Pharmacologic and compression therapies for postthrombotic syndrome: a systematic review of randomized controlled trials

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CRD summary
The authors concluded there was moderate evidence for short-term use of intermittent pneumatic compression devices in treating post-thrombotic syndrome. Evidence for veno-active medication and graduated compression stockings was limited. Given the limitations of the evidence and the discrepancies between authors' conclusions and meta-analysis results, the findings are unlikely to be reliable.

Authors' objectives
To evaluate the efficacy and safety of pharmacologic and compression therapies in the treatment of post-thrombotic syndrome.

Searching
PubMed was searched up to March 2010 for articles published in English or French. Search terms were reported. The references of included studies were handsearched. A review of other known literature was conducted. Further searches were made of reverse citation searches using ISI web of science and SCOPUS databases.

Study selection
Randomised controlled trials (RCTs) that investigated pharmacological or compression therapies in patients with post-thrombotic syndrome were eligible for inclusion. Compression therapies included both intermittent and continuous therapies using stockings or pneumatic devices. The control group was not specified and could include active intervention. Outcomes eligible for inclusion were improvement in symptoms, success or failure of treatment, ulcer healing, changes in ankle or calf circumference, improvement in quality of life and adverse effects of medication. Studies that evaluated only physiological outcomes were excluded.

Included studies of pharmaceutical interventions evaluated rutoside, hidrosmin and defibrotide administered over two to 12 months. Studies of compression therapies evaluated graduated compression stockings worn for at least one year or a Jobst compression pump or a venowave device used for 4-8 weeks. Pharmacotherapy controls included placebo (no treatment), placebo elastic stockings without drugs, stockings and drugs, compression stockings alone and no drugs. All patients had suffered a deep vein thrombosis (DVT), but criteria used to define post-thrombotic syndrome varied between studies. A variety of validated measures were used to assess symptom improvement. The median length of follow-up was one year. Studies were carried out in Spain, Italy, Canada and the Netherlands.

One reviewer selected the included studies for review.

Assessment of study quality
The authors reported on randomisation, allocation concealment, blinding, use of intention-to-treat analyses and loss to follow-up.

The quality of evidence was evaluated using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach. This approach assessed the strength of evidence of an intervention as high, moderate, low or very low based on study design, methodological issues, strength and precision of treatment effect, importance of outcome, risks and burdens of intervention and costs of intervention.

The authors did not state how many reviewers performed the quality of evidence assessment.

Data extraction
For dichotomous outcomes, the number of events in each group was extracted and used to calculate risk ratios (RRs) with 95% confidence intervals (CI). For continuous data, the mean difference between groups was calculated with 95% confidence intervals. The main findings of each study were also presented in tables and text.
One reviewer extracted the data for review.

**Methods of synthesis**
For dichotomous data, pooled risk ratios with 95% confidence intervals were calculated. Pooled standardised mean differences (SMDs) with 95% confidence intervals were calculated for continuous data. Fixed-effects models were used. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ tests. The results of individual studies were also reported in a narrative synthesis. The authors assessed publication bias.

**Results of the review**
Seven studies were included for review (703 participants reported; calculated 723). Five parallel RCTs (647 participants) and three crossover trials (76 participants).

**Effect of pharmaceutical therapies on post-thrombotic syndrome (four studies, 521 participants):**
Pharmaceutical medication did not significantly improve symptoms of post-thrombotic syndrome compared to placebo or graduated compression stockings. There was evidence of significant statistical heterogeneity ($I^2=77\%$). Veno-active medication did not significantly increase the risk of side-effects compared to placebo or compression stockings. There was no evidence of statistical heterogeneity ($I^2=7\%$).

Of the three studies that measured changes in calf and ankle circumference, one reported significant reductions in calf and ankle circumference at eight weeks with rutoside, one reported a significant reduction in ankle but not calf circumference with defibrotide and one reported small improvements in ankle and calf circumference with hidrosmin but not with rutoside. The levels of evidence were low for pharmaceutical therapies and symptoms and moderate for pharmaceutical therapies and side-effects. Effects were not sustained in the study with a six month follow-up.

**Effect of Compression Therapies on post-thrombotic syndrome (four studies, 202 participants):**
Graduated compression stockings, with or without medication, did not significantly improve symptoms compared to medication alone or placebo stockings (two studies). The authors stated that the two intermittent pneumatic compression studies found the devices to have been more effective than placebo devices, but meta-analysis of the two studies indicated no statistically significant difference. There was no evidence of statistical heterogeneity for either of these outcomes ($I^2=0\%$).

One study reported a significant improvement in quality of life at eight weeks with a Venowave device compared to placebo ($p=0.04$). The quality of evidence for graduated compression stockings was low and for intermittent pneumatic compression devices was moderate. Where reported, the incidence of side-effects for compression therapies was low (2.5% and 9%).

The findings of individual studies were also reported in a narrative synthesis.

**Authors’ conclusions**
There was moderate quality evidence that intermittent pneumatic compression devices were effective in relieving symptoms in the short-term in moderate-to-severe post-thrombotic syndrome. There was limited, low quality evidence for the effectiveness of veno-active medication and graduated compression stockings in post-thrombotic syndrome.

**CRD commentary**
The review addressed a clear question, but inclusion criteria for intervention and outcomes were broad. Only one database was searched so relevant data may have been missed. Appropriate steps did not appear to have been taken to minimise the risk of publication or language bias. Publication bias was assessed, but the number of included studies was too small to obtain reliable results. Only one reviewer selected studies for review and extracted the data and it was unclear how many reviewers performed the quality assessment; risk of reviewer error and bias could not be ruled out.

Methodological weaknesses were evident in most studies, which affected the reliability of the results. For example, the absence of a wash-out period in some crossover trials may affect the findings. There was clinical heterogeneity between studies which meant that only a small number of studies could be pooled for each intervention and outcome. For some outcomes there was evidence of significant statistical heterogeneity. There were discrepancies between the findings of
the meta-analysis for intermittent pneumatic compression devices and the authors' conclusions drawn from this meta-analysis. Given the limitations of the evidence and the discrepancies between authors' conclusions and meta-analysis results, the findings are unlikely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that intermittent pneumatic compression devices should be used in patients with moderate-to-severe post-thrombotic syndrome in the short-term. Veno-active medication should be used where patients did not respond to intermittent pneumatic compression devices.

**Research:** The authors stated that further rigorous studies were needed investigating the safety and efficacy of pharmaceutical and compression therapies for post-thrombotic syndrome in the long-term and including quality of life as an outcome measure. The authors stated that standardised outcome definitions were needed in future research.

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