A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers

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Objectives: **We evaluated the effectiveness of pentoxifylline, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandaging for venous ulceration.**

Method: **A factorial randomized controlled trial with 24-week follow-up was conducted in leg ulcer clinics in Scotland with blinded allocation to pentoxifylline (1200 mg) or placebo, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandages. The study enrolled 245 adults with venous ulcers. The main outcome measure was time to complete healing. Secondary outcomes included proportions healed, withdrawals, and adverse events. Analysis was by intention to treat.**

Results: **There was no evidence of interaction between the drug, bandages, and dressings. Pentoxifylline was associated with nonsignificant increased ulcer healing (62% vs 53%; $P = .21$). Four-layer bandages were associated with significantly higher healing rates (67% vs 49%; $P = .009$). There was no difference in healing between knitted viscose and hydrocolloid dressings (58% and 57%; $P = .88$). Cox regression models increased the significance of the pentoxifylline effect (relative risk of healing, 1.4; 95% confidence interval, 1.0 to 2.0).**

Conclusions: **Pentoxifylline increased the proportion healing compared with placebo to the same extent as shown in recent systematic reviews, although this finding was only statistically significant when a secondary adjusted analysis was conducted. Four-layer bandaging produced higher healing rates than single-layer bandaging. There was no difference in time to healing between knitted viscose and hydrocolloid dressings. (J Vasc Surg 2007;45:134-41.)**

Leg ulceration is a chronic, recurring condition affecting about 1% of the adult population in industrialized countries.[1,2] Most ulcers are secondary to venous insufficiency; others are due to arterial insufficiency, diabetes mellitus, rheumatoid arthritis, and connective tissue disorders. The primary functional abnormality in venous ulceration is ambulatory venous hypertension caused by venous reflux or obstruction that gives rise to changes at the tissue level, including white cell trapping, capillary tufting, and pericapillary fibrin cuffs.[3] Externally applied compression, such as bandages, stockings, or pneumatic boots, reduces venous hypertension and promotes healing.[4]

A systematic review has found that compression heals more ulcers than dressings alone.[4] It has not been possible, however, to determine the dose-response relationship between compression levels and healing rates, and whether, for example, multiple layers of bandage are necessary.[4] Four-layer bandaging is widely used but it can be bulky, and we sought to compare it with a single-layered bandage that can supply and sustain high levels of pressure.[5]

Ulcer management includes wound dressings to prevent bandages from adhering to the wound and to provide a moist environment for wound healing.[6] Modern dressings such as hydrocolloids promote moist wound healing by restricting moisture loss from the wound. The role of such semi-occlusive dressings in venous ulcers is unclear, however, because bandages also restrict moisture loss,[7] and a moist wound environment can thus be achieved with a dry dressing. Hydrocolloids cost more and have higher rates of contact sensitivity than simple dressings[8]; therefore, we set out to compare the relative effectiveness of knitted viscose and hydrocolloid dressings.

Another goal was to determine whether adjuvant therapy of sustained release pentoxifylline (oxpentifylline) with compression and dressings would increase healing rates, as four previous trials in 247 people receiving compression did not provide conclusive results,[9-12] and one trial found a statistically significant benefit with pentoxifylline.[10]

A factorial trial design allows examination of the interaction between interventions and comparison of a number of independent interventions with no increase in trial size.

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In this way, we were able to simultaneously undertake three comparisons to answer these questions efficiently and in a manner that allowed for the identification of interactions between elements of treatment.[13]

METHODS

We undertook a 2 × 2 × 2 factorial trial of pentoxifylline, dressings, and bandages for venous and arterial ulcers. The methods and the results of the evaluation of pentoxifylline for 200 simple venous ulcers included in this trial report are described elsewhere.[13,14] In brief, we showed that complete healing occurred in 65 (64%) of 101 patients receiving pentoxifylline and in 52 (53%) of the 99 patients receiving placebo. This difference in the healing rates did not reach statistical significance.

This report reflects the factorial nature of the study design and describes the results for all three interventions for simple and nonsimple venous ulcers and, therefore, reports interactions between treatments, results of the dressing comparison, and results of the bandage comparison, and includes an additional 45 participants and fully reports on adverse events and withdrawals.

