TREES 60	
	#6 postphlebit*:TI,AB,KY 69	
	#7 (post near3 phlebit*):TI,AB,KY 16	
	#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 10835	
	#9 MESH DESCRIPTOR Rutin EXPLODE ALL TREES 170	
	#10 *rutoside*:TI,AB,KY 211	

(Continued)

	#11 *rutin*:TI,AB,KY 1083 #12 *ruton*: 0 #13 Paroven 14 #14 buckwheat 42 #15 bioflav* 70 #16 MESH DESCRIPTOR Quercetin EXPLODE ALL TREES 158 #17 MESH DESCRIPTOR Escin EXPLODE ALL TREES 53 #18 (aesculus* near hippocastan*):TI,AB,KY 12 #19 (escin* or aescin* or essaven*):TI,AB,KY 112 #20 rosskastani*:TI,AB,KY 2 #21 (horse* near (chestnut or chest-nut)):TI,AB,KY 45 #22 venosta*:TI,AB,KY 20 #23 horsechestnut*:TI,AB,KY 4 #24 *ruton*:TI,AB,KY 216 #25 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 1626 #26 #8 AND #25 120 #27 01/01/2015 TO 21/08/2018:CD 465323 #28 #26 AND #27 107	
Clinicaltrials.gov	Postthrombotic Syndrome OR postthrombotic OR Postphlebitic Syndrome OR post thrombotic | Rutin OR Quercetin OR horsechestnut OR horse chestnut OR venosta | Start date on or after 01/01/2015 | Last update posted on or before 08/21/2018	0
ICTRP Search Portal	Postthrombotic Syndrome OR postthrombotic OR Postphlebitic Syndrome OR post thrombotic | Rutin OR Quercetin OR horsechestnut OR horse chestnut OR venosta	0
Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present (2017 AND 2018 ONLY)	1 exp Postthrombotic Syndrome/ 593 2 postthrombotic.ti,ab. 825 3 (post adj3 thrombot*).ti,ab. 1445 4 PTS.ti,ab. 10187 5 exp Postphlebitic Syndrome/ 626 6 postphlebit*.ti,ab. 456 7 (post adj3 phlebit*).ti,ab. 319 8 or/1-7 13005 9 exp RUTIN/ 3194 10 rutoside*.ti,ab. 320	0

(Continued)

	11 rutin*.ti,ab. 5846 12 ruton*.ti,ab. 4 13 Paroven.ti,ab. 20 14 buckwheat.ti,ab. 1175 15 bioflav*.ti,ab. 1094 16 exp QUERCETIN/ 8221 17 quercetin*.ti,ab. 14786 18 exp ESCIN/ 509 19 (aesculus* adj hippocastan*).ti,ab. 200 20 (escin* or aescin* or essaven*).ti,ab. 721 21 rosskastani*.ti,ab. 1 22 (horse* adj chestnut).ti,ab. 326 23 (horse* adj chest-nut).ti,ab. 1 24 venosta*.ti,ab. 135 25 horsechestnut*.ti,ab. 7 26 or/9-25 23915 27 8 and 26 26 28 randomized controlled trial.pt. 467161 29 controlled clinical trial.pt. 92599 30 randomized.ab. 419927 31 placebo.ab. 191212 32 drug therapy.fs. 2041627 33 randomly.ab. 296034 34 trial.ab. 437243 35 groups.ab. 1826471 36 or/28-35 4266660 37 exp animals/ not humans.sh. 4489180 38 36 not 37 3688450 39 27 and 38 18 40 (2017* or 2018*).ed. 1605748 41 39 and 40 0	
Embase 1974 to present (2017 AND 2018 ONLY)	1 exp postthrombosis syndrome/ 2495 2 postthrombotic.ti,ab. 1173 3 (post adj3 thrombot*).ti,ab. 2128	6

(Continued)

4 PTS.ti,ab. 89652

5 exp chronic vein insufficiency/ 3524

6 postphlebit*.ti,ab. 400

7 (post adj3 phlebit*).ti,ab. 285

8 or/1-7 96449

9 exp rutoside/ 8835

10 rutoside*.ti,ab. 396

11 rutin*.ti,ab. 7476

12 ruton*.ti,ab. 8

13 Paroven.ti,ab. 20

14 buckwheat.ti,ab. 1368

15 bioflav*.ti,ab. 1281

16 exp quercetin 3 methyl ether/ or exp quercetin/ or exp quercetin derivative/ 26894

17 quercetin*.ti,ab. 19521

18 escin/ 957

19 (aesculus* adj hippocastan*).ti,ab. 256

20 (escin* or aescin* or essaven*).ti,ab. 913

21 rosskastani*.ti,ab. 3

22 (horse* adj chest-nut).ti,ab. 5

23 (horse* adj chestnut).ti,ab. 335

24 venosta*.ti,ab. 122

25 horsechestnut*.ti,ab. 10

26 or/9-25 40827

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28 randomized controlled trial/ 508322

29 controlled clinical trial/ 457706

30 random$.ti,ab. 1317690

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33 placebo.ti,ab. 273498

34 (compare or compared or comparison).ti. 456092

35 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 1772659

36 (open adj label).ti,ab. 65124

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	37 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 208272 38 double blind procedure/ 151682 39 parallel group$1.ti,ab. 21940 40 (crossover or cross over).ti,ab. 93088 41 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 284855 42 (assigned or allocated).ti,ab. 334811 43 (controlled adj7 (study or design or trial)).ti,ab. 296056 44 (volunteer or volunteers).ti,ab. 224312 45 trial.ti. 248469 46 or/28-45 4041516 47 27 and 46 109 48 (2017* or 2018*).dc. 2797896 49 47 and 48 6 50 from 49 keep 1-6 6	
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16 (escin* or aescin* or essaven*).ti,ab. 13

17 rosskastani*.ti,ab. 6

18 (horse* adj chest-nut).ti,ab. 0

19 (horse* adj chestnut).ti,ab. 10

20 venosta*.ti,ab. 0

21 horsechestnut*.ti,ab. 3

22 or/7-21 552

23 6 and 22 0

WHAT'S NEW

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

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 for inclusion. Review updated to reflect current Cochrane standards. No change to conclusions.
2 September 2015	New search has been performed	New search run. No studies identified for inclusion.
3 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

JM: selected trials, developed data extraction tool, and wrote the review
SEY: wrote the review
DK: selected trials, wrote the protocol, and checked the review

DECLARATIONS OF INTEREST

JM: declared that she is currently receiving a MRC Clinical Scientist Fellowship grant and this does not conflict with this review
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.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The co-primary outcomes defined in the protocol (development of oedema and development of PTS) were amended to a single primary outcome: the development of PTS. This reflects that the development of PTS includes oedema and that to develop oedema without PTS would not fulfil the objective of the review. According to Cochrane guidelines the assessment of the quality of the trials for the updated versions are now described using the Cochrane risk of bias tool (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Aesculus [*chemistry]; Phytotherapy [*methods]; Plant Extracts [*therapeutic use]; Postthrombotic Syndrome [*prevention & control]; Rutin [*therapeutic use]; Venous Thrombosis [complications]

MeSH check words

Humans