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 2.8:1.¹

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 review³ 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 review⁴ 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 review³² 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 review⁴⁶ 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 review⁵⁸ 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 I 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.

References

- Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J (Clin Res Ed)*. 1985;290(6485):1855–1856.
- Iglesias CP, Nelson EA, Cullum N, Torgerson DJ; VenUS I collaborators. Economic analysis of VenUS I, a randomized trial of two bandages for treating venous leg ulcers. *Br J Surg*. 2004;91(10):1300–1306.
- O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. *Cochrane Database Syst Rev*. 2009;(1):CD000265.
- O'Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. *BMJ*. 2009;338:b1344.
- Hendricks WM, Swallow RT. Management of stasis leg ulcers with Unna's boots versus elastic support stockings. *J Am Acad Dermatol*. 1985;12(1 Pt 1):90–98.
- Eriksson G. Comparison of two occlusive bandages in the treatment of venous leg ulcers. *Br J Dermatol*. 1986;114(2):227–230.
- Kikta MJ, Schuler JJ, Meyer JP, et al. A prospective, randomized trial of Unna's boots versus hydroactive dressing in the treatment of venous stasis ulcers. *J Vasc Surg*. 1988;7(3):478–483.
- Rubin JR, Alexander J, Plecha EJ, Marman C. Unna's boot vs polyurethane foam dressings for the treatment of venous ulceration. A randomized prospective study. *Arch Surg*. 1990;125(4):489–490.
- Charles H. Compression healing of ulcers. *J Dist Nurs*. 1991;10(3):4–8.
- Cordts PR, Hanrahan LM, Rodriguez AA, Woodson J, LaMorte WW, Menzoian JO. A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. *J Vasc Surg*. 1992;15(3):480–486.
- Travers JP, Dalziel KL, Makin GS. Assessment of a new one-layer adhesive bandaging method in maintaining prolonged limb compression and effects on venous ulcer healing. *Phlebology*. 1992;7:59–63.
- Danielsen L, Madsen SM, Henriksen L. Venous leg ulcer healing. A randomised prospective study of long-stretch versus short-stretch compression bandages. *Phlebology*. 1998;13:59–63.
- Gould DJ, Campbell S, Newton H, Duffelen P, Griffin M, Harding EF. Setopress vs Elastocrepe in chronic venous ulceration. *Br J Nurs*. 1998;7(2):66–70, 72–73.
- Morrell CJ, King B, Brereton L. Community-based leg ulcer clinics: organisation and cost-effectiveness. *Nurs Times*. 1998;94(9):51–54.
- Morrell CJ, Walters SJ, Dixon S, et al. Cost effectiveness of community leg ulcer clinics: randomised controlled trial. *BMJ*. 1998;316(7143):1487–1491.
- Scriven JM, Taylor LE, Wood AJ, Bell PR, Naylor AR, London NJ. A prospective randomised trial of four-layer versus short stretch compression bandages for the treatment of venous leg ulcers. *Ann R Coll Surg Engl*. 1998;80(3):215–220.
- Taylor AD, Taylor RJ, Marcuson RW. Prospective comparison of healing rates and therapy costs for conventional and four-layer high compression bandaging treatments of venous leg ulcers. *Phlebology*. 1998;13:20–24.