Study population. People >18 years old with clinical signs of venous disease (lipodermatosclerosis, varicose eczema, and varicose veins) were considered for the trial if they had been clinically diagnosed as having a venous leg ulcer of at least 1cm in length and 8 weeks' duration. Exclusion criteria were:

- Significant arterial disease (ankle-brachial pressure index <0.8)
- Diabetes mellitus
- Pregnant or lactating women
- Premenopausal women not using contraceptives
- Known concurrent severe illness; for example, myocardial infarction or renal failure
- Sensitivity to methylxanthines or caffeine containing drinks
- Taking warfarin, steroids, oxpentifylline, oxerutins, or naftidrofuryl
- Life expectancy <6 months
- Grossly infected or gangrenous ulcers (eligible after resolution of infection)
- Immobile patients
- Immunosuppression
- Unable or unwilling to provide written, informed consent

Recruitment and randomization. We recruited 245 patients with venous leg ulcers treated in the community or as outpatients from two centers in Scotland. After written informed consent was obtained, sealed, sequentially numbered, opaque envelopes were used to allocate participants to placebo or pentoxifylline, knitted viscose or hydrocolloid dressings, and four-layer or adhesive single-layer bandages. There was no lead-in phase, but patients were recruited from community services with widespread use of high compression. Randomization was stratified by clinical center and simple/nonsimple venous disease using permuted blocks of length 8. The nonsimple group was defined as participants either with seropositive rheumatoid arthritis or in whom venous pathology was not confirmed on examination using hand-held Doppler. In planning the trial, we believed it important not to presume that people with seropositive rheumatoid arthritis would have the same prognosis as people without because they may, for example, have cutaneous vasculitis, skin fragility, and venous disease; hence, we stratified participants by its presence.[15]

Both patients and nurses were aware of the allocated bandage and dressing treatment after assignment. Pentoxifylline or placebo tablets were supplied from the pharmacy in numbered containers; therefore, clinicians and patients were unaware of the allocation to active or placebo tablet.

Intervention. All ulcers were cleansed using tap water and the skin moisturized with arachis or olive oil. Experienced trial nurses renewed dressings and bandages weekly, or more frequently if required.

Drug. Pentoxifylline (oxpentifylline), sustained-release 400-mg tablets, three times daily, or identical placebos.

Dressing. Hydrocolloid dressing (HCD), Granuflex E (ConvaTec UK Ltd), also known as Duoderm CGF, or knitted viscose dressing (KVD) NA (Johnson & Johnson UK Ltd).

Bandages. Either a four-layer bandage or a single-layer adhesive bandage (SLB) was used. The four-layer bandages were applied using the Charing Cross technique.[16] The single-layer bandage was a hydrocolloid lined, woven, elastomeric, adhesive, Ace-type bandage applied in a figure-8 technique from toe to knee.

Data collection. Nurses completed a dressing log at each leg ulcer dressing visit, which recorded whether or not an ulcer was healed, the date of each visit, the condition of the periulcer skin, and any adverse events. Follow-up of all participants continued from randomization to complete ulcer healing or for 24 weeks. The primary end point was time to complete healing of all ulcers on the reference leg. Secondary outcomes included proportion of patients healed at 24 weeks, withdrawals, and adverse events. A healed ulcer was defined as complete epithelial cover in the absence of a scab.

Sample size calculation and statistical analysis. Using a conservative estimate of 40% of ulcers healed at 24 weeks with four-layer bandage or KVD based on previous trials[4] and assuming a 20% absolute increase in ulcers healed would be clinically important, we calculated that at least 200 patients (100 in each of two treatments) would give us 80% power to detect this difference at 24 weeks ($2\alpha = 5\%$).

The primary analysis was by intention to treat, and we reported healing to 6 months for everyone irrespective of compliance with treatment. Those without evidence of healing at the time they were last seen were considered failures at the end of follow-up. Compliance with treatment was assessed as a separate outcome. Our analyses (R. J. P.) compared the proportions with complete healing of all ulcers on the reference leg between individuals randomized to pentoxifylline or placebo, either bandage system, or either dressing.

