

United States⁷ and £4000 (€5920; \$8000) in the United Kingdom,⁸ mainly because of increased length of hospital stay and use of vancomycin. Clearly substantial savings could be made by the routine use of probiotics.

We thank Winston Banya for statistical advice and conducting the randomisation; Sheila Bacon, Paula Brown, and Linda Wedlake for assistance with data collection; Edward Pawley, Lucy O'Driscoll, Regina Storch, Kuldip Dehal, and the pharmacy departments at each hospital for management and dispensing of the study drinks; the nursing staff on all the wards involved for help with keeping stool charts, monitoring patients, and collecting stool samples; Manfred Almeida and the staff in the division of microbiology, Hammersmith Hospitals Trust, for help with lactobacilli counts and *C difficile* toxin tests; and Ruth Peters for organising data entry.

Contributors: See bmj.com

Funding: Healthcare Foundation and Hammersmith Hospital Trustees research committee and Danone Vitapole (Paris, France). The Healthcare Foundation made initial comments on the design of the study. Once funding was agreed none of the funding sources had any role in the data collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Competing interests: CJB, MH, and ALD'S have received funding from Danone to attend Danone International Conventions on Probiotics. CJB is a member of Danone UK advisory group.

Ethical approval: London multicentre research ethics committee.

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Accepted: 11 May 2007

Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial

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BMJ 2007;335:83-7
doi:10.1136/bmj.39216.542442.BE

This article is an abridged version of a paper that was published on bmj.com on 1 June 2007. Cite this version as: *BMJ* 1 June 2007, doi: 10.1136/bmj.39216.542442.BE (abridged text, in print: *BMJ* 2007;335:83-7).

ABSTRACT

Objective To determine whether recurrence of leg ulcers may be prevented by surgical correction of superficial venous reflux in addition to compression.

Design Randomised controlled trial.

Setting Specialist nurse led leg ulcer clinics in three UK vascular centres.

Participants 500 patients (500 legs) with open or recently healed leg ulcers and superficial venous reflux.

Interventions Compression alone or compression plus saphenous surgery.

Main outcome measures Primary outcomes were ulcer healing and ulcer recurrence. The secondary outcome was ulcer free time.

Results Ulcer healing rates at three years were 89% for the compression group and 93% for the compression plus surgery group (P=0.73, log rank test). Rates of ulcer recurrence at four years were 56% for the compression group and 31% for the compression plus surgery group (P<0.01). For patients with isolated superficial reflux, recurrence rates at four years were 51% for the compression group and 27% for the compress plus surgery group (P<0.01). For patients who had superficial with segmental deep reflux, recurrence rates at three years were 52% for the compression group and 24% for the compression plus surgery group (P=0.04). For patients with superficial and total deep reflux, recurrence rates at

three years were 46% for the compression group and 32% for the compression plus surgery group (P=0.33). Patients in the compression plus surgery group experienced a greater proportion of ulcer free time after three years compared with patients in the compression group (78% v 71%; P=0.007, Mann-Whitney U test).

Conclusions Surgical correction of superficial venous reflux in addition to compression bandaging does not improve ulcer healing but reduces the recurrence of ulcers at four years and results in a greater proportion of ulcer free time.

Trial registration Current Controlled Trials
ISRCTN07549334.

INTRODUCTION

Duplex ultrasonography has shown that incompetence in superficial veins is present in most legs with chronic ulceration, sometimes combined with deep venous reflux.¹⁻³ Several surgical strategies have been attempted. Deep venous procedures may be associated with high complication rates, and studies have shown little clear benefit.⁴ Several studies have suggested that corrective surgery for superficial venous reflux may have clinical benefits for ulcer healing and recurrence.⁵⁻⁷

The effect of surgery and compression on healing and recurrence (ESCHAR) study aimed to assess