- Moody M. Comparison of Rosidal K and SurePress in the treatment of venous leg ulcers. *Br J Nurs*. 1999;8(6):345–355.
- Vowden KR, Mason A, Wilkinson D, Vowden P. Comparison of the healing rates and complications of three four-layer bandage regimens. *J Wound Care*. 2000;9(6):269–272.
- Partsch H, Damstra RJ, Tazelaar DJ, et al. Multicentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. *Vasa*. 2001;30(2):108–113.
- Moffatt CJ, McCullagh L, O'Connor T, et al. Randomized trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration. *Wound Repair Regen*. 2003;11(3):166–171.
- O'Brien JF, Grace PA, Perry IJ, Hannigan A, Clarke Moloney M, Burke PE. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. *Br J Surg*. 2003;90(7):794–798.
- Ukat A, König M, Vanscheidt W, Münter KC. Short-stretch versus multilayer compression for venous leg ulcers: a comparison of healing rates. *J Wound Care*. 2003;12(4):139–143.
- Franks PJ, Moody M, Moffatt CJ, et al; Wound Healing Nursing Research Group. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. *Wound Repair Regen*. 2004;12(2):157–162.
- Nelson EA, Iglesias CP, Cullum N, Torgerson DJ; VenUS I collaborators. Randomized clinical trial of four-layer and short-stretch compression bandages for venous leg ulcers (VenUS I). *Br J Surg*. 2004;91(10):1292–1299.
- Jünger M, Wollina U, Kohnen R, Rabe E. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. *Curr Med Res Opin*. 2004;20(10):1613–1623.
- Nelson EA. 3 layer paste bandages were more effective than 4 layer bandages for healing venous leg ulcers. *Evid Based Nurs*. 2004;7(1):21.
- Polignano R, Bonadeo P, Gasbarro S, Allegra C. A randomised controlled study of four-layer compression versus Unna's boot for venous ulcers. *J Wound Care*. 2004;13(1):21–24.
- Polignano R, Guarnera G, Bonadeo P. Evaluation of SurePress Comfort: a new compression system for the management of venous leg ulcers. *J Wound Care*. 2004;13(9):387–391.
- Blecken SR, Villavicencio JL, Kao TC. Comparison of elastic versus nonelastic compression in bilateral venous ulcers: a randomized trial. *J Vasc Surg*. 2005;42(6):1150–1155.
- Milic DJ, Zivic SS, Bogdanovic DC, et al. A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers. *J Vasc Surg*. 2007;46(4):750–755.
- Nelson EA, Mani R, Vowden K. Intermittent pneumatic compression for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2008;2:CD001899.
- Smith PC, Sarin S, Hasty J, Scurr JH. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. *Surgery*. 1990;108(5):871–875.
- McCulloch JM, Marler KC, Neal MB, Phifer TJ. Intermittent pneumatic compression improves venous ulcer healing. *Adv Wound Care*. 1994;7(4):22–24, 26.
- Schuler JJ, Maibenko T, Megerman J, Ware M, Montalvo J. Treatment of chronic venous ulcers using sequential gradient intermittent pneumatic compression. *Phlebology*. 1996;11(3):111–116.
- Rowland J. Intermittent pump versus compression bandages in the treatment of venous leg ulcers. *Aust N Z J Surg*. 2000;70(2):110–113.