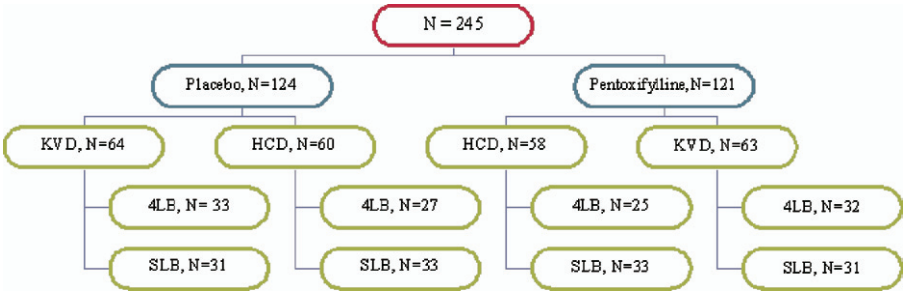


Fig 1. Allocation to trial treatments; drug, dressing, and bandage. *KVD,* knitted viscose dressing; *HCD,* Hydrocolloid dressing; *4LB,* four-layer bandage; *SLB,* single-layer bandage.

Table I. Baseline characteristics in the trial groups by drug, dressing and bandage allocation*

	Drug†			*Dressing*†			*Bandage*†		
Intervention	*Pentoxifylline*	*Placebo*	P‡	*Knitted viscose*	*Hydrocolloid*	P‡	*Single layer*	*Four-layer*	P‡
Center A/B	50/71	52/72	>.99	52/66	50/77	.54	53/75	49/68	>.99
Sex: male/ female	36/85	44/80	.41	37/81	43/84	.78	39/89	41/76	.53
Walks freely/ not	43/78	42/82	.89	38/80	47/80	.51	49/79	36/81	.27
Simple venous/ not simple	101/20	99/25	.57	98/20	102/25	.70	103/25	97/20	.74
Age (years)	71.0 ± 11.4 73 (35-91)	69.0 ± 11.3 69 (34-93)	.10	69.7 ± 10.6 71 (35-93)	70.3 ± 12.0 71 (34-92)	.33	71.5 ± 10.3 73 (46-93)	68.3 ± 12.2 68 (34-91)	.05
Weight (kg)	78.7 ± 18.6 76 (40-148)	77.9 ± 22.6 72 (41-174)	.31	78.1 ± 20.3 74 (40-150)	78.5 ± 21.1 75 (41-174)	.79	76.2 ± 18.9 74 (40-154)	80.5 ± 22.3 76 (42-174)	.21
Reference ulcer Area (mm^2)	1005 ± 2609 378 (50-26311)	705 ± 1178 395 (54-10118)	.71	910 ± 2600 359 (63-26311)	794 ± 1210 404 (50-10118)	.28	1025 ± 2637 385 (54-26311)	661 ± 879 393 (50-5560)	.85
Duration (months)	14.3 ± 28.8 5.0 (2-204)	11.7 ± 26.0 4.0 (2-240)	.35	14.8 ± 29.8 6.5 (2-240)	11.3 ± 25.0 4.0 (2-204)	.17	11.1 ± 17.3 5.0 (2-96)	15.1 ± 35.2 5.0 (2-240)	.78
Episodes since first ulcer	2.5 ± 2.5 2 (1-15)	3.3 ± 3.9 2 (1-20)	.09	2.8 ± 3.3 2 (1-20)	3.0 ± 3.3 2 (1-20)	.79	2.9 ± 3.2 2 (1-20)	2.9 ± 3.5 2 (1-20)	.53
Years since first ulcer	9.2 ± 12.0 3 (0-52)	10.0 ± 12.1 5 (0-56)	.42	9.1 ± 10.5 5 (0-39)	10.0 ± 13.3 3 (0-56)	.44	9.5 ± 11.9 5 (0-56)	9.7 ± 12.2 4 (0-52)	.74

*Significance tests applied to a comparison of baseline characteristics of the randomized groups are reported to comply with common reporting practice, but are presented in parenthesis to emphasise that the usual interpretation of p-values does not apply, as the null hypothesis is known to be true because of randomization.

†Data are presented as numbers for listed for categoric variables; and continuous variables as mean ±SD and as median (range).

‡Mann Whitney *U* test/χ^2.

