Clinical effectiveness and cost-effectiveness of foam sclerotherapy, endovenous laser ablation and surgery for varicose veins: results from the Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) randomised controlled trial

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Scientific summary

Results from the CLASS randomised controlled trial

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Scientific summary

Background

The treatment of patients with varicose veins imposes a considerable workload and financial burden on the NHS. Foam sclerotherapy (foam) and endovenous laser ablation (EVLA) have emerged as alternative treatments to surgery for patients with varicose veins, but uncertainty exists regarding their clinical effectiveness and cost-effectiveness in the medium and long term. In particular, the rate of recurrence of varicose veins is unclear. If this is greater than after conventional surgery, then the potential short-term gains of minimally invasive therapy may be lost by the need for additional treatment.

Aims and objectives

Comparison of LAser, Surgery and foam Sclerotherapy (CLASS) is a pragmatic, parallel-group randomised controlled trial (RCT) designed primarily to assess the clinical effectiveness and cost-effectiveness of three treatment modalities: (a) foam; (b) EVLA (with delayed foam sclerotherapy to residual varicosities when required); and (c) surgery.

Primary outcome measures included disease-specific quality of life (QoL), measured by the Aberdeen Varicose Vein Questionnaire (AVVQ), and generic QoL, measured by the European Quality of Life-5 Dimensions (EQ-5D) and Short Form questionnaire-36 items (SF-36) physical and mental component scores at 6 months (and 5 years), as well as cost-effectiveness, measured as cost per quality-adjusted life-year (QALY) gained.

The secondary objective was to compare the three treatments for (a) clinical success, as determined by residual varicose veins, Venous Clinical Severity Score (VCSS), complication rates and return to normal activities; (b) QoL [AVVQ, SF-36 physical and mental components and domains, EQ-5D and EQ-5D visual analogue scale (VAS) at 6 weeks, and SF-36 domains and EQ-5D VAS at 6 months]; (c) anatomical success, determined by duplex scan [partial or complete ablation of, or the presence of reflux in, the great saphenous vein (GSV) or small saphenous vein (SSV)] at 6 months; and (d) the cost to the health service and to patients of each intervention and any subsequent care.

Methods

Seven hundred and ninety-eight patients referred from primary care to vascular surgery departments in 11 UK centres for treatment of their varicose veins were recruited over 48 months (between November 2008 and October 2012). Research ethical approval and full written informed consent were obtained. The trial involved an off-licensed use of a licensed product, sodium tetradecyl sulphate (STS) (Fibrovein®, STD Pharmaceutical), for which Medicines and Healthcare Products Regulatory Agency (MHRA) approval was obtained.

We included adult patients with primary varicose veins which were symptomatic [clinical, etiological, anatomical, pathological (CEAP) classification C2 grade or above], either unilateral or bilateral, and those with GSV and SSV with reflux > 1 second on duplex ultrasound. We excluded those with current deep-vein thrombosis or acute superficial-vein thrombosis; GSV or SSV < 3 mm or > 15 mm in diameter; tortuous veins that were considered to be unsuitable for EVLA; and contraindications to foam or to general/regional anaesthesia which would be required for surgery.

Study set-up

Patients were randomised within two strata: stratum A included eight hospitals which offered all three treatment options and stratum B included three hospitals which offered only two treatment options (foam sclerotherapy and surgery). Outcomes were assessed at 6 weeks and 6 months post treatment. At 6 weeks, patients in the foam and EVLA arms were offered foam for any residual varicosities.

Randomisation

Participants were randomised using a computer-generated randomisation system managed by the Centre for Healthcare Randomised Trials (CHaRT) at the University of Aberdeen. Participants were randomly allocated 1 : 1 to all the options available at each site. The minimisation algorithm included centre, age (< 50 years, ≥ 50 years), sex, presence of GSV or SSV reflux and unilateral or bilateral varicose veins.

Study interventions

Surgery of the main truncal veins and varicose tributaries was performed concurrently. EVLA of the main truncal veins was performed at an initial treatment, with foam to residual varicosities, if required, carried out at or after 6 weeks. For foam, 3% STS was administered to truncal and 1% to non-truncal veins. Foam to non-truncal varicosities was performed in 31% of patients following EVLA and in 38% randomised to foam.

Statistical analysis

An intention-to-treat analysis was performed. The primary and secondary outcomes were compared using mixed linear repeated-measures models, adjusting for baseline covariates. For secondary outcomes, a p-value > 0.005 was considered to be non-definitive. A trial-based cost-effectiveness analysis assessed mean differences in costs and QALYs at 6 months, and estimates of cost-effectiveness were extrapolated to 5 and 10 years using a Markov model. Estimates of cost-effectiveness were expressed as incremental costs per QALY gained, and the net monetary benefit (NMB) approach was used to identify the optimal treatment modality on grounds of cost-effectiveness, based on a ceiling willingness-to-pay (WTP) ratio of £20,000 per QALY gained.

