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ORIGINAL ARTICLE

Low-grade elastic compression regimen for venous leg ulcers – an effective compromise for patients requiring daily dressing changes

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Key words
Compression bandages; Compression dressing; Ulcer; Venous hypertension; Venous insufficiency; Venous leg ulcer; Wound healing; Wound-healing rate

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Abstract

Venous leg ulcers (VLUs) affect millions of patients worldwide and are a tremendous financial burden on our health care system. The hallmark of venous disease of the lower extremities is venous hypertension, and compression is the current mainstay of treatment. However, many patients are non-compliant, partly because of the complexity of the dressings and the difficulties with application and removal. The aim of our study was to test an effective compression dressing regimen for patients with VLUs who require changing the ulcer primary dressing twice daily. We used two layers of a latex-free tubular elastic bandage for compression. The primary endpoint of our study was increased wound-healing rate and our secondary endpoint was complete wound closure. All active study subjects had positive healing rates at week 4 and week 8. Two subjects achieved complete wound closure by week 8. We conclude that compression with a latex-free tubular elastic bandage can be safely used in patients with VLUs requiring frequent dressing changes. This type of compression allows for daily inspection of wounds, dressing changes at home, flexibility in the context of clinical trials, and is a compromise for patients who are intolerant to compression dressings.

Introduction

It is estimated that approximately 1·2 million adults in the USA have venous leg ulcers (VLUs). Venous ulcers are characterised by loss of epithelium (epidermis) plus variable levels of dermal and subcutaneous tissues. The ulcers occur near or above the malleoli of the distal lower extremities especially on the medial side (1). Once VLUs heal, their recurrence rate is as high as 72% overall, (2) and 21% at 1 year (3). This high recurrence rate, coupled with the long ulcer duration of more than a year in more than half of patients, helps explain the high prevalence of venous ulcers (2). This high prevalence is accompanied by substantial costs to our health care system and personal socioeconomic consequences (4). In the USA, the annual estimated cost of ulcer treatment is around 2·5 billion (2). These types of wounds represent the late effects of chronic venous insufficiency and venous hypertension.

Venous insufficiency results in prolonged venous hypertension, particularly in the lower half of the calf (1). Venous hypertension refers to sustained elevation of ambulatory venous pressure (AVP). It is known that venous hypertension is the result of dysfunction of the calf muscle pump and generally includes the structural and functional damage to the

Key Message

- leg compression with a latex-free tubular elastic bandage can be safely used in patients with venous leg ulcers requiring frequent dressing changes

†These authors have contributed equally to this work.

