Randomized trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration

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To compare a four-layer bandage system with a two-layer system in the management of chronic venous leg ulceration, a prospective randomized open parallel groups trial was undertaken. In total, 112 patients newly presenting to leg ulcer services with chronic leg ulceration, screened to exclude the presence of arterial disease (ankle brachial pressure index <0.8) and causes of ulceration other than venous disease, were entered into the trial. Patients were randomized to receive either four-layer (Profore™) or two-layer (Surepress™) high-compression elastic bandage systems. In all, 109 out of 112 patients had at least one follow-up. After 24 weeks, 50 out of 57 (88%) patients randomized to the four-layer bandage system with follow-up had ulcer closure (full epithelialization) compared with 40 out of 52 (77%) on the two-layer bandage, hazard ratio = 1.18 (95% confidence interval 0.69–2.02), $p = 0.55$. After 12 weeks, 40 out of 57 (70%) patients randomized to the four-layer bandage system with follow-up had ulcer closure compared with 30 out of 52 (58%) on the two-layer bandage, odds ratio = 4.23 (95% confidence interval 1.29–13.86), $p = 0.02$. Withdrawal rates were significantly greater on the two-layer bandage (30 out of 54; 56%) compared with the four-layer bandage system (8 out of 58; 14%), $p < 0.001$, and the number of patients with at least one device-related adverse incident was significantly greater on the two-layer bandaging system (15 out of 54; 28%) compared with four-layer bandaging (5 out of 54; 9%), $p = 0.01$. The higher mean cost of treatment in the two-layer bandaging system arm over 24 weeks ($1374 (£916) vs. $1314 (£876)) was explained by the increased mean number of bandage changes (1.5 vs. 1.1 per week) with the two-layer system. In conclusion, the four-layer bandage offers advantages over the two-layer bandage in terms of reduced withdrawal from treatment, fewer adverse incidents, and lower treatment cost. **(WOUND REP REG 2003;11:166–171)**

Leg ulceration is a common source of morbidity in the elderly, affecting approximately 100,000 people with active ulceration in the United Kingdom and 400,000 in the United States.[1,2] While it is known that substantial resources are consumed treating these patients, until recently there has been little evidence of the effectiveness of this care outside specialist units. Although most patients were treated by community nurses, quality of treatment was patchy, with high costs of care and poor patient outcomes.[3–5] The introduction of guidelines has led to many services adopting an evidence-based approach to care,[6–8] yet there are many treatments available for chronic leg ulcers, few of which have been evaluated in appropriately sized

ABPI	Ankle brachial pressure index
ITT	Intention-to-treat
2LB	Two-layer bandaging system
4LB	Four-layer bandaging system

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randomized controlled trials. Those trials that have been undertaken have taken place in specialist acute units. In the United Kingdom in the late 1980s, specialist community leg ulcer clinics were developed to deliver appropriate assessment and treatment to the majority of patients being treated by community nursing staff. Included in this model was an objective test of ankle brachial pressure index (ABPI) previously rarely performed in community settings, high-compression bandaging in patients with venous ulceration, and appropriate referral for other causes of ulceration.[3] With the development of similar services throughout the United Kingdom, this offers us an opportunity to evaluate treatments for chronic ulceration in community populations by health professionals who normally treat these patients.

There is consensus on the need for high-compression therapy in patients with venous ulceration. However, there is a lack of consensus on the exact mode of delivery of compression to the limb to aid ulcer closure. As an example of this lack of consensus, there is still extensive debate about the relative merits of short stretch or inelastic bandaging in relation to elastic compression. In the United States and United Kingdom, most clinicians use elastic compression, although again there is still no consensus on the exact mode of elastic compression delivery. The aim of this trial was to compare two systems of high-compression elastic bandaging, the four-layer bandage system (4LB) and the two-layer bandage system (2LB), in the management of chronic venous ulceration, and to record secondary factors such as withdrawals from treatment, adverse events, and cost of care.

MATERIALS AND METHODS

This was a five-center prospective randomized stratified parallel groups open trial comparing 4LB (Profore™, Smith & Nephew Healthcare, Ltd., Hull, UK) with 2LB (Surepress™, ConvaTec, Uxbridge, UK) in the management of chronic venous leg ulceration. Both bandage systems are designed to achieve 40–45 mmHg pressure at the ankle sustained for at least 1 week.[9] Randomization took place following consent and eligibility checks, by means of sequential numbers on a randomization list that was stratified for ulcer size. At each center there were two randomization lists, one for patients with a total area of ulceration on the reference limb of less or equal to 10 cm^2 and one for total area greater than 10 cm^2. Separate randomization lists were used in all centers, providing the stratification within the trial. Initial work on the original 4LB system had shown that patients with large or small ankle circumferences experienced different levels of compression in line with La Place's Law;[9] hence only patients with limbs >18 cm were entered into the trial. Ankle circumference was measured at the initial assessment and following 1 week of bandaging to allow for reduction in circumference following compression.

