Venous ulcer review

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Clinical question: What is the best treatment for venous ulcers?

Results: Compression aids ulcer healing. Pentoxifylline can aid ulcer healing. Artificial skin grafts are more effective than other skin grafts in helping ulcer healing. Correction of underlying venous incompetence reduces ulcer recurrence.

Implementation: Potential pitfalls to avoid are:

• Failure to exclude underlying arterial disease before application of compression.
• Unusual-looking ulcers or those slow to heal should be biopsied to exclude malignant transformation.

Keywords: venous ulceration, ulcer healing

Venous ulceration

Definition: A skin defect in a limb with a venous abnormality.

Incidence: A 0.15% point prevalence with women outnumbering men 2.8:1.

Economics: An unhealed leg ulcer costs approximately £1300 per year to treat.

Levels of evidence used in this summary: Systematic reviews, meta-analyses, and randomized controlled trials.


Outcomes: Ulcer healing, time to ulcer healing, pain relief during treatment, and prevention of ulcer recurrence.

Consumer summary: A venous ulcer is a complication of varicose veins. Venous ulcers can be slow to heal and impact on patients’ quality of life. There is good evidence that compression helps heal ulcers. In patients who do not tolerate continuous compression, intermittent compression may help healing. In slow-healing ulcers, the use of pentoxifylline and bilayer artificial skin in conjunction with compression may aid healing. Surgery to incompetent veins reduces the risk of recurrence and endovenous surgery can speed ulcer healing.

The evidence

Does compression aid ulcer healing?
The following were analyzed:

Systematic reviews: 2
Meta-analysis: 0
Randomized controlled trials: 26
One systematic review concluded that ‘compression increases ulcer healing rates compared with no compression. Multicomponent systems are more effective than single component systems. Multicomponent systems containing an elastic bandage appear more effective than those composed mainly of inelastic constituents’.

The second systematic review concluded that ‘… patients with venous leg ulcers treated with four-layer bandages experience faster healing than those treated with short-stretch bandages’.

The randomized trials show a benefit of compression over no compression. They also tend to favor multilayer, long-stretch compression over short-stretch compression (Table 1).

Conclusions
Compression aids ulcer healing.

Does intermittent pneumatic compression aid ulcer healing?
The following were analyzed:
Systematic reviews: 1
Meta-analysis: 0
Randomized controlled trials: 5

The systematic review concluded that ‘IPC may increase healing compared to no compression, but it is not clear whether it increases healing when added to treatment with bandages or if it can be used instead of compression bandages’.

Randomized trials
Two trials have shown a benefit for intermittent pneumatic compression (IPC) with a benefit for fast IPC over slow IPC in one trial. The other two trials didn’t show a benefit for IPC (Table 2).

Conclusions
IPC may help healing when continuous compression cannot be tolerated.

Does pentoxifylline aid the healing of venous ulcers?
The following were analyzed:
Systematic reviews: 1
Meta-analysis: 0
Randomized controlled trials: 6

The systematic review concluded that ‘pentoxifylline is an effective adjunct to compression bandaging for treating venous ulcers and may be effective in the absence of compression’.

Randomized trials
All trials showed increased healing in the pentoxifylline group with no benefit shown for higher doses (Table 3).

Conclusions
Pentoxifylline 400 mg tds has a role in aiding the healing of venous ulcers.

Does skin grafting aid ulcer healing?
The following were analyzed:
Systematic reviews: 1
Meta-analysis: 0
Randomized controlled trials: 11

The systematic review concluded that ‘bilayer artificial skin, used in conjunction with compression bandaging, increases venous ulcer healing compared with a simple dressing plus compression. Further research is needed to assess whether other forms of skin grafts increase ulcer healing’.

Randomized trials
Increased healing was seen compared to no grafting with the greatest difference seen with artificial skin grafts (Table 4).

Conclusions
Artificial skin helps a greater proportion of ulcers heal than other skin grafts.