We plotted the data for time to healing as Kaplan-Meier curves and conducted an unadjusted analysis using a Cox proportional hazards model, comparing the time to healing between people randomized to the comparator interventions. We also conducted a secondary adjusted analysis utilizing prognostic information collected before randomization because this usually gives more precise estimates of treatment effects. Initially, a model was fitted including all three main treatment comparisons and all possible treatment interactions. Interactions among treatments were later dropped from the model, which was refitted with and without a set of covariates. Logistic regression was used to assess treatment withdrawal rates.

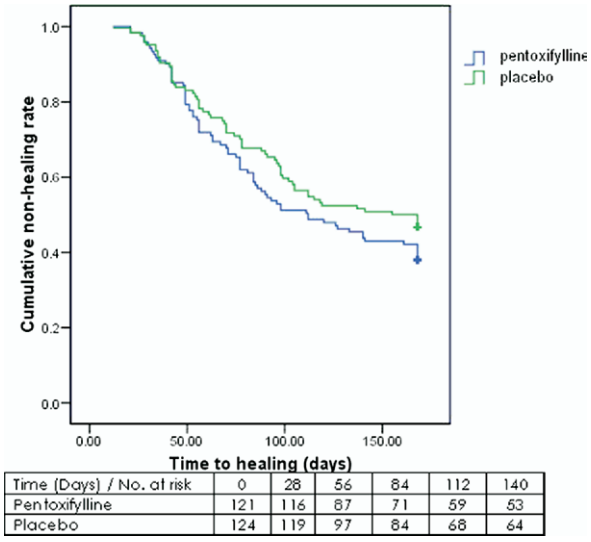
RESULTS

Of 525 people assessed, we recruited 245 with venous ulcers (simple and nonsimple) during a 40-month period. Fig 1 shows the distribution of allocation to drug, dressing, and bandage. Table I presents the baseline descriptive data for the 245 trial participants by intervention (drug, dressing, and bandage). Overall, there were two women for every man in the trial, and the average age was 70. Ulcers were open for a median of 5 months before trial entry and had a median area of just less than 400 mm^2. Overall, ulcers healed within the trial period in 141 (58%) of 245 participants. The proportions of people healing within each of the trial groups are provided in Table II.

Unadjusted analyses. An initial analysis with a Cox proportional hazards model fitting the effect of drug, bandages, dressings, and all possible interactions, gave no suggestion of any interactions among the treatments on time to healing (all interaction values for $P > .14$). Consequently, each mode of treatment is presented separately,

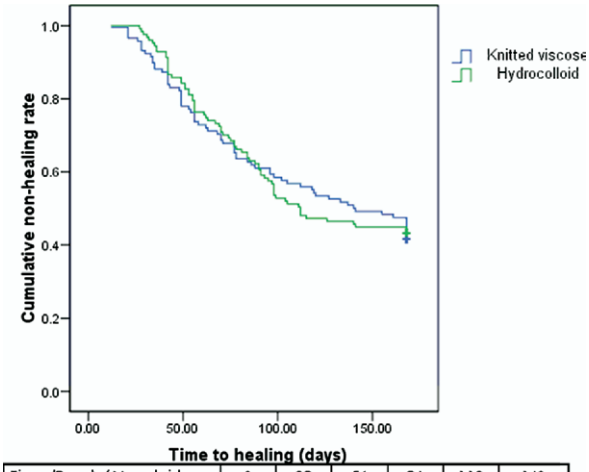
Table II. Healing rate in each group of the trial at 24 weeks

Drug	*Dressing*	*Bandage*	*Healing (%)*
Pentoxifylline	Knitted viscose	Single layer	16/33 (48)
		4 layer	20/25 (80)
	Hydrocolloid	Single layer	18/31 (58)
		4 layer	21/32 (66)
Placebo	Knitted viscose	Single layer	16/33 (48)
		4 layer	17/27 (63)
	Hydrocolloid	Single layer	13/31 (42)
		4 layer	20/33 (60)
Pentoxifylline	—	—	75/121 (62)
Placebo-	—	—	66/124 (53)
	Knitted viscose	—	69/118 (58)
—	Hydrocolloid	—	72/127 (57)
—	—	Single layer	63/128 (49)
—	—	4 layer	78/117 (67)



