Venous Ulcers: What Really Works and What Does Not Based on Level I Evidence

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Nonhealing venous ulcers (CEAP VI) affect 0.3% of the population in the United States, United Kingdom, and Europe and when combined with healed ulcer (CEAP V) the figure increases to 1%.1 The associated direct costs for the treatment of venous ulcer in the United States amounts to $600 to $2,000/yr/patient. The treatment of venous ulcers range from nonsurgical options such as wound care and compression to surgery such as reduction of superficial venous hypertension or in selected cases deep venous valvular reconstruction. The focus of this presentation is to review the available level I evidence for the treatment of venous ulcer. The majority of the studies in the literature, however, are level V or level IV, for example case studies, which lack the statistical power of a level I study (randomized control trial powered by a sufficient number of patients in each cell). Both federal agencies and private insurance plans now make their decision to fund treatments, principally on level I studies. In the past, there have been several comprehensive reviews of the contemporary treatment of venous ulcers: (1) the international task force report (VEIN),1 (2) periodically updated Cochrane reviews of compression treatment,2 and (3) finally a massive four-volume review funded by the United Kingdom's National Health Service (NHS).[3]

The United Kingdom's Health Technology Assessment (HTA) Program examines costs, effectiveness and the broader impact of health technology. This group carried out a systematic review of chronic wound care management and in particular dressings and topical agents used to heal chronic wounds.

The NHS HTA Program employed 19 electronic databases as search engines which included the Cochrane Wound Group's specialized trial register and reviewed all significant publications from 1980 up through October 1997.[1] Besides treatment of pressure ulcers and arterial ulcers, they identified 48 trials for venous leg ulcers and published their review in 1999. The review concluded that "methodological flaws are an issue affecting the validity of most studies in chronic wound care." Small sample size, which failed to provide enough prognostic variables evenly distributed across trial arms, short follow-up and lack of valid endpoints plagued interpretation of the studies' results.1 For example, only 62% recorded baseline wound size and only one half provided the number and reason for patient withdrawal.

Under a contract with a federal agency, we reviewed the literature since the last NHS HTA report, which stopped at 1997 to systematically analyze studies on the management of wounds between 1997 and 2005.2 The current presentation specifically addresses the treatment of venous ulcer while the purpose of our larger review was to determine "the usual care of chronic wounds," for example, accepted contemporary wound management. In addition, the review was expanded by me to assess the efficacy of new wound dressings. To provide information on "usual care," the National Guidelines Clearing House and MedLine for Clinical Practice Guidelines were searched specifically under the topic of the management of venous ulcer. In addition, chapters of standard surgical textbooks on wound care were also reviewed. Finally, English language studies in MedLine, CINAHL and the Cochrane Control Trials Registry DataBases from January 1, 2000, to June 30, 2005, were reviewed, covering the years since the last UK NHS HTA systematic review.

A National Guideline Clearing House search identified three guidelines on the treatment of chronic venous ulcers. The usual modalities identified were as follows: (1) wound cleansing, (2) antibiotics when infected, (3) physical measures such as compression to reduce superficial venous hypertension, (4) débridement, and (5) wound dressings.

Randomized Control Trials (RCT) Eligible Studies

Sixty-six venous ulcer RCTs with nearly 6,500 patients were identified during the review period. The types of wound dressings were divided into nonocclusive, semi-occlusive/occlusive, and biologic. Semi-/and occlusive dressings are defined by their ability to decrease moisture vapor transmission rate because moist wounds have been shown to have a 40% increased epithelialization rate over dry wounds.

Usual or Customary Care

To define "usual care," the review was limited to the nonocclusive and semi-/occlusive wound dressing categories. As shown in Table 1, the mean sample size in the venous ulcer trials approached 100 patients with several studies containing 300 patients. Over half of the trials were performed in the United States or the United Kingdom, principally in an outpatient setting (74%). The patients were older and the mean age (66 years of age) qualified for Medicare. Slightly over one half of the participants were women and the majority of the trials clearly stated the ulcer had a duration longer than 30 days.

Treatment Modalities Reported
When common treatment modalities were analyzed as reported in the control arm, débridement and antibiotics were used infrequently in venous ulcers (see Table 1). By contrast, routine cleansing was carried out in nearly one half of the trials. In excess of 80%
of the trials reported some form of both wound dressing and compression.

Wound Dressings
Table 2 demonstrates the various wound dressing types as reported in the control group. An occlusive type dressing predominated
and was found in 55% of the participants, the greater proportion receiving hydrocolloids (40%). Less common were semi-occlusive dressings and saline wet to dry gauze dressings. Strikingly enough, one-quarter of the control groups employed nonocclusive dressings and a great proportion of these non-occlusive dressings were dry gauze.