Does surgery or endovenous therapy aid ulcer healing and prevent recurrence?
The following were analyzed:
Systematic review: 1
Meta-analysis: 0
Randomized controlled trials: 5

The systematic review concluded that ‘… superficial venous surgery is associated with similar rates of ulcer healing to compression alone, but with less recurrence’.

Randomized trials
Only endovenous surgery seems to aid ulcer healing, but all forms of surgery reduce ulcer recurrence (Table 5).

Conclusions
Correction of venous incompetence is important to reduce the incidence of ulcer recurrence after healing.
Table 1 Randomized controlled trials showing the effect of compression on ulcer healing

<table>
<thead>
<tr>
<th>Author</th>
<th>Number randomized</th>
<th>Interventions</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Hendricks and Swallow   | 21                | Gp1: Unna’s boot
Gp2: below-knee elastic compression stocking | Healing at 78 weeks | Gp1: 70% healed
Gp2: 71% healed |
| Eriksson                | 34                | Gp1: inner stocking plus outer elastic bandage
Gp2: hydrocolloid dressing plus elastic bandage | Healing at 12 weeks | Gp1: 41% healed
Gp2: 53% healed |
| Kikta et al             | 87                | Gp1: Unna’s boot
Gp2: no compression | Healing at 6 months | Gp1: 70% healed
Gp2: 38% healed |
| Rubin et al             | 36                | Gp1: Unna’s boot
Gp2: polyurethane foam dressing | Healing at 12 months | Gp1: 95% healed
Gp2: 41% healed |
| Charles                 | 53                | Gp1: short-stretch compression
Gp2: usual care (no compression) | Healing at 3 months | Gp1: 71% healed
Gp2: 25% healed |
| Cordts et al            | 43                | Gp1: hydrocolloid dressing plus cohesive elastic bandage
Gp2: Unna’s boot | Healing at 12 weeks | Gp1: 50% healed
Gp2: 43% healed |
| Travers et al           | 27                | Gp1: single-layer elastic cohesive bandage
Gp2: 3-layer compression | Mean percentage change at 7 weeks | Gp1: −90% Gp2: −83% |
| Danielsen et al         | 43                | Gp1: long-stretch, nonadhesive compression bandage
Gp2: short-stretch, nonadhesive compression bandage | Healing at 6 and 12 months | Gp1: 39% healed at 6 months and 52% at 12 months
Gp2: 25% healed at 6 months and 15% at 12 months |
| Gould et al             | 46                | Gp1: 3-component, long-stretch compression
Gp2: 3-component, short-stretch compression | Healing at 15 weeks | Gp1: 58% healed
Gp2: 35% healed |
| Morrell et al           | 233               | Gp1: 4-layer compression
Gp2: standard community care | Healing at 12 months | Gp1: 65% healed
Gp2: 55% healed |
| Scriven et al           | 64                | Gp1: 4-layer compression
Gp2: short-stretch compression | Healing at 12 months | Gp1: 55% healed
Gp2: 57% healed |
| Taylor et al            | 36                | Gp1: 4-layer compression
Gp2: standard community care | Healing at 12 weeks | Gp1: 67% healed
Gp2: 17% healed |
| Moody                  | 52                | Gp1: short-stretch compression
Gp2: long-stretch compression | Healing at 12 weeks | Gp1: 31% healed
Gp2: 31% healed |
| Vowden et al            | 149               | Gp1: Charing Cross 4-layer compression
Gp2: modified 4-layer compression
Gp3: 4-layer compression bandage kit | Healing at 12 weeks | Gp1: 60% healed
Gp2: 76% healed
Gp3: 60% healed |
| Partsch et al           | 112               | Gp1: 4-layer compression
Gp2: short-stretch compression | Healing at 16 weeks | Gp1: 62% healed
Gp2: 73% healed |
| Moffatt et al           | 112               | Gp1: 4-layer compression
Gp2: 2-layer compression | Healing at 12 weeks | Gp1: 70% healed
Gp2: 58% healed |
| O’Brien et al           | 200               | Gp1: 4-layer compression
Gp2: standard community care | Healing at 12 weeks | Gp1: 54% healed
Gp2: 34% healed |
| Ukat et al             | 89                | Gp1: 4-layer compression
Gp2: short-stretch compression | Healing at 12 weeks | Gp1: 30% healed
Gp2: 22% healed |
| Franks et al           | 159               | Gp1: 4-layer compression
Gp2: short-stretch compression | Healing at 24 weeks | Gp1: 69% healed
Gp2: 73% healed |
| Nelson et al           | 387               | Gp1: 4-layer compression
Gp2: short-stretch bandage | Healing at 4 and 12 months | Gp1: 55% healed at 4 months and 78% healed at 12 months
Gp2: 45% healed at 4 months and 72% at 12 months |
| Jünger et al           | 134               | Gp1: U-stocking consisting of two stockings
Gp2: short-stretch bandages | Healing at 12 weeks | Gp1: 48% healed
Gp2: 32% healed |

