Pentoxifylline for treatment of venous leg ulcers: a systematic review

Andrew Jull, Jill Waters, Bruce Arroll

Summary

Introduction Venous ulcers are usually treated with compression therapy, but, because this treatment may not be effective for some people, adjuvant therapy could be beneficial. We did a systematic review of randomised controlled trials that compared pentoxifylline (with and without compression treatment) with placebo, or other treatments, in patients with venous leg ulcers.

Methods We identified eight trials (547 adults), five of which compared pentoxifylline compression and placebo and compression (n=445), and three of which compared pentoxifylline alone with placebo (102). Our main aim was to determine whether pentoxifylline, with or without compression, was effective in treatment of venous leg ulcers. Analysis was by intention to treat.

Findings Pentoxifylline was more effective than placebo in complete healing or substantial improvement of venous leg ulcers (relative risk 1.15, 95% CI 1.11–2.01). Pentoxifylline with compression was also more effective than placebo and compression in complete healing (1.30, 1.10–1.54). Patients taking pentoxifylline had no more adverse events than those on placebo (1.25, 0.87–1.80). The most frequent adverse event was mild gastrointestinal disturbance (43%).

Interpretation Our results suggest that pentoxifylline gives additional benefit to compression for venous leg ulcers, and is possibly effective for patients not receiving compression.

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Introduction

Most leg ulcers are venous.1 High compression treatment (three-layer or four-layer short-stretch bandaging, or Unna boot) is an effective cure for venous ulcers,2 but despite compression, almost 30% of people remain unhealed after 1 year of treatment.3 Adjuvants to compression treatment could be beneficial. Pentoxifylline, a haemorheological agent, reduces the viscosity of blood by increasing the flexibility of erythrocytes, encouraging migration of white cells, inhibition of aggregation of platelets, and lowering of the viscosity of plasma,4 actions that might correct microcirculatory disorders. Trials5,6 of the clinical effectiveness of pentoxifylline have had conflicting results, and the usefulness of the drug remains unclear.7 We therefore systematically reviewed randomised controlled trials to quantify the effect of pentoxifylline (Trental, Aventis Pharma, Lyon, France) on healing in venous leg ulcers, either as an adjuvant to compression, or compared with placebo.

Methods

We searched the CENTRAL registers of the Cochrane Wounds Group and the Cochrane Peripheral Vascular Diseases Group to September, 2000. We identified no new controlled trials in our search of the Wound Review Group register to April, 2001. The CENTRAL registers differ from the Cochrane Controlled Trials Register in that they contain references that have not been confirmed as controlled trials, or trials that have not yet been forwarded for inclusion in the Cochrane register. The register of the Wounds Group contains citations from searches of 19 electronic databases, hand-searches of conference proceedings and five journals, and contacts with manufacturers. The register of the Peripheral Vascular Diseases Group contains citations from electronic searches of Medline and Embase, hand-searching of conference proceedings and 38 journals, and contacts with manufacturers. We also reviewed the citations of the retrieved studies and review articles obtained from a search of Medline (1966–99) and Embase (1980–99). To identify unpublished or continuing trials, we contacted the Australasian medical director for the manufacturer of the drug (Aventis Pharma, Lyon, France). No language restrictions were placed on the search.

Trial selection and data extraction

We included trials if they had reported an objective outcome measure (percentage change in ulcer area, proportion of ulcers completely healed), or an operationalised measure (substantial improvement). Two reviewers (BA, AJ) independently assessed citations obtained from the search and selected trials for inclusion. We obtained reports of trials that satisfied the inclusion criteria, and those for which there was any doubt about exclusion. We translated only the methods and results.
sections of reports that were not written in English. One reviewer (AJ), who was aware of the authorship and journal the trial was published in, extracted the data using a standard procedure. A second reviewer (JW) independently assessed the data for accuracy. All disagreements were resolved by discussion. We assessed the methodological characteristics of all included trials on variables required by the Cochrane Wounds Group (table 1). In reports in which the study details were unclear, we sought information from the investigators.

Data analysis and statistical methods
We used RevMan (Review Manager) version 4.1 statistical software to calculate relative risks and 95% CIs for every trial. Analysis was done by intention to treat. We used relative risk instead of odds ratios because the event rates were high. Heterogeneity between trials was assessed using relative risk instead of odds ratios because the event rates were high. Heterogeneity was assessed for significant asymmetry using Begg and Mazumdar's rank-correlation test.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

Results
We included eight trials (table 2), two of which were not written in English. In most studies, the primary outcome was either complete healing of the patients' reference ulcer (usually the largest ulcer) or of all ulcers on the reference leg, or data was provided for individual patients, from which we could calculate the number of patients healed. In one trial, data were presented in a life table, from which the number of patients healed was estimated independently by two reviewers. Investigators of two trials reported outcomes by operationally defined ratings such as good (complete healing or substantial reduction in ulcer area) and substantial improvement (60–94% reduction in ulcer area). In one trial, the area of every participant's ulcer was reported at baseline and trial.