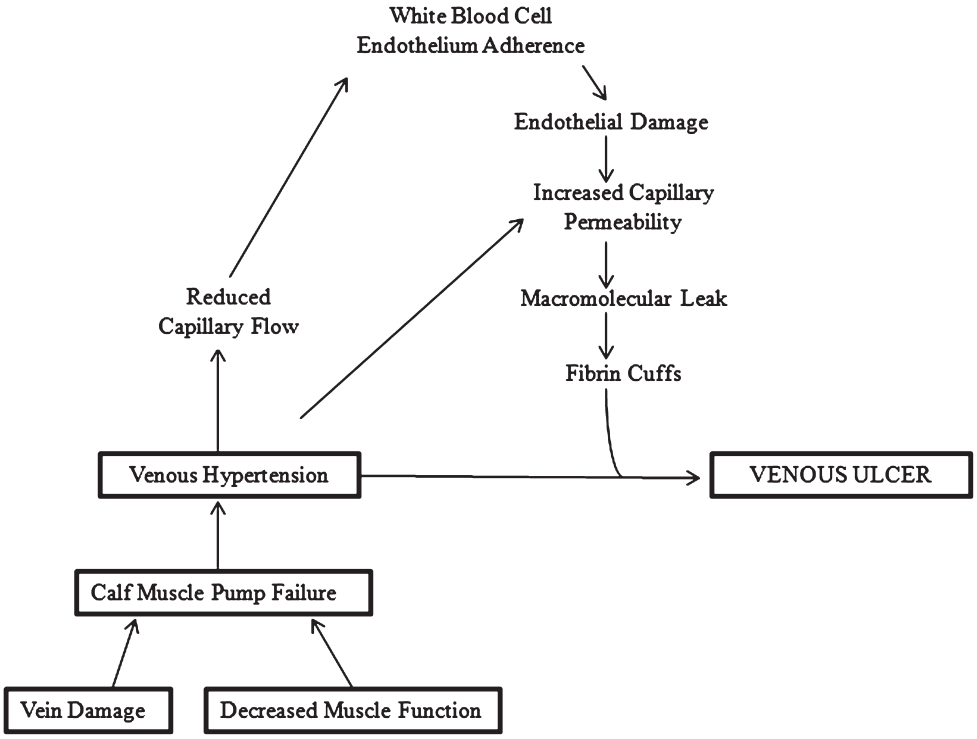

Figure 1 Pathophysiology of venous ulcers. Diagrammatic representation of the pathogenesis of venous ulceration and the proposed hypothesis linking venous hypertension to the formation of ulcers.

veins (Figure 1). The calf muscle pump comprises the calf muscles, the deep venous system, superficial venous system, and the perforating/communicating vein system. In a diseased venous system and faulty calf muscle pump unit, the predicted fall in venous pressure upon ambulation or leg exercise does not occur (1). Venous hypertension is therefore a misnomer because the venous pressure does not actually increase above baseline (1). It has been shown that there is a direct correlation between AVP and the development of venous ulceration. In a study by Shull *et al.*, patients with an AVP greater than 60 mm Hg had a 66% chance of developing an ulcer, while no patients with AVP below 40 mmHg developed ulcers (5).

While the mechanisms causing venous hypertension are fairly well worked out, the pathogenic steps leading from venous hypertension to ulceration are still unknown (4). Over the last several decades, numerous hypotheses have emerged to explain the development of venous ulceration. One such hypothesis by Browse *et al.* suggested that unrelieved venous pressure leads to leakage of fibrinogen into the dermis, with the consequent formation of a pericapillary fibrin layer (6–11) (Figure 1). It was proposed that this layer of fibrin interferes with the normal flux of oxygen and nutrients between blood and tissue. This interference, in turn would lead to tissue anoxia and subsequent necrosis (6–11). Decreased transcutaneous oxygen tension in limbs with venous ulcers and the presence of pericapillary fibrin in the skin adjacent to the ulcers have been described (12). However, it was later found that the correlation between the presence of pericapillary fibrin with venous ulcers and impaired healing was not convincing (8). Indeed confocal microscopy has indicated that large gaps exist within the pericapillary fibrin layer (13). These observations lend credence to an alternative trap hypothesis, whereby the fibrin has a more functional rather than structural role (14). The trap hypothesis suggests that fibrin, fibronectin in the fibrin layer, bind to growth factors and other proteins and matrix components critical to healing. Moreover, the leakage of fluid from blood vessels may bind those wound-healing components (14). Others have suggested that trapping of white blood cells may damage endothelial cells (15).

Treatment of a non-healing venous ulcer first requires an accurate diagnosis, followed by the identification and correction of contributing systemic factors (1). In the absence of cellulitis or severe bacterial colonisation of the wound, which generally require systemic antibiotics, the overall treatment is directed towards improving venous hypertension, and decreasing leg oedema.

Venous ulcers are treated with a primary wound dressing that can absorb excess exudate, fill vacant space and provide a moist environment for optimal healing (16). VLUs can be quite exudative, especially when the legs are oedematous and compression is being initially applied. If the wound dressings cannot keep up with the amount of exudate draining from the ulcer, the surrounding area becomes macerated. This will lead to delayed wound healing and increased risk of infection. Thus, in our experience, treatment of VLUs often requires daily inspection and dressing changes. Many compression bandages, such as Unna boot (short-stretch bandages) and three- or four-layer bandages (long stretch bandages), do not allow for frequent inspection or dressing changes.