(Continued)
The practice

Potential pitfalls

There is a small rate of malignant transformation in ulcers (4.4%), 75% basal cell carcinoma, and 25% squamous cell carcinoma.64 Ulcers in unusual locations, with irregular edges, those with islands of epithelium that do not persist, or those slow to heal should be biopsied.64

Management

Venous leg ulceration can often be managed in the community or in nurse-led venous ulcer clinics. Indications for specialist referral are detailed below.

Table 2 Randomized controlled trials showing the effects of intermittent pneumatic compression on ulcer healing

<table>
<thead>
<tr>
<th>Author</th>
<th>Number randomized</th>
<th>Interventions</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al33</td>
<td>45</td>
<td>Both groups had same dressings and stockings. Sequential IPC for up to 4 h in one group</td>
<td>Healing</td>
<td>48% healed in IPC group and 4% in control group</td>
</tr>
<tr>
<td>McCulloch et al34</td>
<td>22</td>
<td>Both groups had the same dressings and Unna's boots. IPC for 60 min twice weekly in one group</td>
<td>Healing</td>
<td>100% healed in IPC group and 80% in control group</td>
</tr>
<tr>
<td>Schuler et al35</td>
<td>53</td>
<td>Unna’s boots versus elasticated stockings plus IPC for 60 min in the morning and 120 min in the evening</td>
<td>Healing</td>
<td>71% healed in IPC group and 75% in Unna’s boot group</td>
</tr>
<tr>
<td>Rowland36</td>
<td>16</td>
<td>Crossover trial of dressing alone with dressing and IPC for 60 min twice daily for 2–3 months</td>
<td>Healing</td>
<td>No ulcers healed in either arm before crossover</td>
</tr>
<tr>
<td>Kumar et al37</td>
<td>47</td>
<td>Both groups had 4-layer bandaging IPC for 60 min twice daily for 4 months in one group</td>
<td>Healing</td>
<td>87% healed in IPC group and 92% in control group</td>
</tr>
<tr>
<td>Nikolovska et al38</td>
<td>104</td>
<td>Both groups had same dressings and stockings. Sequential IPC for up to 4 h in one group</td>
<td>Healing</td>
<td>86% healed with fast IPC and 61% with slow IPC</td>
</tr>
</tbody>
</table>

Abbreviation: IPC, intermittent pneumatic compression.
Table 3 Randomized controlled trials showing the effect of pentoxifylline on ulcer healing