Exclusion criteria

This study was approved by the local ethics committees from the first four centers. With the later addition of a further center we also gained consent from a multicenter ethics committee (MREC). Patients newly presenting for treatment were considered for the trial provided that they were at least 18 years of age. Both genders were included, all suitable males, and females providing that they were not pregnant. Patients were considered to have chronic venous ulceration if they had signs and symptoms of venous disease and an ABPI of greater or equal to 0.8. A minimum ulcer duration was set at 2 weeks with no upper limit. The patient was provided with an information sheet and encouraged to discuss any questions or uncertainties with the research nurse. Following this consultation, the patient was asked to provide written informed consent. Causes of ulceration other than venous disease based on their clinical presentation were also excluded, as were patients with active cellulitis who were receiving systemic antibiotics. Patients who had previously entered the trial were not re-entered if they developed a new area of ulceration.

Reference limb

Patients with bilateral ulceration were randomized to one bandage system only (assuming that this was clinically appropriate). For this study, the reference limb was the limb with the largest estimated total area of ulceration. Note was also made of the contralateral limb to determine whether closure was also achieved in this limb, although this was not included in the formal analysis of the trial results.

Randomization was performed on a ratio of 1 : 1 between 4LB and 2LB systems after being stratified for estimated ulcer area. The nurses making the assessment were asked to make a subjective judgment by comparing the size of the ulcer with a template of 10 cm^2. This allowed for stratification prior to the formal measurement of ulcer area.

Participants

All patients newly presenting to community leg ulcer clinics were considered for entry into the trial. A standard procedure was used to screen patients for inclusion, with the inclusion criteria met before the patient was randomized and treatment initiated.

The duration of the trial was 24 weeks or until closure of all areas of ulceration on the reference limb. In cases where the original ulcer closed but a new area developed while the original ulcer was still present, the limb was considered to be open until this new area of ulceration had closed. If patients withdrew from their randomized treatment, they continued to be followed up to the 24-week limit.

Treatment regimen

The standard regimen was to wash the limb using an emollient dissolved in tap water, debride the wound, and apply a simple hypoallergenic cream to hydrate the skin. A simple nonadherent dressing was applied (Tricotex™ Smith & Nephew Healthcare, Ltd., Hull, UK) and patients were then bandaged using the randomized bandage system. All bandages were applied according to the manufacturers' instructions. Re-dressing and rebandaging was undertaken weekly unless specifically required more frequently.

Sample size

The original study sample size was estimated at 120 patients (60 patients in each group). The trial was designed to detect a difference in absolute closure rates of 25%, with an 80% power and level of significance of 5%. Due to the logistical difficulties in ascertaining suitable patients during the time frame of the trial, a cutoff point of December 31, 1999, was chosen for last patient entered. The inclusion of 109 patients in the intention-to-treat (ITT) population reduced the power of the study from 80% to 74% assuming that 54 patients were in each treatment group.

Outcome measures

The principal end point of this trial was time to complete closure of the ulcerated limb up to 24 weeks from trial entry. When the ulcer was closed the patient was prescribed compression stockings and returned to the regular follow-up clinics. The principal analysis was by proportional hazards survival analysis, which was performed on an ITT basis. Baseline measures were assessed for relationships with ulcer closure.

Patients remained in the trial until complete ulcer closure or until the patient had received 24 weeks of treatment. Patients who withdrew from the randomized treatment were allocated to an alternative treatment, and continued to be followed up until closure or until they had reached 24 weeks. The analysis based on ITT meant that patients remained in their original randomized groups irrespective of subsequent treatments applied. All adverse incidents were detailed on an adverse incident form and reasons for withdrawal were ascertained whenever possible.

RESULTS

A total of 112 patients were entered into the trial, of which 109 had at least 1 week of follow-up, making up the ITT population. Fifty-seven patients were randomized to 4LB and 52 to 2LB. Baseline characteristics are given in Table 1, which shows that the two groups were well matched for age, sex, medical history, and ulcer characteristics. Recording was made of drugs that could have influenced healing in this patient group (steroids, oxpentifylline, oxerutins, and long-term NSAIDs). In the trial only one patient randomized to Profore™ was on steroids, and none of the other drugs were used during this trial.