Compression therapy is the established treatment for venous ulcers (17). Compression may improve venous return, reduce oedema and stimulate healthier granulation of tissue within venous ulcers (18). There are several types of compression bandages including, in particular, short- and long-stretch bandages. Elastic stockings are best applied after complete wound closure has taken place. All compression bandages have pros and cons. The majority of bandages are difficult for patients to apply on their own, and some of them require a well-trained physician or nurse. This difficulty leads to more doctor visits and helps contribute to the health care costs for caring for such wounds. Importantly, in the context of testing a topical agent to be applied more than once or twice a week, compression bandages may become an obstacle. Thus, there is a need for a compression bandage regimen that patients can apply on their own, and which still provides some pressure to help reverse the effects of venous hypertension. The results of this study represent a compromise in terms of delivering an ideal compression to the legs.

Methods

This was an investigator-initiated clinical trial. The trial was approved by the Institutional Review Board (IRB) at Roger Williams Medical Center. The subjects enroled in our study were recruited from our wound-healing clinic and referrals from the community. Written informed consent was obtained from all subjects prior to study entry.

The inclusion criteria were the following: (i) patients 18 years or older, (ii) non-healing VLUs $\geq 2\,cm^2$ in size, (iii) ankle to brachial index (ABI) ratio $>0{\cdot}7$, (iv) venous disease including lipodermatosclerosis, dependent peripheral oedema, dermatitis and/or hyper-pigmentation and (v) female patients of reproductive age having a negative pregnancy test within 1-week of study entry and using adequate birth control methods.

The exclusion criteria were the following: (i) known allergy to the hydrofibre dressing (Aquacel, ConvaTec, Princeton, NJ) or components, (ii) those taking systemic corticosteroids >20 mg/day, (iii) involvement in another experimental drug trial within a month prior to the study, (iv) clinical evidence of infection or cellulitis in or around the ulcer, (v) history of medical non-compliance, (vi) inability to understand the study or provide written informed consent, (vii) pregnancy and (viii) a presence of peripheral arterial insufficiency, uncontrolled congestive heart failure (CHF), vasculitis, uncontrolled diabetes mellitus or severe contact dermatitis.

This was an investigator-initiated, single-centre, non-randomised, open-label, pilot study examining an effective way to apply compression in the home setting in patients with VLUs requiring change to the ulcer primary dressing twice daily. The study was designed to have a screening visit, followed by a 1- to 2-week run, 8-week open-label treatment phase and 1 follow-up visit 4 weeks after completion of the study. A total of 11 clinical visits were conducted over a 14-week period.

Study subjects were treated with the following topical treatment regimen: a primary dressing, which consisted of a hydrofibre (Aquacel) impregnated with normal saline, an absorbent pad (Allevyn, Smith and Nephew, London, UK) as a secondary dressing, and a gauze wrap to stabilise the secondary dressing (which is wrapped from the bottom of the toes to just below the knees). This is followed by the application of compression using two layers of a latex-free tubular elastic bandage (SurgiGrip, Derma Sciences, Princeton, NJ; Figure 2). The amount of exudate from a wound is dynamic and different for every