<table>
<thead>
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</tr>
</thead>
</table>
| Colgan et al40  | 80                | All had 2-layer compression  
Gp1: 400 mg tds pentoxifylline  
Gp2: placebo  
Gp3: dressing   | Healing at 24 weeks | Gp1: 60% healed  
Gp2: 29% healed   |
| Barbarino41     | 12                | All had 2-layer compression  
Gp1: 400 mg tds pentoxifylline  
Gp2: placebo  
Gp3: dressing   | Healing           | Gp1: 66% healed  
Gp2: 17% healed   |
| Dale et al42    | 200               | All had compression  
Gp1: 400 mg tds pentoxifylline  
Gp2: placebo  
Gp3: dressing   | Healing at 24 weeks | Gp1: 64% healed  
Gp2: 52% healed   |
| Falanga et al43 | 129               | All had compression  
Gp1: 800 mg tds pentoxifylline  
Gp2: 400 mg tds pentoxifylline  
Gp3: placebo  
Gp4: dressing   | Healing at 24 weeks | Gp1: 73% healed  
Gp2: 75% healed  
Gp3: 63% healed   |
| Belcaro et al44 | 172               | All had 2-layer compression  
Gp1: 400 mg tds pentoxifylline  
Gp2: placebo  
Gp3: dressing   | Healing and reduction in ulcer size  
Gp1: 65% healed  
Gp2: 87% size reduction  
Gp3: 47% size reduction   | Gp1: 65% healed  
Gp2: 87% size reduction  
Gp3: 47% size reduction   |
| Nikolovska et al45 | 80              | All had hydrocolloid dressing  
One group had 400 mg tds pentoxifylline  
Gp1: 400 mg tds pentoxifylline  
Gp2: placebo  
Gp3: dressing   | Healing at 24 weeks | 58% healed in pentoxifylline group  
and 28% in no tablet group   |

Abbreviations: Gp1, group 1; Gp2, group 2; Gp3, group 3.

Table 4 Randomized controlled trials showing the effect of different types of skin grafting on ulcer healing

<table>
<thead>
<tr>
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<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Poskitt et al47 | 53                | Both groups received compression  
Gp1: pinch skin grafts  
Gp2: porcine dermis  
Gp3: dressing   | Healing at 6 and 12 weeks | Gp1: 64% healed at 6 weeks  
Gp2: 72% healed at 12 weeks  
Gp3: 46% healed at 12 weeks   |
| Mol et al48     | 11                | Gp1: human skin equivalents  
Gp2: punch grafts  
Gp3: dressing   | Healing at 20 days | Gp1: 80% healed  
Gp2: 71% healed   |
| Teepe et al49   | 47                | Both groups received short-stretch bandages  
Gp1: cryopreserved allografts  
Gp2: controls  
Gp3: dressing   | Healing at 6 weeks | Gp1: 25% healed  
Gp2: 22% healed   |
| Warburg et al50 | 31                | Both groups received compression  
Gp1: meshed split-skin graft  
Gp2: surgery for incompetent perforators  
Gp3: controls  
Gp4: dressing   | Healing at 12 months | Gp1: 33% healed  
Gp2: 38% healed   |
| Falanga et al51 | 309               | All received compression  
Gp1: human skin equivalent  
Gp2: dressing  
Gp3: dressing   | Healing at 6 months | Gp1: 63% healed  
Gp2: 49% healed   |
| Lindgren et al52| 27                | Both groups received compression  
Gp1: cryopreserved allografts  
Gp2: no graft  
Gp3: dressing   | Healing at 8 weeks | Gp1: 13% healed  
Gp2: 17% healed   |
| Tausche et al53 | 92                | Gp1: autologous epidermal equivalents derived from hair follicles  
Gp2: meshed skin autograft  
Gp3: dressing   | Healing at 6 months | Gp1: 42% healed  
Gp2: 34% healed   |

(Continued)
Table 4 (Continued)