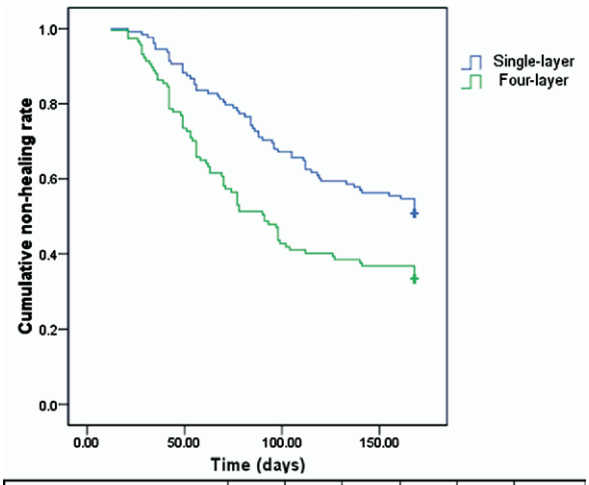
Time (Days) / No. at risk	0	28	56	84	112	140
Pentoxifylline	121	116	87	71	59	53
Placebo	124	119	97	84	68	64

Fig 2. Survival curve for drug: pentoxifylline *(blue line)* or placebo *(green line)*.



Time (Days) / No. at risk	0	28	56	84	112	140
Knitted viscose	118	110	87	74	66	59
Hydrocolloid	127	125	97	81	61	58

Fig 3. Survival curve for dressing: knitted viscose *(blue line)* or hydrocolloid *(green line)*.



Time (Days) / No. at risk	0	28	56	84	112	140
Single layer	128	126	107	95	80	73
Four layer	117	109	77	60	47	44

Fig 4. Survival curve for bandage: single-layer *(blue line)* or four-layer *(green line)*.

with results from the Cox models relating to a model including all three treatment effects.

Drug. Of the 121 people randomized to pentoxifylline, 75 healed (62%), and in the placebo group, 66 (53%) of 124 healed (χ^2_c = 1.58, P = .21). Kaplan-Meier estimates for median time to healing were 98 days for pentoxifylline and 118 for placebo (Fig 2). Analysis of time to healing using a Cox proportional hazards model, including the effect of drug, bandages, and dressings, gave an estimated hazard ratio for healing with pentoxifylline compared with placebo of 1.3 (95% confidence interval [CI], 0.9 to 1.8; P = .12).

Dressing. Of those allocated to the KVD group, 58% (69/118) healed compared with 57% (72/127) in the HCD group (χ^2_c = 0.02, P = .88). Kaplan-Meier estimates for median time to healing were 99 days in HCD and 127 in KVD (Fig 3). Cox proportional hazards model gave an estimated hazard ratio for healing with KVD compared with HCD of 1.1 (95% CI, 0.8 to 1.6; P = .53).

Bandage. Of those in the four-layer bandage group, 67% healed completely (78/117) compared with 49% (63/128) in those in the single-layer bandage group (χ^2_c = 6.92, P = .009). Kaplan-Meier estimates for median time to healing were 78 days in the four-layer bandage group and 168 days in the single-layer bandage group (Fig 4). The Cox proportional hazards model also indicated that the difference in healing rates was statistically significant (P = .001), with the hazard ratio for healing for those with a four-layer bandage group compared with a single-layer bandage estimated as 1.8 (95% CI, 1.3 to 2.5).

Table III. Cox proportional hazard model: hazard of healing with prognostic factors

Variables	*N*	*HR*	*95% CI*	P
Drug				
Placebo	124	1		.046
Pentoxifylline	121	1.4	1.01, 2.01	
Dressing				
Hydrocolloid	127	1		.75
Knitted viscose	118	1.1	0.74, 1.5	
Bandage				
Single layer	128	1		<.0005
Four layer	117	2	1.4, 2.9	
Center				
B	143	1		.45
A	102	1.2	0.80, 1.7	
Type of ulcer				
Simple	200	1		.89
Not-simple	45	0.97	0.61, 1.5	
Area (based on quartiles) mm^2				
50-180	61	1		<.0005
181-390	60	0.52	0.33, 0.80	
391-760	60	0.35	0.21, 0.56	
761 +	60	0.19	0.11, 0.34	
Missing	4	0.2	0.03, 1.5	
Ulcer history (years since first ulcer)				
0-1	91	2.4	1.4, 4.1	
2-5	46	1.9	1.0, 3.6	
6-15	50	2.5	1.4, 4.4	
16+	58	1		0.01
Ulcer duration in months				
≤2	56	1.4	0.72, 2.9	
3-4	60	1.8	0.97, 3.5	
5-7	37	1.1	0.54, 2.4	
8-12	49	1.8	0.95, 3.5	
13+	43	1		0.017

HR, Hazard ratio; *CI,* confidence interval.