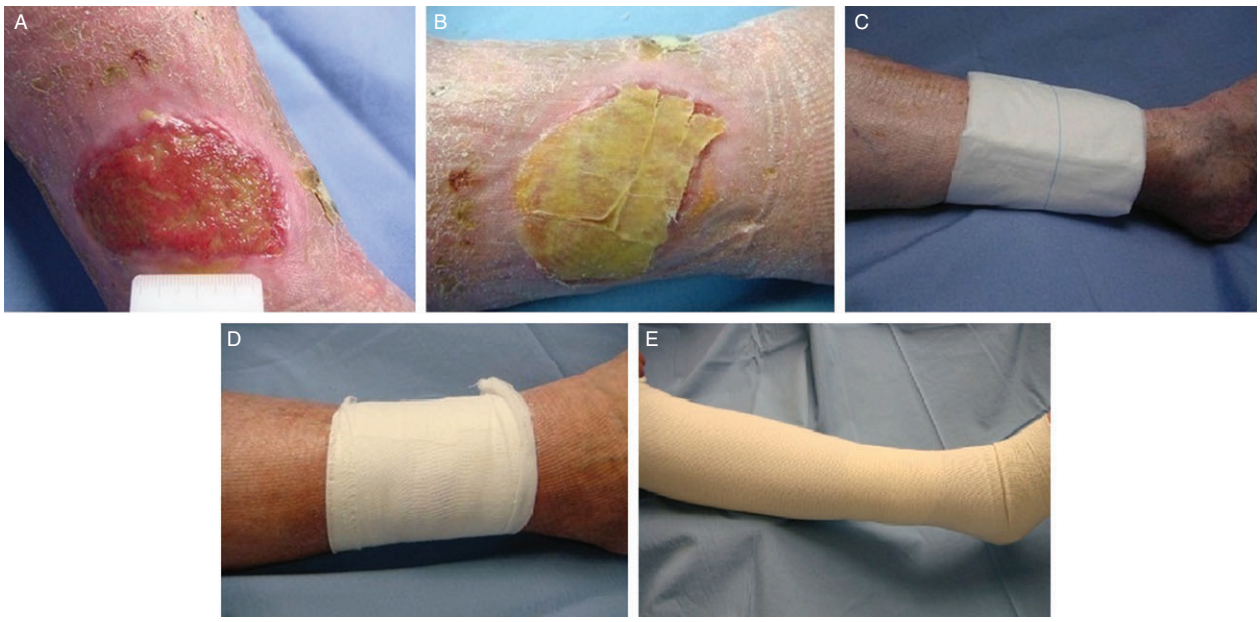

Figure 2 Pictorial description of study dressing. (A) Venous leg ulcer (VLU) with no dressing. (B) Calcium alginate primary dressing impregnated with normal saline. (C) Absorbent pad placed over primary dressing (secondary dressing). (D) Gauze wrap used to stabilise the secondary dressing. (E) Latex-free tubular elastic stocking.

Table 1 Patient demographics, wound area, wound-healing rates and ABI*

Subject	Age (years)	Sex	Site	Duration of time (months)	Screening day area (cm^2)	Day 1 area (cm^2)	WK 2 area (cm^2)	WK 8 area (cm^2)	WK 12 area (cm^2)	HR WK4 mm/wk	HR WK8 mm/wk	ABPI/ ABI
1	56	M	LLML	8	16·6	9·9	6·1	4·6	5·9	0·77	0·39	1·05
2	65	M	LLLL	192	4·2	2·2	0·8	H	H	0·64	0·68	1·04
3	61	M	RLLL	28	30·7	23·3	28·1	16·9	9·1	0·04	0·53	0·96
4	78	F	LLLL	14	6·2	4·7	3·4	†	†	0·99	†	1·07
5	54	F	LLAL	13	6·5	5·3	2·7	H	0·7	1·49	1·51	1·28
6	58	M	RLLL	144	20	16·4	12·5	9·3	6·1	0·53	0·59	1·05
7	47	F	LLLL	240	10·8	9·5	6·4	4·8	NA	0·51	0·49	0·84

ABPI/ABI, ankle-brachial pressure index/ankle-brachial index; F, female; H, healed; HR, wound-healing rate (mean adjusted Gilman); LLML, left lower medial leg; LLLL, left lower lateral leg; LLPL, left lower posterior leg; LLAL, left lower anterior leg; mm/wk; millimetre/week; M, male; NA, not applicable; RLML, right lower medial leg; RLLL, right lower lateral leg; RLPL, right lower posterior leg; RLAL, right lower anterior leg; WK week.
*This table depicts the patient demographics and features of their wounds such as location, duration of wound in months prior to enrolment in study, wound area, wound-healing rate and ABI at screening day.
†Indicates that patient was discontinued from the study after week 4

patient. We believe that a moist wound environment is optimal for wound healing. Therefore, our standard of practice is to impregnate the hydrofibre dressing with normal saline prior to application on wounds. This ensures that the hydrofibre is not drying the wound bed, and is maintaining a moist wound environment while still absorbing the exudate.