Ulcer closure

On the basis of ITT there was no evidence of a difference between groups in either the proportion closed at 24 weeks or in the mean time to ulcer closure. Over the 24 weeks of treatment 50 out of 57 (88%) patients randomized to 4LB and 40 out of 52 (77%) randomized to 2LB experienced complete closure. After 12 weeks of treatment 40 (70%) patients on 4LB and 30 (58%) on 2LB had closure (odds ratio = 4.23, 95% confidence interval 1.29–13.86, $p = 0.02$). When analyzed over the 24 weeks

Table 1. Baseline patient characteristics in 109 patients with evaluable follow-up

	Bandage type	
Parameter	**4LB**	**2LB**
n	57	52
Sex		
Male	24 (42%)	23 (44%)
Female	33 (58%)	29 (56%)
Age-mean (SD)	70.2 (14.4)	71.8 (11.3)
Ulcer size		
≤10 cm^2	48 (84%)	45 (87%)
>10 cm^2	9 (16%)	7 (13%)
Ulcer duration Median (range) weeks	6 (2–104)	6 (2–1040)
Previous ulceration	24 (42%)	24 (46%)
ABPI		
Median (range)	1.10 (0.70–1.80)	1.16 (0.88–1.42)
Hypertension	24 (42%)	15 (29%)
Deep vein thrombosis	4 (7%)	4 (8%)
Diabetes	1 (2%)	4 (8%)
Insulin	0 (0)	0 (0)
Oral	1 (100%)	3 (75%)
Diet	0 (0)	1 (25%)
Rheumatoid arthritis	5 (9%)	3 (6%)
Mobility		
Chair/bed	0 (0)	0 (0)
Walk with aid	17 (30%)	7 (13%)
Walk freely	40 (70%)	45 (87%)
Limb mobility		
Fully mobile	45 (79%)	43 (83%)
Limited	12 (21%)	7 (13%)
Fixed	0 (0)	2 (4%)

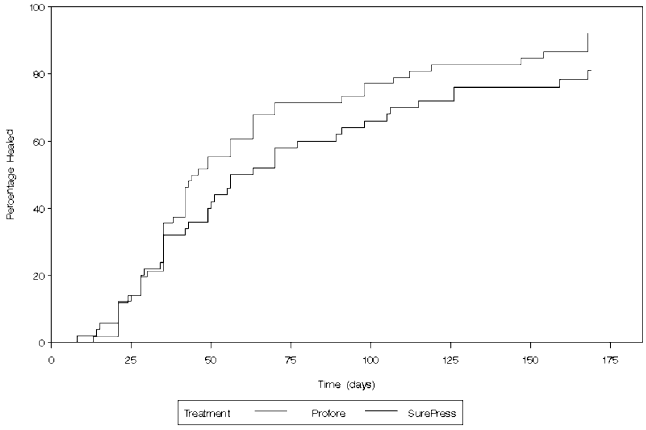

FIGURE 1. Time to healing by treatment group using Kaplan-Meier plot.

using the Cox proportional hazards model, the hazard ratio for complete closure was 1.18 (0.69–2.02), $p = 0.55$ (Figure 1). Forty-seven (82%) of patients had complete ulcer closure on 4LB by treatment discontinuation compared with 24 (46%) on 2LB (difference = 36%, 95% confidence interval 18–55%, $p < 0.001$). The closure curves were similar over the first 6 weeks; thereafter there appeared to be a benefit in patients randomized to Profore™. It is difficult to speculate on the different shapes of the curves because trials of this nature must have substantial follow-up for any differences in closure to become apparent.

Treatment discontinuation

Table 2 gives the treatment discontinuation during the follow-up in the 112 patients. It shows that eight (14%) on 4LB withdrew from their randomized bandage treatment compared with 30 (56%) on 2LB. Forty-seven (81%) of patients had closure on 4LB by study discontinuation, compared with 24 (44%) on 2LB ($p < 0.001$). In all, 26 patients experienced 29 adverse incidents, seven (8 incidents) on 4LB and 19 (21 incidents) on 2LB (Table 3).