The original trial sample size of 1015 (surgery vs. foam: 90% power, 5% significance; EVLA vs. foam or surgery: 80% power, 5% significance) was revised to 779 based on data which showed that the correlation between AVVQ at baseline and 6 months was better than originally assumed. We did not revise our original, minimally clinically important difference.

Results

In total, 6592 patients who attended outpatient clinics with varicose veins were unselectively screened for eligibility, and of these 3369 (51%) met the eligibility criteria. Of those who were ineligible, 43% did not fulfil the criteria for treatment in the NHS because they were asymptomatic, had no reflux, or had concurrent comorbidities or current thrombosis. A further 28% of patients had recurrent varicose veins. Less than 20% were excluded because the vein diameter was too small, too large or too tortuous. Of the 3369 eligible patients, 798 (24%) consented to participate in the trial and 76% (2571 patients) declined. The majority (78%) of patients who were eligible but declined participation did so because they had a preference for a particular treatment. Of the 798 patients who were recruited, 13 (1.6%) were excluded after randomisation. Seven hundred and twenty (92%) received their allocated treatment, 27 (3%) received a study treatment other than their randomised treatment and 38 (5%) did not receive any of the study treatments. Seven hundred and nine (90%) patients attended for the 6-weeks follow-up appointment and 670 (85%) completed the 6-weeks questionnaire. Six hundred and seventy (85%) patients attended for the 6-months follow-up appointment and 627 (80%) completed the 6-months questionnaire.

Quality of life

Aberdeen Varicose Vein Questionnaire

In all groups, disease-specific AVVQ scores improved over time (i.e. scores reduced). In the foam versus surgery comparison, the health gain obtained in the AVVQ was lower in patients undergoing foam [6 weeks $p = 0.002$; at 6 months, effect size −1.74, 95% confidence interval (CI) −2.97 to −0.50; $p = 0.006$]. EVLA and surgery had similar health gains in the AVVQ. The health gain for AVVQ in the foam versus EVLA comparison was similar at 6 weeks and 6 months.

European Quality of Life-5 Dimensions

There were no differences in the EQ-5D and EQ-5D VAS in the surgery versus EVLA or surgery versus foam comparisons at 6 weeks or 6 months. There was a significantly greater health gain at 6 weeks in patients who underwent EVLA than in those in the foam group in the EQ-5D ($p = 0.004$), but not in the EQ-5D VAS. There were no differences at 6 months.

Short Form questionnaire-36 items

There were no differences between surgery and foam for the overall physical and mental component scores or in the surgery versus EVLA comparison. In the comparison of EVLA versus foam, there were no differences in the SF-36 physical or mental component scores at 6 weeks or the SF-36 physical component at 6 months. At 6 months, the health gain in the SF-36 mental component was greater for EVLA than for foam (effect size 1.54, 95% CI 0.01 to 3.06; $p = 0.048$).

Cost-effectiveness

At 6 months, foam sclerotherapy was the least costly option, followed by EVLA and then surgery. Based on consideration of costs and QALYs at 6 months, foam had the highest probability of being considered cost-effective at a ceiling WTP ratio of £20,000 per QALY. A sensitivity analysis showed that EVLA would generate the greatest NMB at this threshold at 6 months, but only if performed in a clinic setting, rather than in an operating theatre.

The cost and effect data from the trial were used to populate a 5-year Markov cost-effectiveness model. For the first 6-month cycle, the model was populated using mean cost and utility data obtained from all randomised patients. Beyond 6 months, the best available evidence on the risk of clinical recurrence following each treatment modality was used to model clinical recurrence and subsequent associated costs and consequences. The model suggests that, for patients considered clinically suitable for all three treatment options, EVLA had the highest probability (≈ 79%) of being cost-effective at 5 years when applying a ceiling ratio of £20,000 per QALY gained, followed by foam (≈ 17%) and then surgery (≈ 5%). In a two-way comparison between foam and surgery, surgery was found to have the greatest probability of being cost-effective at 5 years, although a great deal of uncertainty surrounds this finding owing to the significantly higher cost of surgery and lack of long-term recurrence rates data for both interventions.

Clinical outcomes

At 6 months there were no differences in the VCSS between treatment groups. There were fewer residual veins at 6-months follow-up (lower VAS scores) in the surgery group than in the foam group (nurse- and patient-reported data, $p < 0.001$). Fewer patient-reported residual varicosities were noted in the EVLA group than in the foam group at 6 months ($p = 0.005$).

Ablation rates

At 6 months, both surgery ($p < 0.001$) and EVLA ($p < 0.01$) were more effective than foam. There were no differences between EVLA and surgery.

Complications

The event rate for any procedural complication was similar for surgery and foam (7% for surgery and 6% for foam), but at 6 months complications were significantly more frequent after foam than after surgery ($p < 0.05$). Complications which occurred less frequently after surgery than after foam were lumpiness (6 weeks and 6 months, $p < 0.001$), skin staining (6 weeks, $p < 0.001$; 6 months, $p < 0.001$), persistent tenderness (6 weeks, $p < 0.001$) and headache (6 weeks, $p = 0.047$). Cutaneous numbness was more common after surgery than after foam, at 6 weeks and 6 months ($p < 0.001$).