At the screening visit, a complete medical history and Doppler studies were performed to determine the ABI. The following were carried out at the screening visit and all additional study visits: computerised ulcer planimetry, obtaining the history of concomitant medications, evaluation of adverse events, cleansing of the wound, wound photographs and wound evaluation.

After all the screening tests and evaluations were performed, a 1- to 2-week run-in phase took place in which results from the screening visit were analysed. Following the run-in phase, subjects who met the inclusion criteria for the study began the treatment phase. On day 1 of the study, subjects were given wound supplies and dressings for a week and instructed on how to change their dressings at home. They were then seen weekly for 8 weeks and 1 month later for a follow-up visit. Interim visits were scheduled in the event of a follow-up for an adverse event. Subjects were withdrawn from the study if they were non-compliant with dressing changes, intolerant to the primary or secondary dressing, intolerant to compression, if they developed an infection or if the principal investigator believed it was in their best interest. As per protocol, subjects were followed up for any type of adverse event, including irritation from wound dressing, infection, etc.

The data collected from these weekly visits, for example, digital planimetry, were used to determine chronic wound-healing rates (HRs, Gilman formula) (19). Wound healing was calculated using two methods; digital planimetry and Image J. Digital planimetry was accomplished by tracing the wounds with Visitrak (a Smith and Nephew product). The wound tracings were then scanned onto a computer and the Image J program was used to determine the area and perimeter of the wound. The program, image J, is available from the National Institute of Health; website http://www.rsbweb.nih.gov/ij. This program analysed planimetry data to facilitate calculation of the overall healing rates with the Gilman formula (19). In this formula, the healing rate $= [(A1 - A2)/\{(P1 + P2)/2\}]/(T2 - T1)$, where A is the area in square centimetres (cm^2), P is the perimeter in centimetres and T the time in weeks. The formula is accepted and used as a practical way to quickly gauge healing with documented perimeter movement towards the centre of the wound. When data was reviewed retrospectively, it became critical to account for healing rate instability and the mean adjusted Gilman formula was derived (20). For data analysis in this study, the mean adjusted Gilman formula was used to calculate the HR.

Results

Overall, seven subjects were enroled in this study and six subjects completed it. One subject was discontinued from the study following non-compliance with the primary dressing. One subject missed the week 12 follow-up visit. There were no screening failures. The patient group comprised four men and three women, with a mean age at enrolment of 60 years (range: 47–78). Baseline wounds had a mean area of 13·28 cm^2 (range: 2·2–30·7 cm^2). The wounds were present for a mean of 91·2 months (range: 8–240 months; Table 1).

The primary endpoint for the study was increased wound healing rate (mm/week) with a secondary endpoint of complete wound closure. We have previously found a wound healing rate of 0·75 mm/week to be 80% sensitive and specific for predicting ultimate wound closure by 4 weeks. A wound healing rate <0·7 mm/week indicates that the wound is not healing optimally and that a change in therapy should be considered (21).

The average wound area at the screening visit for the six subjects who completed all 8-week follow-up visits was 14·8 cm^2. The percentage of decrease in wound area from the screening visit to week 8 was $71 \pm 9{\cdot}8\%$. From screening visit to week 12 there was a $79 \pm 6{\cdot}2\%$ decrease in wound area (Figure 3). For example, the third subject's wound area at screening was 30·7 cm^2, by week 12, the area of the wound

