Review: pentoxifylline with standard compression treatment improves healing of venous leg ulcers


QUESTION: Is pentoxifylline, with or without compression treatment, effective for treating venous leg ulcers?

Data sources
Published and unpublished studies in any language were identified by searching the Cochrane Wounds Group (which includes studies identified from Medline, CINAHL, and EMBASE/Excerpta Medica, and from hand searches of wound care journals and conference proceedings) and the Peripheral Vascular Disease Group trials registers (last searched May 2001); reviewing bibliographies of relevant publications; and contacting the drug manufacturer (Hoechst).

Study selection
Studies were selected if they were randomised trials comparing pentoxifylline with placebo or other treatment (with or without compression treatment) in patients with venous leg ulcers, and used an objective outcome measure of leg ulcer healing.

Data extraction
Data were extracted on study design, intervention, patients, and outcomes. Individual study quality was assessed on the basis of clarity of inclusion/exclusion criteria, randomisation method, allocation concealment, a priori sample size calculation, baseline comparability of groups, blinding, objective and clinically meaningful outcome measures, intention to treat analysis, and reporting of withdrawals. Main outcome was ulcer healing.

Main results
9 trials (n=572, mean age range 46–71 y) met the selection criteria. All trials used oral pentoxifylline (1200 mg/d in 3 doses [8 trials] or 2400 mg/d in 5 doses [1 trial]); 1 trial added intravenous pentoxifylline, 400 mg/day in 2 doses. Pentoxifylline increased rates of ulcer healing or significant improvement more than placebo overall, and increased rates of complete healing in patients who received standard compression treatment (table); no differences in adverse effects (primarily gastrointestinal disturbances) were found (8 trials, 17% v 13%). Pentoxifylline was also more effective than placebo in patients who did not receive standard compression treatment (table). However, the quality of trials included in this analysis was poor, and the summary result became non-significant when 1 trial with a poorly operationalised outcome was excluded. One small trial (n=23) found no difference between pentoxifylline and defibrotide for proportion of ulcers healed at 3 months in patients who received standard compression treatment (92% v 82%, p=0.48)*.

Conclusions
Pentoxifylline with standard compression treatment improves healing of venous leg ulcers. It may also be effective in the absence of compression treatment.

COMMENTARY
The review by Jull et al on the effectiveness of pentoxifylline for leg ulcers is important because leg ulcers are a common, costly, recurring condition, and compression treatment is the only intervention supported by good evidence.1 Unfortunately, compression does not work for every patient, and some cannot or will not tolerate it.

The review is of high quality. Its methodological strengths include a subgroup analysis to test whether pentoxifylline makes a difference in patients who do not wear compression (it appears that it does) and use of a funnel plot to test for the possibility of publication bias (this seems unlikely). Sensitivity analyses were done to test various assumptions. For example, when trials that did not report the outcome of complete ulcer healing were excluded, the result was still significant. All of these methodological approaches increase our confidence in the conclusions of the study. As discussed by Jull et al, the vagueness of the diagnostic criteria used by individual trialists made it difficult to ascertain whether patients with peripheral vascular disease were excluded from a study. Because pentoxifylline is an effective vasodilator in peripheral vascular disease, its effect may be partly a result of this property. Many of the participants in the studies reviewed had ulcers of long duration and/or were unresponsive to local treatments. The improved healing rates in these patients is heartening.

Nurses often manage the care of leg ulcers and, as such, they have a responsibility to consider adjunctive and alternative treatments such as pentoxifylline when compression does not achieve healing. Nurses are well placed to suggest a course of pentoxifylline to the prescribing physician and to monitor its effects.

Liz Scanlon, RGN, RM, MSc Nurse Consultant – Tissue Viability Leeds North West Primary Care Trust Leeds, UK


*Calculated from data in article

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Adjunctive compression treatment</th>
<th>Number of studies (n)</th>
<th>Pent</th>
<th>Placebo</th>
<th>RBI (85% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing or significant improvement†</td>
<td>With or without compression</td>
<td>8 (549)</td>
<td>60%</td>
<td>42%</td>
<td>49% (11 to 101)</td>
<td>6 (4 to 19)</td>
</tr>
<tr>
<td>Complete healing</td>
<td>With compression</td>
<td>5 (447)</td>
<td>62%</td>
<td>47%</td>
<td>30% (10 to 54)</td>
<td>7 (5 to 18)</td>
</tr>
<tr>
<td>Complete healing or significant improvement</td>
<td>Without compression</td>
<td>3 (102)</td>
<td>51%</td>
<td>21%</td>
<td>142% (34 to 335)</td>
<td>4 (3 to 8)</td>
</tr>
</tbody>
</table>

†Abbreviations defined in glossary; RBI, NNT, and CI calculated from data in article using a fixed effects model except †, which was based on a random effects model. Follow up times of individual studies ranged from 2–6 months.
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