### Table 1: Methodological characteristics of included studies

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Inclusion and exclusion criteria</th>
<th>A priori sample size calculation</th>
<th>Method of randomisation</th>
<th>Allocation concealment</th>
<th>Baseline comparability of groups</th>
<th>Masking</th>
<th>Intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colgan and colleagues</td>
<td>Exclusion only</td>
<td>Not stated</td>
<td>Not stated</td>
<td>B</td>
<td>Not stated</td>
<td>Double</td>
<td>No</td>
</tr>
<tr>
<td>Colgan and colleagues</td>
<td>Inclusion only</td>
<td>Not stated</td>
<td>Block, sealed envelope*</td>
<td>A</td>
<td>Yes</td>
<td>Double</td>
<td></td>
</tr>
<tr>
<td>Dale and colleagues</td>
<td>Yes</td>
<td>Yes</td>
<td>Sealed envelope A</td>
<td>Yes</td>
<td>Double</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falanga and colleagues</td>
<td>Yes</td>
<td>Yes</td>
<td>Pharmacy*</td>
<td>A</td>
<td>Yes</td>
<td>Double</td>
<td></td>
</tr>
<tr>
<td>Schiampur and Eberhardt</td>
<td>Exclusion only</td>
<td>Not stated</td>
<td>Central list*</td>
<td>B</td>
<td>Favoured control</td>
<td>Single</td>
<td></td>
</tr>
<tr>
<td>Weitgasser</td>
<td>Inclusion only</td>
<td>Not stated</td>
<td>Not stated</td>
<td>B</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Information obtained from investigators directly. 
**Includes participants excluded from analysis after randomisation. We added these participants to the denominator in the treatment groups as treatment failures.

### Table 2: Summary of trials that met inclusion criteria

<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Diagnostic Method</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
<th>Length of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arenas and Attocce</td>
<td>ABI&gt;0</td>
<td>Pentoxifylline 1200 mg daily</td>
<td>Placebo</td>
<td>Healing and substantial improvement</td>
<td>6 months</td>
</tr>
<tr>
<td>Barbannino</td>
<td>Clinical signs</td>
<td>Pentoxifylline 1200 mg daily plus 2-layer compression bandaging</td>
<td>Placebo plus 2-layer compression bandaging</td>
<td>Complete healing</td>
<td>67 days</td>
</tr>
<tr>
<td>Colgan and colleagues</td>
<td>ABI&gt;0</td>
<td>Pentoxifylline 1200 mg daily plus 2-layer compression bandaging</td>
<td>Placebo plus 2-layer compression bandaging</td>
<td>Complete healing</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Dale and colleagues</td>
<td>Clinical signs</td>
<td>Pentoxifylline 1200 mg daily plus either elastic single layer or 4-layer compression bandaging (evenly balanced)</td>
<td>Placebo plus either elastic single layer or 4-layer compression bandaging (evenly balanced)</td>
<td>Complete healing</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Falanga and colleagues</td>
<td>ABI&gt;0</td>
<td>Either pentoxifylline 1200 mg or 2400 mg daily plus compression by Unna boot and elastic bandage</td>
<td>Placebo plus compression by Unna boot and elastic bandage</td>
<td>Complete healing</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Herdy and colleagues</td>
<td>Clinical signs</td>
<td>Pentoxifylline 1200 mg daily</td>
<td>Placebo</td>
<td>Individual data</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Schiampur and Eberhardt</td>
<td>Clinical signs*</td>
<td>Pentoxifylline 1200 mg daily plus short-stretch compression bandages*</td>
<td>Placebo plus short-stretch compression bandages</td>
<td>Individual data</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Weitgasser</td>
<td>Not reported</td>
<td>Pentoxifylline 1200 mg daily</td>
<td>Placebo</td>
<td>Complete healing or substantial reduction in ulcer area</td>
<td>8 weeks</td>
</tr>
</tbody>
</table>

*ABI=ankle brachial index. +Data obtained from investigators directly.

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pentoxifylline on its own was compared with placebo. The relative risk of healing or substantial improvement for all studies combined was 1.49 (95% CI 1.11–2.01). This result was robust to inclusion only of trials that used that used only complete healing as an outcome. Heterogeneity between the groups of trials was significant (p=0.06). In six of eight trials, the number of adverse events did not differ between patients in the treatment group and those on placebo (relative risk 1.25, 95% CI 0.87–1.80). Exclusion of the 2400-mg group in the trial by Falanga and colleagues had little effect on the risk of adverse events. In the studies in which adverse events were reported, the most frequent were minor gastrointestinal disturbances (loss of appetite, heartburn, nausea, vomiting, diarrhoea). Other adverse events included headache, sleep disturbance, hot flushes, itching, and hypotension. Of the reported withdrawals, only 25% were for adverse events.