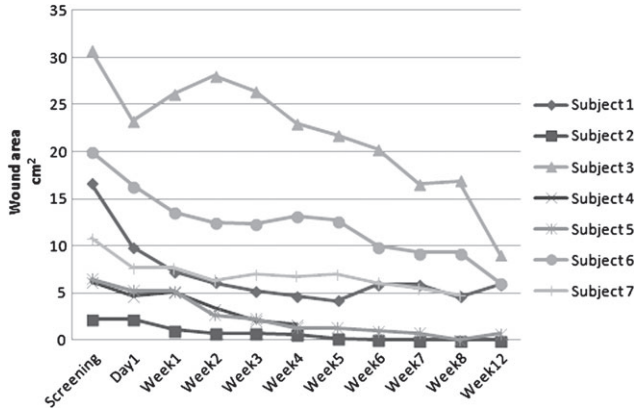

Figure 3 Wound area by study visit for each study subject. Wound area progression for each study patient per visit. Subject 4 was withdrawn from the study after week 4. Subject 7 did not return for the week 12 visit.

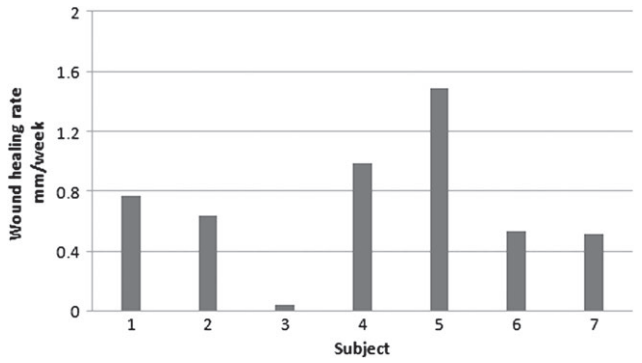

Figure 4 Wound-healing rate at week 4. Calculated using the mean adjusted Gilman formula. Three of seven patients had a wound-healing rate >0·75 mm/week. All seven subjects had a positive wound-healing rate. The average wound-healing rate was 0·71 ± 0·16 mm/week.

measured 9·1 cm^2 (Table 1), which is approximately a 70% improvement from baseline (Figure 3).

By using the mean adjusted Gilman's equation, the wound size was measured and compared using the most previous visit (20). The average HR calculated at week 4 and week 8 for all subjects was 0·71 ± 0·16 and 0·69 ± 0·17 mm/week, respectively. At week 4, three of the subjects had HR >0·75 mm/week. All seven subjects had positive HR at week 4. All active subjects at week 8 had positive HR (Figures 4 and 5).

With regard to our secondary study outcome, two of seven subjects achieved complete wound closure by week 8 (Figures 6 and 7). One of these subject's ulcers had not healed in 192 months (Figure 6). This study subject failed numerous other treatments including standard compression and bioengineered skin. It is important to note that the average ulcer duration for patients in our trial was over 60 months, yet we achieved complete wound closure in two of the subjects in less than 10 weeks. In one of the subjects with healed wound, the wound reopened slightly (0·7 cm^2) by the week 12 follow-up, and it is unclear why it reopened.

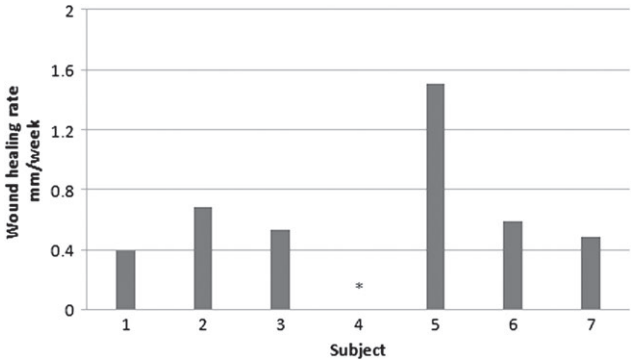

Figure 5 Wound-healing rate at week 8. Calculated by the mean adjusted Gilman formula. One study subject had a wound-healing rate >0·75 mm/week. All active subjects had positive wound-healing rates. The average wound-healing rate was 0·69 ± 0·17 mm/week.

None of the subjects developed additional ulcers or clinically worsening inflammation while using the latex-free tubular elastic bandage. All of the subjects tolerated this form of compression well. In addition, no adverse effects such as contact dermatitis resulted from the primary hydrofibre dressing or secondary dressing used in the study.