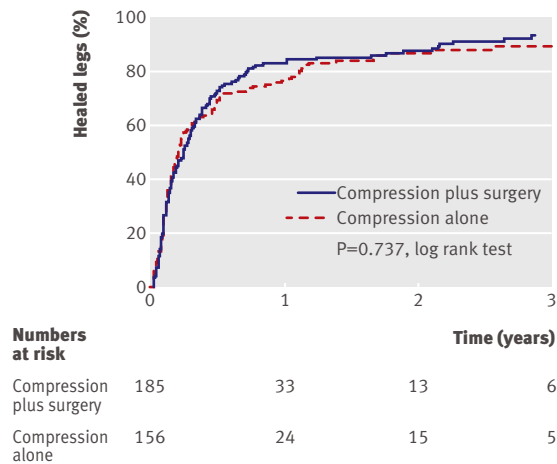


Fig 1 | Kaplan-Meier survival analysis showing ulcer healing at three years

these outcomes in patients with chronic leg ulceration. The early results have been published.⁸ We present the long term findings.

METHODS

In January 1999 we started recruitment to the study at three centres in south west England. Since 1995 leg ulcers have been managed in two of the centres by a nurse led service. The model was extended to the third centre for participants in the trial.

Consecutive patients underwent a standardised assessment (see *bmj.com*). We recruited those with open or recently healed ulceration (within six months) between knee and malleoli of greater than four weeks' duration, an ankle brachial pressure index of 0.85 or greater, and superficial or deep venous reflux on duplex scanning. We classed patients without deep reflux as having isolated superficial reflux, patients with reflux in some deep veins as having superficial and segmental deep reflux, and those with reflux throughout the deep system as having superficial and total deep reflux. Superficial venous reflux was diagnosed on duplex scan results.

Patients were randomly allocated to treatment with compression only or to compression plus saphenous surgery (see *bmj.com*). Patients with open ulceration were treated weekly with multilayered compression bandaging (Smith & Nephew, Hull). Patients with healed legs were prescribed class 2 elastic stockings (Medi, Hereford).

Patients with open ulceration were reviewed monthly, or more often if necessary, until ulceration had healed. After healing, patients were reviewed at one month then every three months for one year and every six months thereafter. If recurrence occurred, follow-up was continued to three years (two centres).

Primary outcome measures were ulcer healing (complete re-epithelialisation of leg) and ulcer recurrence (any breakdown of epithelium between knee and malleoli after ulcer healing). Ulcer free time (total

time with healed leg) was assessed as a secondary outcome measure to three years.

Statistical analysis

Analyses were carried out on an intention to treat basis with no per protocol analyses planned. We calculated ulcer healing and recurrence using Kaplan-Meier survival analysis with log rank comparisons (time zero was the date of recruitment for patients with healed legs and date of healing for patients recruited with open ulceration). We planned subgroup analyses for patients with isolated superficial reflux, superficial with segmental deep reflux, and superficial with total deep reflux. Tests for interaction were carried out using Cox regression analysis. All analyses were carried out using SPSS version 13.0.1, with P values less than 0.05 considered significant.

RESULTS

Between January 1999 and August 2002, 500 of 1418 patients with open or recently healed leg ulcers and superficial venous reflux participated in the study (see *bmj.com*): 258 were allocated to compression and 242 to compression plus surgery. Fifty four patients were lost to follow-up and were censored from Kaplan-Meier analyses. Forty seven patients in the compression plus surgery group did not attend for surgery and three in the compression group requested surgery.

The groups were similar at baseline (see *bmj.com*). Three hundred had isolated superficial reflux, 126 had superficial with segmental deep reflux, and 74 had superficial with total deep reflux. Overall mortality was 17% at three years, with the groups showing similar mortality (19% compression, 16% compression plus surgery; P=0.245).

Overall, 195 (81%) patients in the compression plus surgery group attended for operation; surgery was carried out to the long saphenous vein in 141 (72%), the short saphenous vein in 27 (14%), and the long and

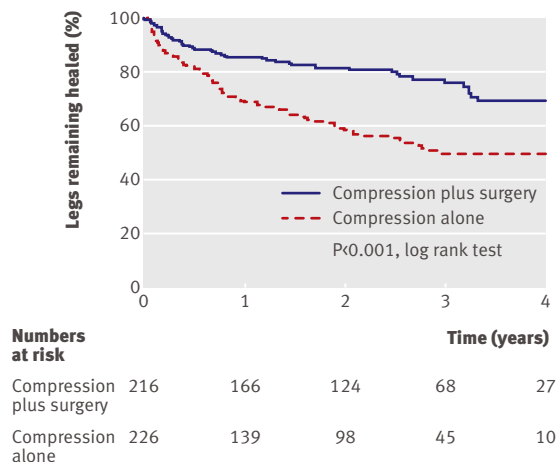


Fig 2 | Kaplan-Meier survival analysis showing ulcer recurrence at four years

short saphenous veins in 21 (11%). Six patients (3%) underwent calf perforator surgery only.