Adjusted analysis: Cox model. We used a Cox proportional hazards model to identify other factors that may influence healing as well as the interventions being evaluated. This analysis also takes into account any imbalances in the distribution of prognostic variables between the groups. Although randomization of patients avoids systematic bias with respect to prognostic variables, it is likely that, by chance, there will be some imbalance in the groups. Within this model, we incorporated terms for the drug, dressing, bandage, center, and simple or nonsimple venous ulceration, because these were intrinsic to the study design. We also included area (obtained by acetate tracing and blinded area scanning) and duration of current ulceration in view of their widely accepted prognostic importance. We examined the other variables recorded in the data set and on the basis of their significance. Also included was years since the first ulcer categorized as 0-1 years, and so on. The model is presented in Table III.

This shows that area of the ulcer had the most impact on the subsequent ulcer healing relative to those in the lowest quartile (ulcer area, 50 to 180 mm^2); the relative rate of healing in the next three quartiles were 52%, 35%, and 19% compared with the lowest quartile.

The next most important variable was the bandage applied, where the relative healing rate with the four-layer bandage compared with the single-layer bandage was 2.0 (95% CI, 1.4 to 2.9; $P < .0005$).

The number of years since first ulceration was also statistically significant. Relative to individuals with ≥16 years' history of ulceration, all other categories showed an approximate doubling of the healing rate. Duration of reference ulcer has been found to be prognostic in other studies, and this was confirmed in this study, with the worst rate of healing in those with the longest ulcer duration.

Neither the center, the dressing applied, nor whether the ulcer was simple or not had any effect on healing.

In this model, pentoxifylline is just significant at the conventional 5% level, with a relative healing rate of 1.4 (95% CI, 1.0 to 2.0). Other models examined with nonsignificant terms dropped from our model resulted in the significance level for pentoxifylline varying across the commonly used cutoff value of $P = .05$.

Adverse events. A similar number of adverse events occurred in the two groups: 97 patients in the pentoxifylline group reported 245 adverse events (treatment related and unrelated), and 90 patients in the placebo group reported 246 adverse events. Most events were reports of ulcer deterioration, infection, and digestive upsets. Serious adverse events described as unrelated to the study medication were recorded for 16 people in the pentoxifylline group: skin ulceration in 3 patients, bone fracture, surgery, stroke, coronary thrombosis, syncope, skin carcinoma, cellulitis, heart and kidney failure, hostility, accidental overdose, myocardial infarction, and aggravation of rheumatoid arthritis. In four patients, serious adverse events were described as possibly related to the treatment: hematemesis, reduced platelet count, gastric upset, and gastrointestinal hemorrhage. Ten serious adverse events described as unrelated to the study medication were recorded for eight people in the placebo group: lack of healing, heart failure in 3 patients, cholecystitis, skin carcinoma, cerebral ischemia, skin aggravation, myocardial infarction, and urinary retention.

Withdrawals. Although all effectiveness analyses were performed on an intention-to-treat basis, it is interesting to look at how many people continued to use the allocated intervention. We recorded withdrawals from drug therapy, bandages, and dressings.

Drugs. There were 34 withdrawals from each arm of the trial. These were due to serious adverse events (4 in pentoxifylline group), other adverse reactions (23 in pentoxifylline, 27 in placebo group), development of exclusion criteria for the trial (4 pentoxifylline, 2 placebo) or an intercurrent illness developed (3 pentoxifylline, 5 placebo) that required withdrawal from the study.

