A Randomized, Controlled, Parallel-Group Clinical Trial Comparing Multilayer Bandaging Followed by Hosiery versus Hosiery Alone in the Treatment of Patients with Lymphedema of the Limb

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BACKGROUND. Multilayered, low stretch bandages (MLB) combined with exercises, skin care, and manual lymphatic drainage therapy are recommended as an intensive phase of treatment for lymphedema patients. The relative efficacy of each of the components of this comprehensive treatment program have not been determined. This study aimed to compare the effect of multilayer bandaging as an initial phase of lymphedema treatment followed by elastic hosiery versus hosiery alone.
METHODS. A randomized, controlled, parallel-group trial was undertaken in the setting of the Lymphedema Clinic, The Royal Marsden Hospital, London. Ninety women with unilateral lymphedema (of the upper or lower limbs) were enrolled in the study. The interventions consisted of 18 days of multilayer bandaging followed by elastic hosiery or hosiery alone, each for a total period of 24 weeks. The main outcome measure was the percentage reduction in excess limb volume.
RESULTS. The reduction in limb volume by MLB followed by hosiery was approximately double that from hosiery alone and was sustained over the 24-week period. The mean overall percentage reduction at 24 weeks was 31% (n = 32) for MLB versus 15.8% (n = 46) for hosiery alone, for a mean difference of 15.2% (95% confidence interval, 6.2–24.2) ($P = 0.001$).
CONCLUSIONS. Multilayer bandaging as an initial phase of treatment for lymphedema patients, followed by hosiery, achieves greater and more sustained limb volume reduction than hosiery alone. ***Cancer* 2000;88:2832–7.**

KEYWORDS: lymphedema, carcinoma, bandaging, compression.

The major manifestation of lymphedema is chronic limb swelling, which can cause discomfort, heaviness, and tightness. Complications include recurrent acute inflammatory episodes (cellulitis) and malignancy in the form of lymphangiosarcoma.[1] Psychologic handicap occurs as a result of disfigurement.[2]

A strategy of care has been introduced that exploits physical therapies. It depends on the principle that the drainage of lymph through collateral routes can be enhanced by physical means. The first, intensive phase of treatment, a course of daily bandaging (multilayer bandaging [MLB]), exercises, and massage (manual lymph drainage),[3] seeks to decongest the lymphedematous area of the body; subsequent treatment with compression hosiery aims to control the reaccumulation of edema.

In February 1998, the American Cancer Society held an international conference addressing the highest priority strategies for breast

carcinoma treatment-related lymphedema. At the conclusion, one of the recommendations for research and clinical practice was to determine the relative efficacy of each of the components of the comprehensive treatment program.[4] Evidence of the benefits of physical treatment is limited to prospective open studies of consecutively treated patients.[5] Although the results are impressive, there have been no randomized controlled trials. We undertook a prospective, randomized, controlled, between-patient trial to determine whether a course of MLB, as it is used in intensive physical therapy, followed by the use of compression hosiery was more effective at reducing and controlling the volume of swollen limbs than hosiery used on its own.

MATERIALS AND METHODS

Design of the Trial

There were two study groups: patients who received a course of MLB followed by hosiery (MLB+H) and patients who received only hosiery and no MLB (H alone).

Patients

Patients with unilateral upper or lower limb lymphedema were enrolled in the study irrespective of cause. Recruitment continued for 2 years from a consecutive series of patients who presented at the Lymphedema Service, The Royal Marsden Hospital, London and Surrey. Approval for the study was obtained from the Ethics Committee, and written consent was received from all patients. Lymphedema was diagnosed on a clinical basis alone in cancer patients who developed a swollen limb, but the diagnosis was confirmed by lymphoscintigraphy in patients with primary lymphedema.[6]

Inclusion and Exclusion Criteria

Cancer patients had to be at least 12 months post-treatment for their disease with no sign of active disease at the time of randomization. All patients had to have swelling of at least 20% excess volume over the normal limb.[7]

Patients with bilateral limb swelling were excluded, because a contralateral normal limb was needed to predict normal size. Also excluded were patients with paralysis or with a history of compromised arterial flow in the affected limb or patients with limbs that were too big for hosiery.

Treatment Regimens

The first layer in MLB consisted of a length of tubular stockinette. The digits were then bandaged using a retention bandage (Peha Crepp™). Foam (Dalzofoam™; Seton) and padding (Velband™; Johnson & Johnson) were used to protect joint flexures and to even out the contours of the limb, creating an almost cylindrical profile and ensuring that pressure was distributed evenly around the limb. The final layers were of short-stretch, extensible bandages (Comprilan™; Beiersdorf). On lower limbs, a minimum of two layers of bandages were applied, the first in a spiral and the last in a figure eight. Occasionally, more layers were used if the swelling was severe enough. On upper limbs, the bandages were applied in a spiral only: The first bandages covered the hand and forearm, and the second bandage started at the wrist. The bandages were left in place around the clock and were replaced once a day.