Ulcer healing

Ulcer healing rates at three years were 89% in the compression group and 93% in the compression plus surgery group ($P=0.737$; fig 1). The subgroups stratified by venous reflux pattern were too small to calculate healing rates at three years. Analysis for interaction showed that the effect of surgery on healing did not differ between the subgroups ($P=0.053$, hazard ratio 0.756, 95% confidence interval 0.513 to 1.004).

Ulcer recurrence

Ulcer recurrence rates at four years were significantly lower in the compression plus surgery group than in the compression group (31% *v* 56%, $P<0.001$; fig 2). For patients with isolated superficial reflux, recurrence rates at four years were 27% in the compression group and 51% in the compression plus surgery group ($P<0.001$; fig 3). For patients with superficial plus segmental deep reflux, recurrence rates at three years were 24% in the compression plus surgery group and 52% in the compression group ($P=0.044$; fig 3). In patients with superficial plus total deep reflux, recurrence rates at three years were 24% in the compression plus surgery group and 46% in the compression group, although this was not significant ($P=0.23$; fig 3). Cox regression analysis confirmed that randomisation to surgery significantly reduced recurrence ($P<0.001$, hazard ratio 2.926, 95% confidence interval 1.723 to 4.133), although the influence of surgery on recurrence did not differ between the subgroups ($P=0.227$, hazard ratio 0.833, 95% confidence interval 0.479 to 1.191).

Ulcer free time

Ulcer free time was assessed to three years in 365 of the 500 (73%) patients. Those randomised to compression plus surgery experienced significantly longer absolute (100 *v* 85 weeks, $P=0.013$) and proportional (78% *v* 71%, $P=0.007$) ulcer free time up to three years than

those randomised to compression. Overall, 122 episodes of recurrent ulceration occurred: 81 in the compression group, 41 in the compression plus surgery group ($P=0.001$).

DISCUSSION

Superficial venous surgery in addition to compression therapy for chronic leg ulceration reduced ulcer recurrence and improved ulcer free time when compared with compression alone. As with previous, smaller studies, the clinical benefit seemed greatest for patients with isolated superficial reflux⁵⁻⁷ but was also present for patients with coexistent segmental deep reflux. For patients with isolated superficial reflux, four would need to undergo surgery to prevent one episode of ulceration in four years.

Although the improvement in ulcer recurrence rates was less impressive in the groups with segmental and total deep reflux, the subgroups were smaller and the benefit of surgery may have been underestimated. Other authors have reported reversal of venous reflux in deep and perforating veins after superficial venous surgery,⁹⁻¹¹ and postoperative duplex scans of patients in our study showed a similar effect.^{12,13} Therefore deep venous reflux should not be considered an absolute contraindication to superficial venous surgery as patients may experience significant haemodynamic and clinical benefits. Ulcer healing was not improved by superficial venous surgery possibly because the haemodynamic benefit of multilayer compression bandaging was not significantly improved by the addition of surgery.^{14,15}

Strengths and weaknesses of the study

Our study was set within a leg ulcer service across three centres, and we considered consecutive patients. Inclusion criteria were open and surgery was carried out by surgeons of varying grades consistent with standard patient care. The study was designed to emulate standard clinical practice to ensure that results could be widely applicable to the patient population with leg