Effectiveness of Newer Wound Dressing Types in the Healing of Venous Ulcers
This portion of the review included newer semiocclusive dressings, occlusive dressings, as well as "biologic" dressings, for example, the experimental arm of the study. The interactive or biologic dressings can be divided into human skin equivalent (HSE), platelet product growth factors, and other growth factors. Following exclusion of ulcers of mixed etiology, the 66 venous ulcer trials were assessed to identify whether elastic compression was used as standard treatment to accompany wound dressings. Further inclusion criteria were valid objective outcome measures: (1) proportion of wounds healed in a given period and (2) rate of ulcer healing. As a result of these prerequisites, the number of studies was narrowed down to fourteen studies for the type of wound dressing: three human skin equivalent trials; four growth factors trials and seven interactive dressing trials. Figure 1 demonstrates the results for complete wound healing. Two of three human skin equivalent trials showed a significant increase in the proportion of wounds healed, whereas two of the five biologic wound dressing trials and three of the seven interactive wound dressing trials showed a statistically improved proportion of wounds healed. A similar trend was found when time to complete healing by log rank test or healing rate was assessed. Only 2 of the 16 trials for venous ulcers reported ulcer recurrence and no difference was observed between the control and treatment groups.

Compression Therapy
The Cochrane Group reviewed compression for venous leg ulcers and identified 22 trials, which reported 24 comparative studies.2 The review dealt with both compression by bandages and by stockings as well as combination systems. They concluded that compression increases the rate of ulcer-healing when compared with no compression. In addition, multi-layered systems appeared more effective than single layer systems and as might be expected high compression was more effective in ulcer healing than low compression. They were unable to delineate any clear difference between the types of high compression. The review concluded that the quality of research in this area was generally poor and the trials were small in number with a short follow-up period. The conclusions were strikingly similar to those of the NHS HTA Task Force on wound treatments. Results were expressed in terms of the relative benefit of a specific therapy, that is, the proportional increase in the rate of healing. For elastic high compression bandaging, the improvement was 54%, for multilayer high compression over single layer compression 41%. No difference in compression by Unna Boot versus single layer compression was observed in one randomized control trial. When compression stockings were compared to compression bandaging, there was a relative increase in ulcer healing for stockings of 39% over compression bandaging which just missed statistical significance at the confidence interval.

Ulcer Recurrence
There were no trials comparing compression with no compression for the prevention of ulcer recurrence. There is circumstantial -evidence to show compression is beneficial. Higher compression appeared of greater benefit than medium compression, but compliance was a problem in the higher compression group. No trials evaluated compression bandages in the prevention of ulcer recurrence.

Surgery for Venous Ulcer
The role of the surgical reduction of superficial venous hypertension in ulcer healing and prevention of recurrence by saphenous ablation was examined in the recent ESCHAR Trial.4 Five hundred patients, of whom 70% had an open ulcer (class VI), were randomly assigned to compression with wound dressing versus ligation and stripping with compression. No advantage in the proportion of ulcers healed at 6 months was observed between either group, 6% in the compression and 82% in the surgical treatment arm. At a median of 14 months follow-up, a twofold reduction in ulcer recurrence, however, was identified for surgery, 34% ulcer recurrence rate in the compression group and 15% ulcer recurrence rate in the surgically treated group. A second large RCT, the Dutch SEPS Trial, compared subfascial endoscopic ligation of incompetent perforating veins to elastic compression.5 This data was presented at the 2003 Society for Vascular Surgery meeting and the data was updated at the American Venous Forum meeting in February 2005. This study showed statistically favorable results for SEPS over compression and wound care in several subgroups: (1) longstanding ulcer, (2) recurrent ulcer, (3) medial based ulcer, and (4) large ulcer area (> 2.5 cm).

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Conclusions

The usual care of venous ulcer as determined from the control group of 66 RCTs recognizes the importance of compression but had some variability in the type and degree. Occlusive dressings which require less frequent changing were described in over half the patients. "Older" forms of wound dressings such as Unna Boot, dry gauze, saline wet-to-dry gauze bandage were used in a significant proportion of studies.

Also, very few RCT qualified by strength of study design when the effectiveness of wound dressings was assessed (16 of 66, 24%). Although human skin equivalent (artificial skin) showed promising results, a larger number of studies are required to validate this option and the biologic category. Finally, the surgical reduction of superficial venous hypertension either by ligation and stripping alone or by SEPS appears effective in reducing ulcer recurrence, something which none of the wound trials and compression had attained.

References

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Table 1. Study Characteristics and Treatment

Modality in Venous Studies (N = 66)	
Study Characteristics*	Number (%)
Study size, mean and range	97 (9–500)
Average age, mean and range	66 (50–76)
% women, mean and range	55% (15–84)
Ulcer duration (> 30 d)	43 (65)
Treatment Modality*	Number (%)
Surgical débridement	12 (18)
Nonsurgical débridement	6 (9)
Cleansing	34 (52)
Antibiotics	10 (15)
Dressing	57 (86)
Compression	55 (83)

*As reported in control groups

Table 2. Types of Wound Dressings in Venous Studies (N = 66)

Wound Dressing Type*	Number (%)
Nonocclusive	16 (24)
Ointment/cream	6 (9)
Dry gauze	10 (15)
Semiocclusive	10 (16)
Saline wet-to-dry	3 (5)
Wet dressing	2 (3)
Paraffin or Vaseline gauze	5 (8)
Occlusive	35 (55)
Unna Boot	10 (15)
Hydrocolloid	25 (40)

*As reported in control group.

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