Discussion

The standard of care for venous ulcer treatment includes the use of compression therapy to reverse the effects of venous hypertension and the use of a dressing to maintain a moist wound-healing environment (22). Although all compression bandages are designed to improve venous return, there are many different types and factors that need to be considered when choosing the best option for patients. Compression bandaging systems vary by the following factors: construction (knitted and woven), components (elastic and non-elastic), performance (long-stretch and short-stretch) and layers (single-layer and multiple-layer) (23). They are classified into three groups based on the amount of pressure supplied at the ankle in mm Hg: classes I, II, and III. Class III stockings supply 40 mm Hg or higher and are further subdivided based on the amount of pressure they produce (24). The selection of compression type depends on many factors including the ease of use and application, patient compliance and acceptability for both the healthgiver (doctors and nurses) and patient, amount of pressure supplied, and cost (25). Four-layer compression bandage therapy provides a high compression level of 40 mmHg and good healing rates (25). However, these bandages can be very uncomfortable to patients owing to their bulky nature and can lead to non-compliance (25). In addition, these types of bandages take a great deal of time and effort to apply, and must be applied by a trained professional. They are also much more costly compared with compression stockings. This is not only due to the cost of the dressing itself, but also the labour required including physician and nurse time (26). A Cochrane meta-analysis of 39 randomised controlled studies made the following conclusions: compression bandages with an elastic component are more effective than those of inelastic constituents, application of two-layer stockings appears to be

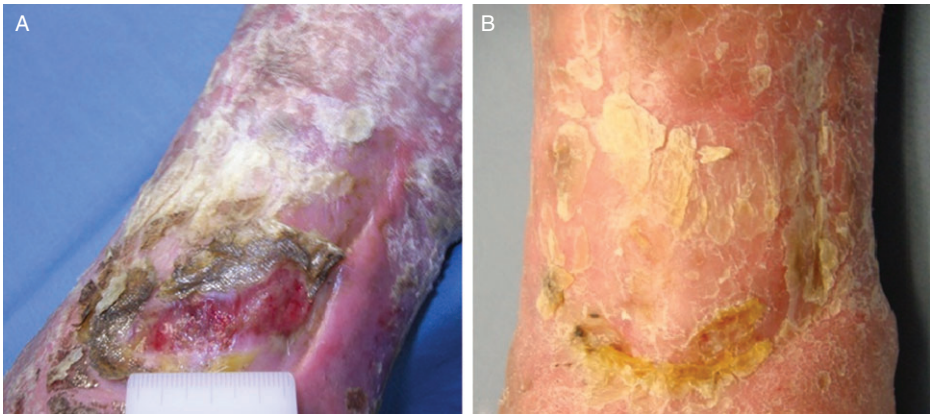

Figure 6 Representative image of subject 2. (A) Screening visit photograph of venous leg ulcer (VLU). (B) Week 8 visit. The wound has healed. Their ulcer was present for 192 months prior to enrolment.

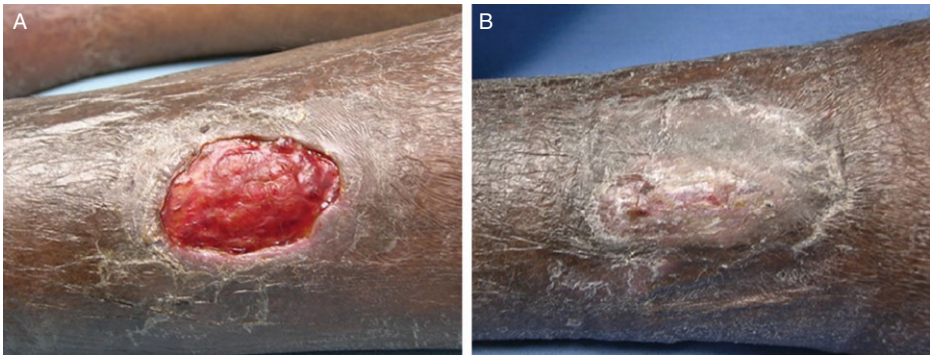

Figure 7 Representative image of subject 5. (A) Screening visit photograph of venous leg ulcer (VLU). (B) Week 8 visit. The wound has healed. The ulcer was present for 13 months prior to enrolment.

more effective than a single layer, and two-component bandage systems appear to perform as well as four-layer bandage systems in terms of healing (27).

