Clinical, Cosmetic and Investigational Dermatology

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EVIDENCE 2 PRACTICE

Venous ulcer review

This article was published in the following Dove Press journal:
Clinical, Cosmetic and Investigational Dermatology
3 March 2011
Number of times this article has been viewed

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Date of preparation: 3 February 2011

Conflict of interest: None declared.

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.[1]

Economics: An unhealed leg ulcer costs approximately £1300 per year to treat.[2]

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

Search sources: PubMed, Cochrane Library, clinical evidence, and Google Scholar.

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

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One systematic review[3] 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[4] 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[32] 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'.[39]

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[46] 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[58] 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

Author	Number randomized	Interventions	Outcome measures	Results
Hendricks and Swallow[5]	21	Gp1: Unna's boot Gp2: below-knee elastic compression stocking	Healing at 78 weeks	Gp1: 70% healed Gp2: 71% healed
Eriksson[6]	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[7]	87	Gp1: Unna's boot Gp2: no compression	Healing at 6 months	Gp1: 70% healed Gp2: 38% healed
Rubin et al[8]	36	Gp1: Unna's boot Gp2: polyurethane foam dressing	Healing at 12 months	Gp1: 95% healed Gp2: 41% healed
Charles[9]	53	Gp1: short-stretch compression Gp2: usual care (no compression)	Healing at 3 months	Gp1: 71% healed Gp2: 25% healed
Cordts et al[10]	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[11]	27	Gp1: single-layer elastic cohesive bandage Gp2: 3-layer compression	Mean percentage change at 7 weeks	Gp1: –90% Gp2: –83%
Danielsen et al[12]	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[13]	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[14,15]	233	Gp1: 4-layer compression Gp2: standard community care	Healing at 12 months	Gp1: 65% healed Gp2: 55% healed
Scriven et al[16]	64	Gp1: 4-layer compression Gp2: short-stretch compression	Healing at 12 months	Gp1: 55% healed Gp2: 57% healed
Taylor et al[17]	36	Gp1: 4-layer compression Gp2: standard community care	Healing at 12 weeks	Gp1: 67% healed Gp2: 17% healed
Moody[18]	52	Gp1: short-stretch compression Gp2: long-stretch compression	Healing at 12 weeks	Gp1: 31% healed Gp2: 31% healed
Vowden et al[19]	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[20]	112	Gp1: 4-layer compression Gp2: short-stretch compression	Healing at 16 weeks	Gp1: 62% healed Gp2: 73% healed
Moffatt et al[21]	112	Gp1: 4-layer compression Gp2: 2-layer compression	Healing at 12 weeks	Gp1: 70% healed Gp2: 58% healed
O'Brien et al[22]	200	Gp1: 4-layer compression Gp2: standard community care	Healing at 12 weeks	Gp1: 54% healed Gp2: 34% healed
Ukat et al[23]	89	Gp1: 4-layer compression Gp2: short-stretch compression	Healing at 12 weeks	Gp1: 30% healed Gp2: 22% healed
Franks et al[24]	159	Gp1: 4-layer compression Gp2: short-stretch compression	Healing at 24 weeks	Gp1: 69% healed Gp2: 73% healed
Nelson et al[25]	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[26]	134	Gp1: U-stocking consisting of two stockings Gp2: short-stretch bandages	Healing at 12 weeks	Gp1: 48% healed Gp2: 32% healed

(*Continued*)

Table 1 (*Continued*)

Author	Number randomized	Interventions	Outcome measures	Results
Nelson[27]	133	Gp1: 3-layer compression Gp2: 4-layer compression	Healing at 52 weeks	Gp1: 80% healed Gp2: 65% healed
Polignano et al[28]	68	Gp1: 4-layer compression Gp2: Unna's boot	Healing at 24 weeks	Gp1: 74% healed Gp2: 66% healed
Polignano et al[29]	56	Gp1: short-stretch compression Gp2: multilayer high compression system	Healing at 12 weeks	Gp1: 17% healed Gp2: 44% healed
Blecken et al[30]	12	Gp1: adjustable compression boot system Gp2: 4-layer compression	Healing at 12 weeks	Gp1: 93% healed Gp2: 51% healed
Milic et al[31]	150	Gp1: tubular compression device (35–40 mm Hg) Gp2: 2medium-stretch compression bandages (20–25 mm Hg)	Healing at 500 days	Gp1: 33% healed Gp2: 33% healed

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

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.

Assessment

Nutritional status of patients should be assessed.

- There may be a history of varicose veins.
- Any history of intravenous injection should be elicited.
- Any medication or medical condition potentially affecting healing should be assessed.
- Concomitant arterial disease should be excluded using ankle brachial pressure indices before the application of any compression.
- Patients should be examined for evidence of superficial venous incompetence.
- Any history of deep vein thrombosis should be elicited.

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

Author	Number randomized	Interventions	Outcome measures	Results
Smith et al[33]	45	Both groups had same dressings and stockings. Sequential IPC for up to 4 h in one group	Healing	48% healed in IPC group and 4% in control group
McCulloch et al[34]	22	Both groups had the same dressings and Unna's boots. IPC for 60 min twice weekly in one group	Healing	100% healed in IPC group and 80% in control group
Schuler et al[35]	53	Unna's boots versus elasticated stockings plus IPC for 60 min in the morning and 120 min in the evening	Healing	71% healed in IPC group and 75% in Unna's boot group
Rowland[36]	16	Crossover trial of dressing alone with dressing and IPC for 60 min twice daily for 2–3 months	Healing	No ulcers healed in either arm before crossover
Kumar et al[37]	47	Both groups had 4-layer bandaging IPC for 60 min twice daily for 4 months in one group	Healing	87% healed in IPC group and 92% in control group
Nikolovska et al[38]	104	Both groups had same dressings Fast IPC for one group and slow IPC in the other group	Healing at 6 months	86% healed with fast IPC and 61% with slow IPC

Abbreviation: IPC, intermittent pneumatic compression.