Bandages and dressings. We considered withdrawals from bandage and dressing together because the performance of one intervention (eg, absorption capacity) could potentially influence the acceptability of the other. Sixty-eight people withdrew from their original bandage or dressing allocation, or both. Reasons for withdrawal included

Table IV. Estimates of effectiveness from randomized controlled trials of pentoxifylline (1200 mg) vs placebo in people wearing high compression

Scenario	*Trials*	*Participants (n)*	*Pooled relative risk of healing (random effects)*	*95% CI*	I^2*
1. Without this trial	Barbarino[11]	12	1.51	0.91, 2.48	45.50%
	Colgan[10]	80			
	Falanga[12]	91			
	Schuman[9]	24			
	Total	207			
2. With this trial	Barbarino[11]	12	1.32	1.01, 1.72	36.80%
	Colgan[10]	80			
	Falanga[12]	91			
	Schuman[9]	24			
	Nelson	245			
	Total	452			

CI, Confidence interval.
*Measure of statistical heterogeneity.

skin maceration, pain, and lack of progress. Twenty-six withdrew from both bandage and dressing (not necessarily at the same time), 27 withdrew from the bandage alone, and 15 from the dressing alone (Table IV,). KVD was associated with a 36% withdrawal rate (42/118), with 20% requiring a change in dressing; HCD had a 20% (26/127) withdrawal rate, with 14% requiring a change in dressing. Of the 128 people allocated to single-layer bandage, 36 (28%) had a bandage change compared with 17 (15%) in the four-layer bandage group.

Logistic regression investigating the chance of withdrawing from bandage demonstrated that both bandage and dressing predicted withdrawal. The interaction between the dressing and bandage was statistically significant ($P < .001$), indicating that a combination of KVD and single-layer bandage results in a higher withdrawal rate than would be anticipated from their individual withdrawal rates. With this combination, 25 (38%) of 66 patients did not continue with their bandage, compared with 11 (18%) of 62, 10 (15%) of 65, and 7 (13%) of 52 with the other bandage/dressing combinations. A further six patients with this combination changed their dressings, producing an overall noncompletion rate of 47%.

DISCUSSION

The trial has a number of strengths, and these include the simultaneous evaluation of the effects of three treatment modalities used in the treatment of venous ulcers. This is, to our knowledge, the first factorial trial in venous ulcers to simultaneously evaluate dressings, bandages, and adjuvant drug therapy. The factorial design allowed us to examine the relationship between drugs, dressings, and bandages in venous ulcer healing. Because venous ulcer treatment always requires bandages and dressings as a minimum, this design means we could test for the presence of interaction, such as whether a dressing was less effective in the presence of a particular bandage. This is theoretically possible because the ulcer environment and, hence, ulcer healing may be influenced by both dressings and bandages. Multiple layers of bandages reduce water vapor loss from ulcers and therefore act as semi-occlusive dressings.[7]

Although there was no suggestion of interaction between interventions on rates of healing on the intention-to-treat analysis, the combination of dressings and bandage did affect rates of withdrawal from treatment. The single-layer bandage and the knitted viscose dressing, when used together, may not have been sufficiently absorbent and led to maceration. The combinations used currently have layers of wool padding to absorb wound exudates to prevent skin damage and maceration.

If there had been an interaction between the three interventions for healing, then we would not have been able to make straight comparisons. This, however, would have been an interesting finding in itself: that the effect of one element of leg ulcer treatment can be affected by selection of another element.

Research nurses in two sites undertook the bandaging and data collection with one coordinator to ensure that compression-bandaging techniques were comparable between centers and throughout the study. We used time to healing as our main outcome measure rather than proportions healed at a specific time point, and this conveys speed of healing as well as number achieving healing. In addition, we defined healing as complete healing of all ulcers on the leg being monitored because this is more meaningful than the healing of an isolated, reference ulcer.

The trial was adequately powered to detect a clinically meaningful difference, and it monitored people for 6 months, sufficiently long to detect healing in almost 60% of the population. To reduce selection bias, allocation was concealed by using sealed, opaque, sequentially numbered envelopes. Having a placebo intervention for the drug, rather than making a comparison against standard care, ensured that performance bias did not influence the results of this comparison.

We have reported in detail the withdrawal from bandages and dressings, in contrast to many previous trials. In addition, we did not arbitrarily exclude people with large

ulcers because we believed it was important to determine the effect of intervention in this hard-to-heal group.

Limitations. The limitations of the study included the lack of verification of venous pathology using duplex ultrasound evaluation before trial entry. At the time the trial was set up, it was not possible to arrange this for all potential trial patients before trial entry, although many did have a vascular assessment during the study. A trained nurse used a hand-held Doppler at recruitment to assess the presence of venous insufficiency, but this is less reliable than duplex. Given that many patients are treated for venous ulceration after clinical assessment, this limitation reflects the reality of current clinical practice. This means we cannot confirm the importance of saphenous patency for clinical outcomes.