37. Kumar S, Samraj K, Nirujogi V, Budnik J, Walker MA. Intermittent pneumatic compression as an adjuvant therapy in venous ulcer disease. *J Tissue Viability*. 2002;12(2):42–44, 46, 48 passim.
38. Nikolovska S, Arsovski A, Damevska K, Gocev G, Pavlova L. Evaluation of two different intermittent pneumatic compression cycle settings in the healing of venous ulcers: a randomized trial. *Med Sci Monit*. 2005;11(7):CR337–CR343.
39. Jull A, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev*. 2007;(3):CD001733.
40. Colgan MP, Dormandy JA, Jones PW, Schraibman IG, Shanik DG, Young RA. Oxpentifylline treatment of venous ulcers of the leg. *BMJ*. 1990;300(6730):972–975.
41. Barbarino C. Pentoxifylline in the treatment of venous leg ulcers. *Curr Med Res Opin*. 1992;12(9):547–551.
42. Dale JJ, Ruckley CV, Harper DR, Gibson B, Nelson EA, Prescott RJ. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. *BMJ*. 1999;319(7214):875–878.
43. Falanga V, Fujitani RM, Diaz C, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. *Wound Repair Regen*. 1999;7(4):208–213.
44. Belcaro G, Cesarone MR, Nicolaidis AN, De Sanctis MT, Incandela L, Geroulakos G. Treatment of venous ulcers with pentoxifylline: a 6-month randomized, double-blind, placebo controlled trial. *Angiology*. 2002;53 Suppl 1:S45–S47.
45. Nikolovska S, Pavlova L, Petrova N, Gocev G, Ivanovski M. Pentoxifylline – efficient in the treatment of venous ulcers in the absence of compression? *Acta Dermatovenol Croat*. 2002;10(1):9–13.
46. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev*. 2007;2:CD001737.
47. Poskitt KR, James AH, Lloyd-Davies ER, Walton J, McCollum C. Pinch skin grafting or porcine dermis in venous ulcers: a randomised clinical trial. *Br Med J (Clin Res Ed)*. 1987;294(6573):674–676.
48. Mol MA, Nanninga PB, van Eendenburg JP, Westerhof W, Mekkes JR, van Ginkel CJ. Grafting of venous leg ulcers. An intraindividual comparison between cultured skin equivalents and full-thickness skin punch grafts. *J Am Acad Dermatol*. 1991;24(1):77–82.
49. Teepe RG, Roseeuw DI, Hermans J, et al. Randomized trial comparing cryopreserved cultured epidermal allografts with hydrocolloid dressings in healing chronic venous ulcers. *J Am Acad Dermatol*. 1993;29(6):982–988.
50. Warburg FE, Danielsen L, Madsen SM, et al. Vein surgery with or without skin grafting versus conservative treatment for leg ulcers. A randomized prospective study. *Acta Derm Venereol*. 1994;74(4):307–309.
51. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol*. 1998;134(3):293–300.
52. Lindgren C, Marcusson JA, Toftgård R. Treatment of venous leg ulcers with cryopreserved cultured allogeneic keratinocytes: a prospective open controlled study. *Br J Dermatol*. 1998;139(2):271–275.
53. Tausche AK, Skaria M, Böhlen L, et al. An autologous epidermal equivalent tissue-engineered from follicular outer root sheath keratinocytes is as effective as split-thickness skin autograft in recalcitrant vascular leg ulcers. *Wound Repair Regen*. 2003;11(4):248–252.
54. Krishnamoorthy L, Harding KG, Griffiths D, et al. The clinical and histological effects of Dermagraft in the healing of chronic venous leg ulcers. *Phlebology*. 2003;18(1):12–22.
55. Liu JY, Hafner J, Dragieva G, Seifert B, Burg G. Autologous cultured keratinocytes on porcine gelatin microbeads effectively heal chronic venous leg ulcers. *Wound Repair Regen*. 2004;12(2):148–156.
56. Navrátilová Z, Slonková V, Semrádová V, Adler J. Cryopreserved and lyophilized cultured epidermal allografts in the treatment of leg ulcers: a pilot study. *J Eur Acad Dermatol Venereol*. 2004;18(2):173–179.
57. Omar AA, Mavor AI, Jones AM, Homer-Vanniasinkam S. Treatment of venous leg ulcers with Dermagraft. *Eur J Vasc Endovasc Surg*. 2004;27(6):666–672.
58. Howard DP, Howard A, Kothari A, Wales L, Guest M, Davies AH. The role of superficial venous surgery in the management of venous ulcers: a systematic review. *Eur J Vasc Endovasc Surg*. 2008;36(4):458–465.
59. Guest M, Smith JJ, Tripuraneni G, et al. Randomized clinical trial of varicose vein surgery with compression versus compression alone for the treatment of venous ulceration. *Phlebology*. 2003;18(3):130–136.
60. Zamboni P, Cisno C, Marchetti F, et al. Minimally invasive surgical management of primary venous ulcers vs. compression treatment: a randomized clinical trial. *Eur J Vasc Endovasc Surg*. 2003;25(4):313–318.
61. van Gent WB, Hop WC, van Praag MC, Mackaay AJ, de Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *J Vasc Surg*. 2006;44(3):563–571.
62. Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial. *BMJ*. 2007;335(7610):83.
63. Viarengo LM, Potério-Filho J, Potério GM, Menezes FH, Meirelles GV. Endovenous laser treatment for varicose veins in patients with active ulcers: measurement of intravenous and perivenous temperatures during the procedure. *Dermatol Surg*. 2007;33(10):1234–1242; discussion 1241–1242.
64. Yang D, Morrison BD, Vandongen YK, Singh A, Stacey MC. Malignancy in chronic leg ulcers. *Med J Aust*. 1996;164(12):718–720.

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