Table 3 Randomized controlled trials showing the effect of pentoxifylline on ulcer healing

Author	Number randomized	Interventions	Outcome measures	Results
Colgan et al[40]	80	All had 2-layer compression Gp1: 400 mg tds pentoxifylline Gp2: placebo	Healing at 24 weeks	Gp1: 60% healed Gp2: 29% healed
Barbarino[41]	12	All had 2-layer compression Gp1: 400 mg tds pentoxifylline Gp2: placebo	Healing	Gp1: 66% healed Gp2: 17% healed
Dale et al[42]	200	All had compression Gp1:400 mg tds pentoxifylline Gp2: placebo	Healing at 24 weeks	Gp1: 64% healed Gp2: 52% healed
Falanga et al[43]	129	All had compression Gp1: 800 mg tds pentoxifylline Gp2: 400 mg tds pentoxifylline Gp3: placebo	Healing at 24 weeks	Gp1: 73% healed Gp2: 75% healed Gp3: 63% healed
Belcaro et al[44]	172	All had 2-layer compression Gp1: 400 mg tds pentoxifylline Gp2: placebo	Healing and reduction in ulcer size	Gp1: 65% healed, 87% size reduction Gp2: 27% healed, 47% size reduction
Nikolovska et al[45]	80	All had hydrocolloid dressing One group had 400 mg tds pentoxifylline	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

Author	Number randomized	Interventions	Outcome measures	Results
Poskitt et al[47]	53	Both groups received compression Gp1: pinch skin grafts Gp2: porcine dermis	Healing at 6 and 12 weeks	Gp1: 64% healed at 6 weeks and 72% at 12 weeks Gp2: 29% healed at 6 weeks and 46% healed at 12 weeks
Mol et al[48]	11	Gp1: human skin equivalents Gp2: punch grafts	Healing at 20 days	Gp1: 80% healed Gp2: 71% healed
Teepe et al[49]	47	Both groups received short-stretch bandages Gp1: cryopreserved allografts Gp2: controls	Healing at 6 weeks	Gp1: 25% healed Gp2: 22% healed
Warburg et al[50]	31	Both groups received compression Gp1: meshed split-skin graft Gp2: surgery for incompetent perforators	Healing at 12 months	Gp1: 33% healed Gp2: 38% healed
Falanga et al[51]	309	All received compression Gp1: human skin equivalent Gp2: dressing	Healing at 6 months	Gp1: 63% healed Gp2: 49% healed
Lindgren et al[52]	27	Both groups received compression Gp1: cryopreserved allografts Gp2: no graft	Healing at 8 weeks	Gp1: 13% healed Gp2: 17% healed
Tausche et al[53]	92	Gp1: autologous epidermal equivalents derived from hair follicles Gp2: meshed skin autograft	Healing at 6 months	Gp1: 42% healed Gp2: 34% healed

(*Continued*)

Table 4 (*Continued*)

Author	Number randomized	Interventions	Outcome measures	Results
Krishnamoorthy et al[54]	53	All received 4-layer compression Gp1: Dermagraft, weekly for 12 applications Gp2: Dermagraft at 0, 1, 4, and 8 weeks Gp3: Dermagraft at 0 weeks Gp4: No Dermagraft	Healing at 12 weeks	Gp1: 38% healed Gp2: 38% healed Gp3: 7% healed Gp4: 15% healed
Liu et al[55]	10	Both groups had ulcers debrided and multilayer compression bandaging Gp1: keratinocytes cultured on porcine gelatin microbeads Gp2: keratinocytes cultured on porcine collagen pads	Healing at 12 weeks	25% healed in both groups
Navrátilová et al[56]	50	Gp1: cryopreserved cultured epidermal keratinocytes Gp2: lyophilized cultured epidermal keratinocytes	Healing at 90 days	Gp1: 84% healed Gp2: 80% healed
Omar et al[57]	18	Both groups received 4-layer bandaging Gp1: Dermagraft Gp2: no graft	Healing at 12 weeks	Gp1: 50% healed Gp2: 13% healed

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

Author	Number randomized	Interventions	Outcome measures	Results
Guest et al[59]	76	Gp1: compression alone Gp2: compression and superficial venous surgery ± perforator surgery	Healing	Gp1: 64% healed Gp2: 68% healed
Zamboni et al[60]	45	Gp1: compression alone Gp2: compression and minimally invasive surgical hemodynamic correction of reflux	Healing and recurrence	Gp1: 96% healed, 38% recurrence Gp2: 100% healed, 9% recurrence
Van Gent et al[61]	200	Gp1: compression alone Gp2: compression and subfascial endoscopic perforating vein surgery	Healing and recurrence	Gp1: 73% healed, 23% recurrence Gp2: 83% healed, 22% recurrence
Gohel et al[62]	500	Gp1: compression alone Gp2: compression and superficial venous surgery	Ulcer healing and ulcer recurrence at 3 years	Gp1: 89% healed, 56% recurrence Gp2: 93% healed, 31% recurrence
Viarengo et al[63]	52	Gp1: compression alone Gp2: endovenous laser therapy and compression	Healing at 12 months	Gp1: 24% healed Gp2: 82% healed

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.

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