Dalteparin improved chronic foot ulcers and reduced the number of amputations in diabetic peripheral arterial occlusive disease


Clinical impact ratings Endocrine

**Q** In diabetic patients with peripheral arterial occlusive disease (PAOD), is dalteparin more effective than placebo for improving chronic foot ulcers?

**METHODS**

- **Design:** randomised placebo controlled trial.
- **Allocation:** concealed.*
- **Blinding:** blinded [patients and healthcare providers].
- **Follow up period:** 6 months.
- **Setting:** 4 hospitals in Sweden.

**Patients:** 87 diabetic patients (mean age 72.5 y, 71% men) with PAOD, chronic foot ulcers (Wagner classification ulcer stage I and II) with duration >2 months; toe blood pressure (TBP) to arm blood pressure index <0.6; and a daily dose of aspirin, 75 mg, for ≥4 weeks. Exclusion criteria included vascular reconstruction or angioplasty in previous 3 months, renal insufficiency (serum creatinine ≥200 μmol/l), and anticoagulants. All patients continued to receive aspirin.

**Intervention** patients were stratified by systolic TBP and ulcer characteristics and allocated to once daily subcutaneous injection of dalteparin, 3000 units (n=44) or placebo (n=43).

**Outcomes** ulcer outcome (healed with intact skin; improved [reduction of ulcer area ≥50%], unchanged, or impaired [increase of ulcer area >50%]; and amputation above or below the ankle level).

**Patient follow up** 98%.

*See glossary.

**MAIN RESULTS**

Analysis was by intention to treat. Patients who received dalteparin had greater improvement in ulcer outcome (p = 0.042) and fewer amputations than those who received placebo (table).

**CONCLUSION**

In diabetic patients with peripheral arterial occlusive disease, dalteparin improved chronic foot ulcers and reduced the number of amputations.

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Dalteparin v placebo for chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease at 6 months*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dalteparin</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>5%</td>
<td>19%</td>
<td>76% (6 to 94)</td>
<td>7 (4 to 142)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.

**Commentary**

The data in the study by Kalani et al show a trend toward increased healing, decreased ulcer size, and decreased amputation rate in the dalteparin group. Unfortunately, it is not known if patients underwent testing to exclude osteomyelitis prior to randomisation. In patients with diabetes, osteomyelitis is not a medically treatable condition (surgical debridement of all infected bone is essential), and wounds with osteomyelitis are unlikely to heal regardless of whether dalteparin is used. Therefore, the random inclusion of a few patients with occult osteomyelitis in the placebo group could skew the data and change the conclusions.

Clearly, it is bad to be a diabetic patient with a foot ulcer. Among patients in the placebo group, only 21% healed, 19% underwent amputation, and 59% still had an ulcer at final follow up. After the addition of dalteparin, the picture is still not pretty: only 33% of patients healed, 5% had an amputation; and a whopping 63% continued to have persistent ulceration.

Before dalteparin can be construed as producing a “benefit,” we need to consider 2 questions: (1) does the presence of a small foot ulcer improve the quality of life relative to a bigger ulcer? and (2) how often is a patient better off with an amputation and a good prosthesis compared with a persistent (or even healed) ulcer on an ischaemic, poorly functioning marginal limb?

If these data are correct, treating 100 patients with diabetic foot ulcer with dalteparin will heal roughly 12 additional patients and prevent 14 amputations. At our institution, the lowest bulk purchase price for 5000 units of Fragmin is US $33 per syringe. If the average patient requires 6 months of treatment, the cost of therapy would be approximately US $6000 per patient, or $25 000 per ulcer healed or amputation avoided. Is it worth it? I don’t know. This may be a social rather than a medical decision, but I agree with the authors’ assessment that these data justify a larger, more definitive study.

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