Four of eight trials lasted for 8–12 weeks, and four lasted for 24 weeks. In the 108 participants of trials that lasted for less than 12 weeks (short duration), relative risk of healing or substantial improvement with pentoxifylline versus placebo was 2.30 (95% CI 1.30–4.10). However, the combination was sensitive to exclusion of Weitgasser’s findings, which shared healing or substantial improvement as a single outcome. In the 441 participants in trials lasting 12 weeks or longer, relative risk of healing or substantial improvement was 1.30 (1.10–1.54). This risk was not sensitive to exclusion of Arenas and Atoche, who reported healing or substantial improvement as a single outcome.

The heterogeneity recorded when all studies were combined was probably caused by differences in treatment between subgroups. One subgroup (five trials, n=441), which compared pentoxifylline with placebo with compression as standard therapy, all reported the outcome of complete healing, or this outcome could be determined from individual patient data. In a fixed-effect model, patients in the treatment groups of these trials combined were 30% more likely to heal than those on placebo (figure 1). Heterogeneity was not significant (figure 1). This result was robust to sensitivity analysis with the random-effects model, masking, dose, route of drug administration, and study setting. The results did not change by much when the two trials with unclear allocation concealment were excluded (relative risk 1.30, 95% CI 1.09–1.54).

A second subgroup (three trials, n=102) compared pentoxifylline with placebo without compression bandaging as standard treatment. In this subgroup, patients in the treatment groups were almost 2.5 times more likely to heal completely than those in the placebo group (figure 2). Heterogeneity was not significant in this subgroup (figure 2). However, Weitgasser judged substantial improvement as “considerable reduction” in ulcer sizes, without reporting a numerical criterion. The summary result was sensitive to exclusion of this trial (relative risk 1.49, 95% CI 0.50–4.42). We created a funnel plot with all trials apart from that which had zero events in both groups. The adjusted rank-correlation test suggests that the funnel plot is symmetrical (Spearman’s ρ=0.214, p=0.64). Similarly the funnel plots of trials comparing compression and pentoxifylline to compression and placebo were not significantly asymmetrical (Spearman’s ρ=0.300, p=0.62).

Discussion

Our results showed that pentoxifylline improves healing rates compared with placebo. Pentoxifylline was effective for treatment of leg ulcers, but the evidence for pentoxifylline on its own is not as strong as that for this drug as an adjuvant to compression treatment. The finding is stronger in trials that lasted longer than 12 weeks, although this result could be because the longer trials were of better quality than the shorter trials. Although which microcirculatory events link venous hypertension with ulceration is not clear, one explanation...
could be that white cells aggregate and release proteolytic enzymes that damage tissue.\textsuperscript{18} Pentoxifylline, which has an inhibitory effect on expression of cellular adhesion molecules,\textsuperscript{18} could interfere in these processes. However, the inhibitory effect has not been investigated in venous ulceration. The inhibitory effect could be a consequence of the immunosuppressive activity of pentoxifylline on tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)).\textsuperscript{16} Expression of cellular adhesion molecules by endothelial cells is upregulated in early venous disease, remains upregulated as the disease progresses, and is accompanied by increased extravasation of leucocytes.\textsuperscript{17} Expression of these molecules is regulated by proinflammatory mediators such as TNF-\(\alpha\).\textsuperscript{18} Pentoxifylline might also interfere with the production and action of oxygen metabolites.\textsuperscript{19,20} Although these are physiological studies, a double-blind randomised controlled trial comparing two scavengers of free radicals—allopurinol or dimethyl sulphoxide—with placebo (with compression as a standard treatment) suggested that free radicals derived from oxygen are implicated in the mechanism of ulceration, and that management of these free radicals significantly increases healing of venous ulcers at 12 weeks.\textsuperscript{21}

In our study, heterogeneity could have arisen from differences in study populations, design, and treatment; the diagnostic criteria for inclusion of participants ranged from extensive non-invasive testing to simple clinical examination. The small number of studies meant that the effect of the different methods could not be explored. Venous disease accounts for about 70\% of all ulcers.\textsuperscript{1} Only one participant in the five trials was reported as being misdiagnosed, with a pemphigoid.\textsuperscript{19} If more ulcers had been misdiagnosed, they would probably have been arterial ulcers, this being the next most common cause after venous disease. Pentoxifylline has been used in treatment of claudication, although its efficacy has not been broadly established.\textsuperscript{22} Thus, pentoxifylline might have an effect on arterial ulcer healing. However, in the studies in which compression was used, no participants were reported as withdrawing for ischaemia related to compression, a complication that is associated with undiagnosed arterial insufficiency.\textsuperscript{23} For this reason, we were satisfied that the participants in the included studies had venous ulcers.