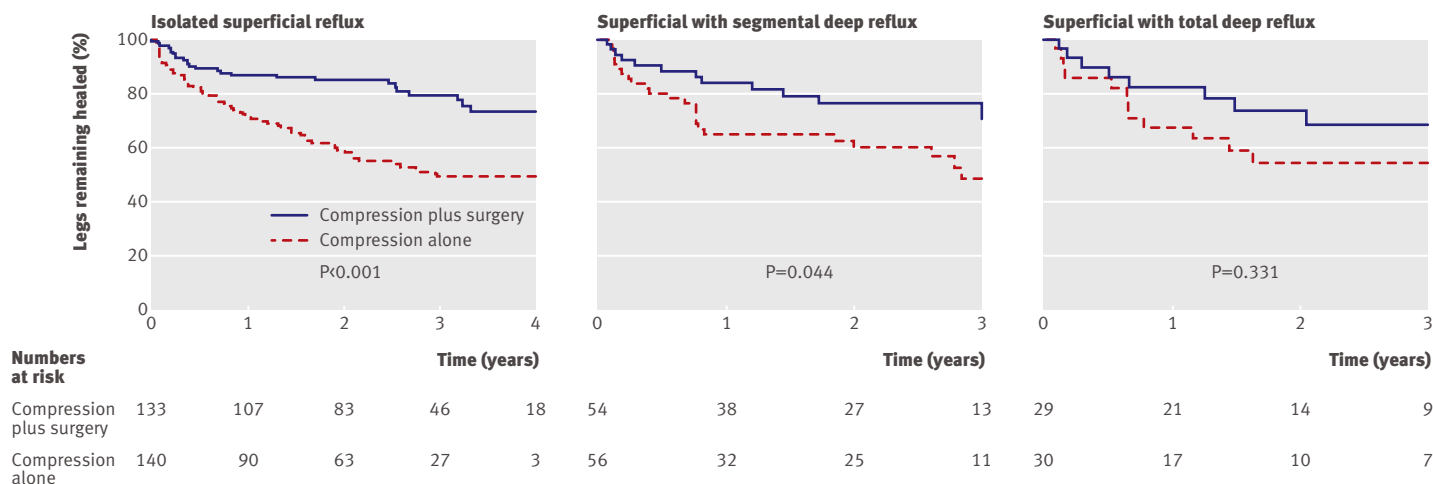


Fig 3 | Kaplan-Meier survival curves showing ulcer recurrence stratified for venous reflux pattern. Groups compared using log rank test

WHAT IS ALREADY KNOWN ON THIS TOPIC

Chronic venous ulceration is a common and expensive clinical problem
Venous reflux in superficial veins is commonly seen in these patients

WHAT THIS STUDY ADDS

Surgical correction of superficial venous reflux in addition to compression bandaging does not improve ulcer healing rates
Surgical correction can, however, reduce the chance of recurrent ulceration and increase ulcer free time

ulceration. Our choice of surgery and patient stratification were based on findings from duplex ultrasonography. Other studies have suggested that non-invasive assessment of venous refill time using photoplethysmography may help predict success after surgery.¹⁶ Refinement of the selection process could improve the identification of patients most likely to derive a clinical benefit from venous surgery.

Poor compliance with surgery for patients with leg ulceration has been reported.¹⁷ In our study 24% of patients randomised to surgery refused to attend for their operation despite extensive counselling before recruitment. Moreover, patients waited a median of seven weeks for their operation and therefore may not have received an immediate benefit. Despite these factors we carried out all analyses on an intention to treat basis, suggesting that the benefits of surgery may have been underestimated. In recent years several less invasive procedures for the treatment of superficial venous reflux have been forwarded, including foam sclerotherapy,¹⁸ radiofrequency ablation,¹⁹ and endovenous laser.²⁰ These techniques, often carried out under local anaesthetic, may have a role for patients reluctant to undergo traditional surgery, although long term durability remains unproved.

Class 2 stockings have been shown to reduce ulcer recurrence and we prescribed them for all patients after ulcer healing.²¹ We did not formally assess compliance with stocking use, although patients were given similar written and verbal advice. Others have reported poor compliance with stocking use,²² which may partly explain the high incidence of recurrent ulceration without surgery (56% at four years in this study). Of the patients randomised to compression plus surgery, 31% had recurrent ulceration within four years. Some did not attend for their operation and others underwent surgery under local anaesthetic without stripping of the long saphenous vein. Factors other than venous reflux, such as coexisting medical problems or ankle stiffness causing poor calf muscle function,²³ may have contributed to recurrent ulceration in individual cases. Whether these patients experienced more ulcer free time after surgery as a result of less frequent or shorter episodes of recurrent ulceration remains unproved. Nevertheless, residual venous reflux and neovascularisation are common after superficial venous procedures, and stripping of the long saphenous vein to the knee is preferable.²⁴

Conclusions

Chronic leg ulceration is common and distressing for patients and an important financial burden for health-care providers. These long term findings support our earlier results and present a cogent argument for the widespread provision of colour duplex scanning and superficial venous surgery for patients with chronic venous leg ulcers.