In our patient population we observed that patients were non-compliant with four-layer compression bandages and non-elastic stockings such as the Unna boot. It has been previously reported that there are many advantages to the use of elastic stockings as opposed to multi-layer compression bandages. They are much easier for patients to apply at home, allow the use of ordinary shoes, bathing, and are much more comfortable. These factors should improve patient compliance and their quality of life (28). In addition, this simplified compression regimen is much cheaper and the patients can make far less office visits (28). This was a small, short-term study to introduce the use of two layers of a latex-free tubular elastic bandage as a compromise to other forms of compression dressings that are not well tolerated by some patients. The results of this study were meant to be taken as 'proof of principle'. Admittedly, the two layer tubular compression bandages reported here represent a compromise in terms of delivering an ideal compression to the leg. The advantage of applying double compression has also been previously reported in the literature. A study by Ham *et al.* showed that doubling compression on compression hosiery increased measured compression from 10 mm Hg to 25–35 mmHg. The patients in this study did not report increased discomfort with the addition of the second stocking (29). For this compression strategy to be fully implemented, a study would need to be implemented, requiring many more patients and arms to the study.

As previously reported, HR $<0{\cdot}7$ mm/week indicates that the wound is not healing optimally and that a change in therapy should be considered. Our results show that by week 4, the average HR was $0{\cdot}71 \pm 0{\cdot}16$ mm/week and by week 8 the average HR was $0{\cdot}68 \pm 0{\cdot}17$ mm/week. Recent review of the literature has shown that two-component bandage systems appear to perform as well as the four-layer bandage system (27). Therefore, it is important to remember that some compression in patients with chronic VLUs is better than no compression. On the basis of our preliminary results, two layer latex-free tubular elastic compression stocking lead to acceptable HRs, substantial decrease in wound area after 8 weeks of compression, and can lead to wound closure. Therefore, two layer latex tubular elastic compression is a good compromise in patients with chronic VLUs intolerant of high compression stockings.

Compression is only one piece in the complex process required to treat VLUs (30). Creating the optimal wound environment with a primary dressing is of great importance. A major breakthrough in the management of chronic wounds

was the recognition that a moist environment is critical for wound healing (18). Moisture retentive wound dressings stimulate collagen synthesis, promote angiogenesis, accelerate reepithelialisation, and may decrease pain (18). Moist occlusive dressings actually decrease wound infection rates (18).

This trial was designed to help choose a form of compression that would be easy for our patients to change, at home, twice daily, and yet be capable of delivering enough pressure to help healing of their wounds. There is a need for frequent dressing changes because of the exudative nature of many of these wounds. If chronic wound fluid is left to accumulate the surrounding area can become macerated which can lead to increase in infection rates and further deterioration of the wound. Chronic wound fluid contains cytokines and matrix metalloproteinases (MMPs) production, which can adversely affect the function of resident cells (18). Therefore, we decided on the moist hydrofibre as a primary dressing to be changed twice daily. They require moisture to function and are highly absorbent (can absorb approximately 20 times their weight) (22). The form of compression we chose was two layers of latex-free tubular elastic stocking because this type of compression allows for daily inspection of wounds, dressing changes at home, flexibility in the context of clinical trials and is a compromise for patients who are intolerant to compression dressings. As our results indicate, the wound area decreased substantially in all subjects, HRs were optimal, and two subjects obtained wound closure after 8 weeks of compression with two layers of compression bandage. In this pilot study, it appears that latex-free tubular elastic bandages can be safely used as a compromise in patients with VLUs that require frequent dressing changes. For this compression strategy to be fully implemented, a study would need to be implemented, requiring many more patients and arms to the study.

Acknowledgement

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