A further limitation is the lack of blinding of nurses, clinicians, or outcome assessment with regards to bandages and dressings. It is not possible to easily mask these interventions. We were not able to use photographs for blinded outcome assessment because the skin was marked by the dressings and bandages in such a manner that experienced clinicians could determine which dressing or bandage had been used; for example, the skin surrounding ulcers treated with hydrocolloid, compared with an embossed appearance underneath a woven dressing.

People taking warfarin were excluded from the trial because pentoxifylline is contraindicated in this situation; therefore, this limits the generalizability of our trial because some people with venous ulcers will be taking warfarin. Because we have no evidence that warfarin is a prognostic factor for healing, it is not clear whether our trial population differs from the larger population to any significant extent.

We have reported both an unadjusted and an adjusted Cox proportional hazards model. At the outset of the study we envisaged the primary analysis would be the unadjusted one, but the adjusted model includes prognostic variables and hence is capable of producing additional insights. The final model is dependent on associations found in the data, and because there is the possibility of choosing the model to best fit with preconceptions, we also reported the unadjusted analysis.

How our results fit in with other findings. Eight other trials have compared simple dressings (eg, gauze or knitted viscose) with hydrocolloid dressings. Seven of these found no evidence of benefit; the eighth, which did find a difference, had imbalanced groups at randomization.[17]

We have been able to identify two other randomized controlled trials comparing single-layer and four-layer bandages.[18,19] These trials were small, involving 44 participants, and neither used survival analysis. Both reported no difference in healing rates but were too small to exclude anything but a massive difference in healing rates.

A systematic review of five trials (404 people) evaluating 1200 mg pentoxifylline as an addition to compression concluded that it is associated with higher healing rates, although it just reaches statistical significance at the conventional 5% level (relative risk of healing with pentoxifylline, 1.31;95% CI, 1.00 to 1.74; random effects, I^2 37.7%).[20] Summary data from 200 ulcers from this trial are, however, included in this estimate. Table IV summarizes the impact of adding the results from the 245 participants of this trial to the previous four studies making this comparison (1200 mg vs placebo, all wearing compression). This trial doubles the population considered, increasing the precision of the estimate. Without this trial, the relative risk of healing with pentoxifylline is 1.51 (95% CI, 0.91 to 2.48), and by adding our study, this becomes 1.32 (95% CI, 1.01 to 1.72). These pooled results suggest the probability of a venous ulcer healing in 6 months is increased by 32% by adding 1200 mg of pentoxifylline to a regimen of compression therapy.

Pentoxifylline is a generic drug, and we found similar numbers withdrawing from the trial in both groups, hence it appears to be well tolerated. The effect size is moderate but may be considered to be clinically worthwhile because treatment is simple and inexpensive. An absolute difference in healing rates of 9% translates to a number needed to treat of 12 over 6 months. This number needed to treat means that for every 12 people treated with pentoxifylline, one additional person would heal by 6 months. The improvement in healing rate from 53% to 62% with pentoxifylline is certainly smaller than the 49% to 63% reported in one randomized controlled trial of an engineered human skin equivalent.[21] This trial was not designed to follow-up patients to recurrence to determine the effect of pentoxifylline on the durability of healing, and this question remains unanswered.

Implications for clinical practice. We found no benefit for hydrocolloid dressings compared with knitted viscose dressings when venous ulcers are treated with high-compression bandaging. Given the higher cost of hydrocolloid dressings compared with simple dressings, and the lower allergic and irritant potential for simple, low-adherent dressings, then these are preferred.

CONCLUSION

Patients with venous ulcers treated with four-layer compression are significantly more likely to heal than those treated with an adhesive, single-layer bandage. Adding oral pentoxifylline (1200 mg daily) to a regimen of high-compression therapy may increase the chance of healing in line with recent overviews, but this finding is analysis dependent.

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AUTHOR CONTRIBUTIONS

Conception and design: RJP, DRH, BG, DB, CVR
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Critical revision of the article: DRH, BG, DB, CVR
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Statistical analysis: EAN, RJP
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