We thank CE Davies, G Turton, G Woolfrey, J Waldron (Gloucestershire Leg Ulcer Service); C Wakely, J Minor, K Harvey, A Sassano (vascular scientists); and B Whitman (research assistant) for their support and assistance.

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Funding: NHS Executive South and West Research and Development Directorate, Southmead Hospital Research Foundation, and Medical Research Council. The funding sources had no financial or other interest in study outcome and had no role in study design, data control, or reporting.

Competing interests: None declared.

Ethical approval: Gloucestershire and Southmead research ethics committees.

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Accepted: 26 April 2007

Effects of treatments for symptoms of painful diabetic neuropathy: systematic review

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BMJ 2007;335:87-90

doi:10.1136/bmj.39213.565972.AE

ABSTRACT

Objective To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.

Design Systematic review.

Data sources Articles (English and full text) on double blind randomised trials found by searching with the key words anticonvulsant, antidepressant, non-steroidal anti-inflammatory drugs, tramadol, opioid, ion channel blocker, diabetic neuropathy, diabetic peripheral neuropathy, peripheral neuropathy, and neuropathy. The search included Medline, Embase, EMB reviews-AP Journal club, and the Cochrane central register of controlled trials.

Study selection Randomised controlled trials comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.

Data extraction Data were extracted to examine quality of methods, characteristics of studies and patients, efficacy, and side effects. The primary outcome was dichotomous information for 50% or moderate reduction of pain. Secondary outcomes were 30% reduction of pain and withdrawals related to adverse events.

Results Odds ratios were calculated for achievement of 30%, 50%, or moderate pain relief and for withdrawals related to adverse effects. Twenty five reports were included and seven were excluded. The 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), N-methyl-D-aspartate antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% confidence interval 1.77 to 16.02) for traditional anticonvulsants, 3.25 (2.27 to 4.66) for newer generation anticonvulsants, and 22.24 (5.83 to 84.75) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (0.33 to 6.96) for traditional anticonvulsants, 2.98 (1.75 to 5.07) for newer generation anticonvulsants, and 2.32 (0.59 to 9.69) for tricyclic antidepressants. Insufficient dichotomous data were available to calculate the odds ratios for ion channel blockers.

Conclusion Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers.

INTRODUCTION

Diabetic neuropathy is a common complication of diabetes. An Australian population based survey of 2436 patients with known or newly diagnosed diabetes showed that 13.1% of them had peripheral neuropathy.¹ Another multicentre study in the United Kingdom showed that 22-32% of 6363 diabetic patients had peripheral neuropathy.² Similar results have been reported by an Italian multicentre study, which showed that 32.3% of 8757 diabetic patients had neuropathy.³

Symptoms of neuropathic pain are commonly reported in patients with diabetic neuropathy. Partanen and colleagues found that among 132 patients, 7-13% had pain and paraesthesias when they were diagnosed as having type 2 diabetes mellitus.⁴ The prevalences of pain and of paraesthesia were 20% and 33% 10 years after diagnosis.⁴

Tight glycaemic control has been shown to be effective in slowing the progression of diabetic neuropathy.⁵⁻⁸ Antidepressants and anticonvulsants are commonly used to reduce the intensity of pain in patients with painful diabetic neuropathy. In the clinical setting, despite the use of various analgesics to manage the neuropathic pain of diabetic neuropathy, the problem persists. We did a systematic review to explore the effectiveness of analgesics in managing diabetic neuropathy.

METHODS

Search strategy to identify studies—We identified randomised trials that studied analgesics used to treat

This article is an abridged version of a paper that was published on bmj.com on 11 June 2007. Cite this version as: *BMJ* 2007;335:87-90. doi: 10.1136/bmj.39213.565972.AE (abridged text, in print: *BMJ* 2007;335:87-90)