Hosiery, after bandaging or used on its own, was selected in terms of style, class of compression, and number of layers according to each patient's needs. Patients were asked to wear their garments from morning until bedtime. Arm sleeves were replaced every 3–4 months, and stockings were replaced every 6 months.

Patients in the MLB+H group started on Day 1 with an 18-day course of MLB and then wore hosiery for the rest of the trial. Patients in the H-alone group were fitted with hosiery on Day 1 and continued with hosiery for the remainder of the trial period (Table 1).

Patients in the MLB+H group either were admitted to the rehabilitation ward or attended the clinic

TABLE 1
Demographic Details of Patients by Treatment Group

Variable	No. with bandage and hosiery (n = 34 patients) (%)	No. with hosiery alone (n = 49 patients) (%)
Gender		
Female (%)	31 (91)	45 (92)
Male (%)	3 (9)	4 (8)
Site of edema		
Upper limb (%)	21 (62)	33 (67)
Lower limb (%)	13 (38)	16 (33)
Age (yrs)		
Mean (SD)	57.3 (14.5)	57.4 (14.6)
Range	23 – 81	24 – 86
Duration of edema (months)		
Mean (SD)	48 (96)	60 (96)
Range	5 – 432	7 – 480
Excess limb volume at Day 1 (%)		
Mean (SD)	48.6 (25.6)	41.9 (18.4)
Range	5.0 – 110.4	17.9 – 95.2
Weight at Day 1 (kg)		
Mean (SD)	73 (14)	71 (13)
Range	49 – 105	48 – 106

SD: standard deviation.

daily as outpatients. Outpatients had their bandages left in place over the weekend, whereas inpatients had their bandages replaced daily over the weekend. Hosiery was fitted on Day 18, allowing 24 hours of observation in case of any problems. The course of treatment finished on Day 19.

All of the patients were given advice on the positioning of the swollen limb, exercises to promote lymph drainage, and daily skin care. They were all taught self-massage (based on the principles of manual lymph drainage) and were asked to perform exercises, skin care, and massage daily for the duration of the trial. Patients who suffered adverse reactions or problems during the trial (for example, cellulitis or dermatitis) were allowed to continue with appropriate additional treatment.

Measurements and Assessments

Limb volumes were measured either by using an electronic volumeter (Perometer™), which is an optoelectronic device that scans the limb and determines multiple circumferences from which volume is then calculated automatically, or by manual surface measurements from which volume was calculated by using the formula $\text{Circumference}^2/\pi$. Reproducibility of the Perometer measurements has been confirmed by our own group[8] and by others.[9] Agreement between the electronic measurements and those based on manual surface measurements also was established.[7]

The severity of swelling was determined by subtracting the volume of the patient's normal limb from that of the swollen limb; the difference represented the excess volume in the swollen limb, which was then expressed as a percentage of the patient's normal limb, i.e., the percent of excess limb volume. The percentage reduction was calculated as the percentage of the excess volume reduced by treatment. Incidents of acute inflammatory episodes (AIE), deep vein thrombosis, and disease recurrence were noted. Assessments were carried out in both study groups at set time intervals on Day 1, Day 19, Week 7, Week 12, and Week 24.

Sample Size and Randomization

The target sample size was 50 patients in each group (n = 100 patients in total). With this number of patients, a standard deviation of 0.65 in the percentage reduction could be detected with a power level of 90% and a significance level of 5% in two-sided tests. Patients were allocated randomly to one of the two treatment groups by telephone to the Section of Epidemiology, Institute of Cancer Research, Sutton.

Statistical Analysis

The primary outcome was the percentage reduction in limb volume at 24 weeks. Measurements collected at Day 19, Week 7, and Week 12 also were analyzed. Limb volume was plotted from baseline for each patient (Fig. 1), and the average reduction was calculated using the area under the curve.[10]

A few patients had missing readings at some time points (13 patients with 18 missing readings in total out of a possible total of 332 readings). The following three analyses were performed to test the sensitivity of our approach: 1) including all patients but averaging over their individual observation periods (n = 83 patients); 2) including all patients who had data up to and including Week 12 (n = 77 patients); and 3) including all patients who had data up to and including Week 24 (n = 78 patients). It was possible for patients to have a reading for 24 weeks but not for 12 weeks; therefore, such patients would be included in analyses 1 and 3 but not in analysis 2.