<table>
<thead>
<tr>
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<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishnamoorthy et al54</td>
<td>53</td>
<td>All received 4-layer compression&lt;br&gt;Gp1: Dermagraft, weekly for 12 applications&lt;br&gt;Gp2: Dermagraft at 0, 1, 4, and 8 weeks&lt;br&gt;Gp3: Dermagraft at 0 weeks&lt;br&gt;Gp4: No Dermagraft</td>
<td>Healing at 12 weeks</td>
<td>Gp1: 38% healed&lt;br&gt;Gp2: 38% healed&lt;br&gt;Gp3: 7% healed&lt;br&gt;Gp4: 15% healed</td>
</tr>
<tr>
<td>Liu et al55</td>
<td>10</td>
<td>Both groups had ulcers debrided and multilayer compression bandaging&lt;br&gt;Gp1: keratinocytes cultured on porcine gelatin microbeads&lt;br&gt;Gp2: keratinocytes cultured on porcine collagen pads</td>
<td>Healing at 12 weeks</td>
<td>25% healed in both groups</td>
</tr>
<tr>
<td>Navrátilová et al56</td>
<td>50</td>
<td>Gp1: cryopreserved cultured epidermal keratinocytes&lt;br&gt;Gp2: lyophilized cultured epidermal keratinocytes</td>
<td>Healing at 90 days</td>
<td>Gp1: 84% healed&lt;br&gt;Gp2: 80% healed</td>
</tr>
<tr>
<td>Omar et al57</td>
<td>18</td>
<td>Both groups received 4-layer bandaging&lt;br&gt;Gp1: Dermagraft&lt;br&gt;Gp2: no graft</td>
<td>Healing at 12 weeks</td>
<td>Gp1: 50% healed&lt;br&gt;Gp2: 13% healed</td>
</tr>
</tbody>
</table>

Abbreviations: Gp1, group 1; Gp2, group 2; Gp3, group 3; Gp4, group 4.

Table 5 Randomized controlled trials showing the effect of different types of surgery and endovenous therapy on ulcer healing and recurrence

<table>
<thead>
<tr>
<th>Author</th>
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<th>Interventions</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guest et al54</td>
<td>76</td>
<td>Gp1: compression alone&lt;br&gt;Gp2: compression and superficial venous surgery ± perforator surgery</td>
<td>Healing</td>
<td>Gp1: 64% healed&lt;br&gt;Gp2: 68% healed</td>
</tr>
<tr>
<td>Zamboni et al60</td>
<td>45</td>
<td>Gp1: compression alone&lt;br&gt;Gp2: compression and minimally invasive surgical hemodynamic correction of reflux</td>
<td>Healing and recurrence</td>
<td>Gp1: 96% healed, 38% recurrence&lt;br&gt;Gp2: 100% healed, 9% recurrence</td>
</tr>
<tr>
<td>Van Gent et al61</td>
<td>200</td>
<td>Gp1: compression alone&lt;br&gt;Gp2: compression and subfascial endoscopic perforating vein surgery</td>
<td>Healing and recurrence</td>
<td>Gp1: 73% healed, 23% recurrence&lt;br&gt;Gp2: 83% healed, 22% recurrence</td>
</tr>
<tr>
<td>Gohel et al62</td>
<td>500</td>
<td>Gp1: compression alone&lt;br&gt;Gp2: compression and superficial venous surgery</td>
<td>Ulcer healing and ulcer recurrence at 3 years</td>
<td>Gp1: 89% healed, 56% recurrence&lt;br&gt;Gp2: 93% healed, 31% recurrence</td>
</tr>
<tr>
<td>Viarengo et al63</td>
<td>52</td>
<td>Gp1: compression alone&lt;br&gt;Gp2: endovenous laser therapy and compression</td>
<td>Healing at 12 months</td>
<td>Gp1: 24% healed&lt;br&gt;Gp2: 82% healed</td>
</tr>
</tbody>
</table>

Abbreviations: Gp1, group 1; Gp2, group 2.
Treatment

A 4-layer compression, if tolerated.
- Short-stretch compression or intermittent compression if 4-layer not tolerated.
- Pentoxifylline (400 mg three times daily) and skin grafting should be considered if ulcers are slow to heal.
- Incompetent veins should be treated to reduce the risk of ulcer recurrence.

Indications for specialist referral

Worsening despite treatment or slow healing.
- Unusual appearance of ulcer.

References