Differences in study design can contribute to heterogeneity, and inclusion of controlled trials that used poor or unclear methods of allocation concealment can overestimate treatment effects by 30–41\%.\textsuperscript{24} The trials describing adequate allocation concealment were all in the compression subgroup. Exclusion of trials with unclear concealment did not affect the results by much. The trials in the pentoxifylline-only subgroup all had unclear allocation concealment, and in one,\textsuperscript{19} investigators used a subjective outcome assessment. In that study, double-blinding was used, making systematic bias unlikely. Little investigation has been done into patients who cannot tolerate compression bandaging, and a large well-designed trial investigating the effect of pentoxifylline on ulcer healing in this group is needed.

The strong association between pentoxifylline and healing in two of the trials\textsuperscript{15,17} in which compression and pentoxifylline were compared with compression and placebo could have been because the ulcers of selected patients were unusually slow to heal. In one trial,\textsuperscript{1} patients had to come back bandaging for at least 2 months with no signs of healing, and compression before the trial was not standardised and varied between centres (personal communication, MP Colgan). In the second trial,\textsuperscript{1} patients must have had a leg ulcer for 2 years before trial entry, but previous treatment was not specified, and attempts to contact the investigator have been unsuccessful. In two other trials,\textsuperscript{6,10} participants might also have received compression for at least 2 months before trial entry. Thus, we could not conclude whether Colgan and colleagues\textsuperscript{5} or Barbarino\textsuperscript{9} did select patients from a slow-to-heal population, or whether they merely selected from populations with longstanding poorly treated ulceration. Patients who receive adequate compression, but are slow to heal are also an under-investigated group, and would benefit from a large well designed trial investigating the effect of pentoxifylline on ulcer healing.

The symmetrical funnel plot suggests that publication bias in this review is unlikely. This bias, however, cannot be ruled out on the basis of the shape of the funnel plots alone. The small number of studies assessed suggests that our results should be interpreted with caution.\textsuperscript{25}

The differences between the trials raise the issue of how generalisable the study results are to clinical practice. The methods by which venous disease was diagnosed varied, indicating the absence of a widely available diagnostic test and an internationally accepted definition of venous ulceration. Furthermore, different systems of compression were used between and within trials. In the factorial trial,\textsuperscript{4} two different systems of compression were evenly balanced between the two groups. In the remaining trials, various systems were used (Unna boot, short-stretch, two-layer, and four-layer elastic bandages). However, such variation is similar to that in clinical practice, with compression systems adjusted to patients’ needs and preferences. A systematic review of compression for venous ulceration reported no clear differences in the effectiveness of the different types of high-compression systems.\textsuperscript{3} The direction of effect in four of the five compression trials favoured compression, suggesting that the effect was independent of the type of compression, and therefore might be broadly generalisable. Furthermore, the variation in bandaging systems used probably leads to underestimation rather than overestimation of the treatment effect, and variation in diagnostic criteria will lead to an overestimation of effect only if patients who are misdiagnosed are more likely to benefit from the treatment than those diagnosed correctly. As we have discussed, we do not believe that many patients were misdiagnosed.

Response in time-to-healing could have been associated with the dose of pentoxifylline used. Falanga and colleagues\textsuperscript{19} showed that, although proportions of healed patients were similar with a 1200-mg and 2400-mg daily dose, median time-to-healing favoured the higher dose (71 days vs 83 days). The number of adverse events was also higher in the 2400-mg group. Investigators of one study\textsuperscript{6} have suggested that adjuvant pentoxifylline is more cost effective than compression alone ($US2190 vs $US2570); however, the full details of this study have not been published, and we could not assess how this conclusion was reached. Recommendation of pentoxifylline for every patient does not therefore seem appropriate. Prediction rules\textsuperscript{17} might serve to screen for patients whose ulcers will probably remain unhealed after 24 weeks of compression treatment. In modelling and validation data sets, ulcers that were bigger than 5 cm\(^2\) and those that had persisted for longer than 6 months were highly predictive of failure to heal. Such patients might benefit from a trial of pentoxifylline, as might those unable to tolerate compression treatment.
Contributors
All authors contributed to the writing of the report. B Arroll and A Jull selected the trials for inclusion in the systematic review. A Jull extracted data from the reports. J Waters checked the extracted data for accuracy.

Conflict of interest statement
None declared.

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References