Table 2. Outcome at 24 weeks in 112 randomized patients

	Bandage type	
Parameter	**4LB**	**2LB**
n	58	54
Ulcer closure	47 (81%)	24 (44%)
Open at 24 weeks	3 (5%)	0 (0%)
Withdrawal	8 (14%)	30 (56%)
Reasons		
Patient request	2	6
Adverse incident	3	11
Lack of response	0	1
Other	3	12

Table 3. Adverse incidents

	Bandage type	
Parameter	**4LB**	**2LB**
Patients	7 (12%)	19 (35%)
Incidents	8	21
Duration of incident (days)	7 (3–31)	5 (1–14)
Device-related	6 (75%)	17 (81%)
Severe event	2 (25%)	2 (10%)
Result		
Improved	6 (86%)	16 (84%)
Same	1 (14%)	1 (5%)
Deteriorated	0	2 (11%)
Device related adverse incidents (all causes given)		
n	6	17
Irritation	2	4
Pain/ discomfort	1	7
Slippage	1	9
Tissue breakdown	1	3
Excessive pressure	2	4

Five (9%) patients on 4LB experienced device-related incidents compared with 15 (28%) of patients on 2LB ($p = 0.01$). Two patients on 4LB experienced severe adverse events (non-device-related) as opposed to two patients on 2LB (one device-related).

In this study, patients withdrawn from one arm of the trial were switched to an alternative treatment. The results of an analysis by ITT may be difficult to interpret in this situation, particularly when there is a difference in the rate of withdrawals between the two groups. Figure 2 shows the progression of 109 patients in the trial who completed at least one follow-up visit.

In this group, 28 of the 52 patients (54%) randomized to receive 2LB were withdrawn, compared with seven patients (12%) randomized to 4LB ($p < 0.001$). The mean time to withdrawal was 32 days (4LB) and 21 days (2LB). Of the 28 patients withdrawn from 2LB, 16 (57%) had ulcer

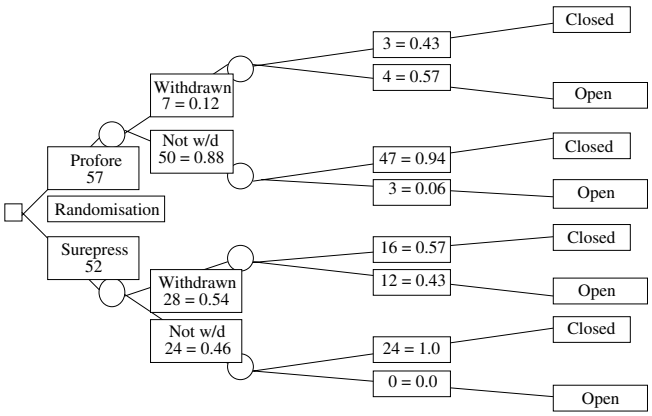

FIGURE 2. Flow of patients into different randomized treatments and subsequent healing outcome. The numbers in each box indicate the total number, and proportion of, patients in each group.

Table 4. Expected costs of treatment@

	4LB		2LB	
Treatment costs	**Itemized**	**Subtotal**	**Itemized**	**Subtotal**
Dressing change – clinic				
Clinic cost*	$102.00 (£68.00)		$102.00 (£68.00)	
Dressings**	$11.91 (£7.94)		$5.42 (£3.61)	
Other materials***	$2.15 (£1.43)	$116.06 (£77.37)	$2.15 (£1.43)	$109.56 (£73.04)
Dressing change – home				
Nurse time*	$24.00 (£16.00)		$24.00 (£16.00)	
Dressings**	$11.91 (£7.94)		$5.42 (£3.61)	
Other materials***	$2.15 (£1.43)	$38.06 (£25.37)	$2.15 (£1.43)	$31.56 (£21.04)
Frequency of dressing changes per week	1.1		1.5	
Mean cost per week	$119.87 (£79.91)		$125.34 (£83.56)	
Proportion closed at 24 weeks	0.825		0.825	
Mean time to closure	8.2 weeks		8.2 weeks	
Mean cost per patient over 24 weeks	$1314 (£876)		$1374 (£916)	

* NHS mean cost per outpatient attendance (generic specialties), 1999–2000. Community nurse home visit, including travel costs, 1999–2000 from Netten and Curtis.[12]
** 4LB (Profore) and 2LB (SurePress) prices from the UK Drug Tariff, July 2000.[13]
*** Dressing pack, gloves, emollient, 50/50 cream, Tricotex. Prices from UK Drug Tariff July 2000[13] and British National Formulary, September 2000.[14]
@ All costs based on year 2000 pricing.

closure at 24 weeks. Similarly, of the seven patients withdrawn from 4LB, three experienced closure (43%). There was no evidence of a significant difference in the rates of closure between these groups. Of the 24 patients randomized to 2LB who remained on the trial treatment until the end of the study, all closed. Ninety-four percent of patients who received 4LB throughout the trial were closed.