The event rate for any procedural complication was lower for EVLA (1%) than for either foam (7%) or surgery (8%) ($p < 0.001$). At 6 weeks, the following occurred less frequently in patients undergoing EVLA than in those undergoing foam: persistent bruising ($p < 0.001$), persistent tenderness ($p < 0.001$), lumpiness ($p < 0.001$) and skin staining ($p < 0.001$). Cutaneous numbness occurred more frequently following EVLA than following foam (6 months, $p = 0.012$).

In the surgery versus EVLA comparison, persistent bruising ($p = 0.012$), persistent tenderness ($p = 0.011$) and lumpiness ($p = 0.018$) occurred more frequently in patients undergoing surgery at 6 weeks, whereas lumpiness ($p = 0.041$) and skin staining ($p = 0.009$) were less frequent after surgery at 6 months. Finally, cutaneous numbness was less common after EVLA than after surgery ($p = 0.037$) at 6 months.

Behavioural recovery

We developed an instrument, BRAVVO (Behavioural Recovery After treatment for Varicose Veins), in order to (a) identify which behaviours are important to patients when recovering from varicose vein treatment, and (b) measure how quickly patients return to performing these activities after treatment. Results showed that patients were able to return to a wide range of behaviours more quickly following foam and EVLA than after surgery.

Conclusions

This is the first RCT involving foam to evaluate disease-specific QoL as a primary outcome measure. It shows that the health gain achieved with foam (AVVQ) was significantly lower than that for surgery at 6-months follow-up. No differences were noted between surgery and foam in the other QoL outcome measures. EVLA was marginally superior to foam in terms of the SF-36 mental component, but there were no differences in the other QoL measures at 6 months. EVLA and surgery were broadly equivalent in terms of QoL at 6 months. Greater gains in QoL were observed for EVLA at 6 weeks than for surgery, and for surgery and EVLA than for foam. Foam sclerotherapy produced the greatest NMB at 6 months, at a ceiling WTP ratio of £20,000 per QALY gained. Markov modelling, based on the trial data and the limited data currently available on longer-term recurrence rates, suggested that, at 5 years, EVLA is most likely to be the treatment of choice for suitable patients, based on considerations of both clinical effectiveness and cost-effectiveness. In a two-way comparison between foam and surgery, we found surgery to have the higher probability of being cost-effective at 5 years.

The presence of residual varicose veins and the frequencies of some complications were higher after foam than after either surgery or EVLA. This may have had an impact on QoL. However, participants returned to normal activities more quickly following foam than following EVLA or surgery. Truncal vein ablation rates were independently assessed and were found to be significantly lower in the foam group than in the surgery and EVLA groups. The reduced ablation rates observed for foam may lead to an increased risk of developing recurrent varicose veins in those patients, with associated reduced QoL and costs of further treatment. However, the 5-year recurrence rates following foam are unknown.

Strengths and weakness

The study experienced recruitment difficulties which led to a revision in the target size based on an interim analysis. This did not lead to any reduction in the predefined clinically important difference in QoL, but may have disadvantaged the EVLA arm, which had reduced power.

Following an unselected screening process, 43% of patients were found to be ineligible for randomisation. Of these, 30% were excluded because they would not be offered treatment in the NHS (i.e. they were asymptomatic, had no truncal reflux or had current thrombosis) and a further 28% had recurrent varicose veins. Less than 20% were excluded because the vein diameter was too small or large, or too tortuous. Thus, the results appear generalisable to the majority of patients undergoing treatment of primary varicose veins in the NHS.

Despite the fact that many eligible patients chose not to take part, those who did appear broadly similar to those in other RCTs, with the exception that there was a lower-than-expected proportion of females. The CEAP classification grade, VCSS (pre/post treatment) and QoL (pre/post treatment) were similar to those in other RCTs. The QoL values were also similar to those published in NHS England patient-reported outcome measures. Although the complete success rates for the GSV are at the lower end of those published in other RCTs, many studies defined 'technical success' as the combination of complete ablation and partial success with no reflux. The overall 'technical success' rate for CLASS is comparable (91% for EVLA and 82% for surgery). The results for foam (67% complete and partial with no reflux) remain lower than in some studies, but are comparable with those of two RCTs.

Overall summary

We believe that the results of this trial are generalisable to patients with primary varicose veins who are suitable for treatment with EVLA, foam or surgery. Our results suggest that EVLA should be considered as the preferred option in terms of both clinical outcomes at 6 months and estimated 5-year cost-effectiveness.

Recommendations for future research

Long-term outcome data from RCTs on QoL, recurrence rates and costs are required for foam and other endovenous techniques, compared against each other and against surgery.

Trial registration

This trial is registered as ISRCTN51995477.

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