The data followed an approximately normal distribution; therefore, the mean reduction in limb volume in the two groups was compared by using a two sample *t* test. Results are presented as the group means and differences of means with 95% confidence intervals. The analyses were performed by using Stata software.[11]

RESULTS

To complete the trial within the period of funding, recruitment of patients had to stop before the full number of patients (50 in each arm) was achieved.

Demographic Details

Ninety patients with unilateral limb edema were enrolled in the trial. Seven patients (four patients in the MLB+H group and three patients in the H-alone group) subsequently were withdrawn: One patient who was randomized to the MLB+H group declined treatment, one patient received only 2 weeks of bandaging, one patient received only 11 days of bandaging, one patient developed disease recurrence, one patient insisted on regular manual lymph drainage, and two patients never attended follow-up visits.

Data were available for analysis on 83 patients. Thirty-four of the patients (41%) were randomized to the MLB+H, whereas the remaining 49 patients (59%) were randomized to the H-alone group. Demographic data on both groups are presented in Table 1. The majority of patients in each study group were female, and $> 60\%$ of the patients in each group had upper limb lymphedema. There were no imbalances between the groups in any of the variables.

Eight patients had AIE (cellulitis) that occurred

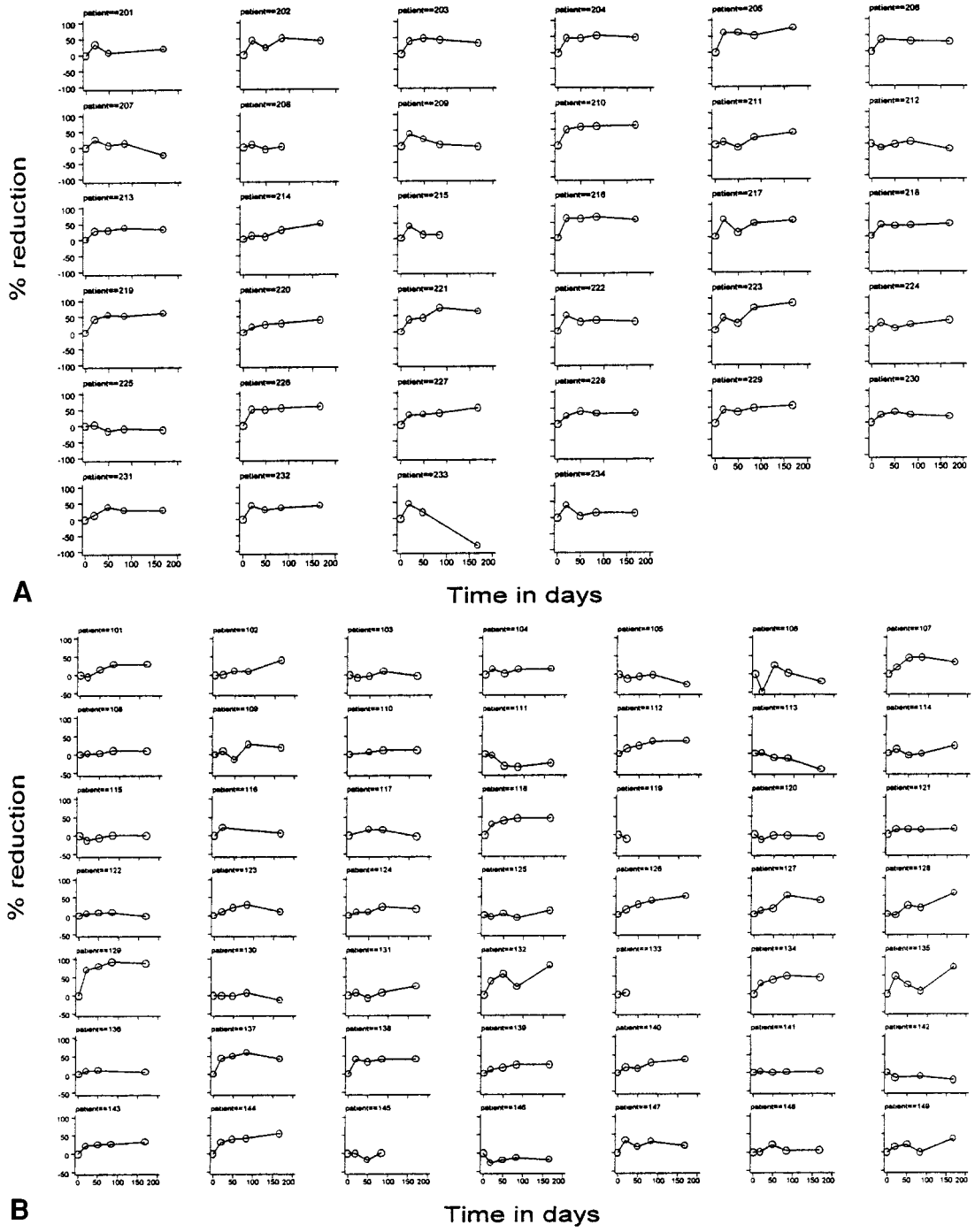

FIGURE 1. Graphs show the reduction in limb volume over time for the intervention group (A) and the control group (B).

during the trial, five in the MLB+H group and three in the H-alone group. A deep vein thrombosis occurred in the upper limb of one patient in the H-alone group, and there were three instances of recurrent tumor (one in the H-alone group and two in the MLB+H group).