The evidence of patient outcomes is consistent with the hypothesis that there is no difference in the rate of ulcer closure or the time to closure for patients managed with 4LB or with 2LB. However, there is evidence of a significantly higher rate of withdrawal of patients randomized to 2LB.

Treatment costs

The expected cost of treatment is a function of the cost per dressing change, the frequency of changes, and the duration of treatment. The cost per dressing change depends on whether the change takes place at a specialist clinic or in the patient's home. The mean cost per dressing change for patients treated at a clinic visit or by a nurse in the patient's home are shown in Table 4. These are national average National Health Service costs, not specific to any particular trial center. Costs are higher with 4LB than with 2LB because of the higher unit cost of 4LB.

There was evidence from the trial of a significant difference in the mean number of weekly dressing changes for patients in the two treatment groups. The mean number of changes in the 4LB group was 1.1 per week, compared with 1.5 per week in the 2LB group ($p = 0.0002$). Patients in the trial attended a specialist clinic once a week and dressing changes between visits were carried out by a nurse in the patient's home. Despite the higher cost of 4LB, the cost per week was higher for patients in the 2LB group because of the higher frequency of dressing changes. Mean costs per week were $119.87 (£79.91) on 4LB and $125.34 (£83.56) on 2LB (Table 4).

By applying these weekly costs to the actual health state profile of each patient in the trial it would be possible to estimate the total costs of treatment for patients in the two arms of the trial. However, this will overstate the cost saving associated with 4LB. Because there is no evidence of a statistically significant difference in the duration of treatment between the two trial bandages, the costing is based on the assumption that the mean time to closure and the proportion of patients closed at 24 weeks is the same, irrespective of the treatment used. In the cost model the mean time to closure was 8.2 weeks, which was the mean time to closure for patients in the 4LB group. The corresponding figure for 2LB patients was 8.6 weeks. The proportion closed at 24 weeks was 82.5%. Differences in the expected costs over a period of 24 weeks are shown in Table 4.

Over 24 weeks, treatment with 2LB is expected to cost $61.50 (£41) more per patient for the same expected clinical outcome. This difference is driven by the significantly higher number of weekly dressing changes observed in the 2LB group ($p = 0.0002$). No additional costs have been assigned because of the higher rate of withdrawal from 2LB. To the extent that such costs are relevant, the cost advantage of 4LB will be enhanced.

DISCUSSION

This trial was designed to evaluate whether 2LB was associated with improved ulcer closure compared with the

4LB systems. It has shown that based on ITT analysis there is no evidence that either bandage is superior over a 24-week follow-up. However, there was evidence that patients on 4LB were more likely than patients on 2LB to experience ulcer closure within 12 weeks. It has shown that patients tolerated the 4LB better than the 2LB, with significantly fewer withdrawals from treatment, and subsequently, a greater proportion of patients whose ulcers closed while on their randomized treatment. The patients who withdrew were given an alternative treatment. Because those patients who withdrew from the 2LB arm did so at an early stage during follow-up (mean time to withdrawal 14 days), they spent most of the follow-up being treated with alternative bandage systems. The failure to find a difference between groups could be explained by treatments being substituted in these patients. However, the 2LB required an increased number of bandage changes, which leads to a greater overall cost of 2LB despite the higher 4LB unit cost.

The 4LB was originally designed for use in an outpatient environment.[9] However, the Riverside Community Leg Ulcer Project revealed that standardized assessment and treatment using 4LB was associated with high closure rates within the community.[3,4] In the Riverside project, closure was achieved in 69% of venous ulcers after 12 weeks, rising to 83% after 24 weeks. The results of the present trial are similar to these findings, indicating that newly presenting patients can achieve good closure when using the 4LB bandage system. Other trials have shown similar rates using similar entry criteria,[10] although studies on more chronic patients have led to lower healing rates.[11] Much of this difference can be explained by differences in factors such as more chronic, larger ulceration. The present trial has confirmed that the 4LB system is associated with excellent leg ulcer closure rates in patients managed in the community by trained nursing staff. While both systems produce similar closure over 24 weeks of follow-up on ITT analysis, this does not take into account the higher withdrawal of patients from the 2LB arm of the trial. It would appear that 4LB has better tolerability than 2LB in this respect, and a lower cost of treatment.

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