Limb Volume

The reduction in limb volume tended to decline in most patients, the trend being more pronounced in the MLB+H group (Tables 2 and 3)(Fig. 1). The reduction in limb volume in the MLB+H group was approximately double that in the H–alone group, with a mean

TABLE 2
Percentage Reduction in Limb Volume at Four Time Points by Treatment Group

	Intervention		Control	
% Reduction	No.	Mean (SD)	No.	Mean (SD)
Day 19	34	33.5 (16.9)	47	9.6 (20.4)
Week 7	33	26.0 (21.0)	45	13.8 (21.6)
Week 12	32	34.5 (20.7)	45	18.0 (23.0)
Week 24	32	32.6 (33.2)	46	19.6 (28.5)

SD: standard deviation.

difference in reduction of 30% between the groups (Table 3). The results were very close under all three analyses, and all differences were highly significant. The results confirm that the beneficial effect of MLB+H still was apparent after 12 weeks and was sustained up to 24 weeks.

DISCUSSION

A course of MLB followed by compression hosiery was significantly more effective than hosiery alone at reducing moderate-to-severe lymphedema (i.e., $>$ 20% excess limb volume), with the benefit maintained for at least 6 months. In an open study that monitored a series of patients with postmastectomy lymphedema, arm volume decreased by only 0.4% compared with the control arm over a 4-week period with no treatment: After 6 months of using hosiery, there was an 8% reduction.[12] In another longitudinal open study, hosiery reduced limb girth measurements by 14.7% over a 6-month period.[13] Pneumatic compression frequently is recommended; however, despite widespread use, only one published randomized clinical trial exists, and that report showed no significant benefit.[14] Evidence confirming a benefit from drugs is disappointing.[15] Results from liposuction are impressive but also involve MLB and compression hosiery.[16]

Intensive physical therapy exploits basic principles of physiology: Any edema, whatever the cause, results from an imbalance between capillary filtration and lymph drainage. If lymph drainage can be stimulated and excess filtration can be curbed, then edema should be contained. Studies of patients with breast carcinoma-related lymphedema indicate the complexities of the mechanisms for such chronic edematous states.[17] Unlike blood flow, lymph flow relies on intermittent changes in interstitial pressures and subsequent contraction of lymphatic collecting vessels. It is likely (but not yet confirmed) that contractility fails in lymphedema, so that lymph drainage becomes dependent on passive processes in a manner similar to external cardiac massage during resuscitation.[18]

Pressures under extensible bandages and compression hosiery differ. The former are supportive rather than compressive,[19] i.e., pressure results from the body tissues pushing outward against a firm, resistant wall of bandage. Under hosiery, forces within the material exert pressure on the tissues of the limb acting compressively. The amplitudes between resting and working pressures are greater[20] under extensible bandages than under hosiery, because the latter gives way to changes in the size of the limb during movement, whereas, under the rigid casing of the extensible bandage, the muscles meet resistance as they contract, causing pressures to rise.

Although improvements in the treatment of patients with cancer may reduce the risk of lymphedema, surgery, radiotherapy, or both to lymphatic regions of the body will continue to create serious morbidity. The adoption of "sentinel node" protocols[21] will not have a rapid effect on decreasing the incidence of lymphedema, because swelling can take years to appear. Guidelines for the treatment of breast

TABLE 3
Overall Percentage Reduction in Limb Volume Using All Data Available, Patients with a Reading at Week 12, and Patients with a Reading at Week 24

	Intervention		Control		Difference	
Criteria	No.	Mean	No.	Mean	Mean (95% CI)	*P* value
All data available[a]	34	30.0	49	15.2	14.8 (6.0 – 23.6)	0.001
Day 1 to Week 12[b]	32	27.3	45	12.1	15.2 (7.5 – 22.9)	$<$ 0.001
Day 1 to Week 24[c]	32	31.0	46	15.8	15.2 (6.2 – 24.2)	0.001

CI: confidence interval.

[a] Included all patients averaged over their individual observation periods.

[b] Included all patients who had data up to Week 12.

[c] Included all patients who had data up to Week 24.

carcinoma-related lymphedema advocate physical therapy;[4] however, further trials are required to prove the efficacy of single as well as combined interventions.

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