Cost-effectiveness of ultrasound guided foam sclerotherapy (UGFS), endovenous laser ablation (EVLA), and surgery as treatments for primary varicose veins: results based on the CLASS trial

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Abstract

Background: The treatment of patients with varicose veins is a considerable workload and financial burden to the NHS. This study aimed to assess the cost-effectiveness of UGFS and EVLA compared to conventional surgery as treatments for primary varicose veins.

Methods: Participant cost and utility data were collected alongside the UK CLASS multicentre randomised controlled trial, which compared EVLA, surgery and UGFS. Regression methods were used to estimate the effects of the alternative treatments on costs to the health service and quality adjusted life years (QALYs) at six months. A Markov model, incorporating available evidence on clinical recurrence rates, was developed to extrapolate the trial data over a five year time horizon.

Results: Compared to surgery at six months, UGFS and EVLA reduced mean costs to the health service by £655 and £160 respectively. When additional overhead costs associated with theatre use were included, these cost-savings increased to £902 and £392, respectively. UGFS produced 0.005 fewer QALYs whilst EVLA produced 0.011 additional QALYs. Extrapolating to five years, EVLA was associated with increased costs and QALYs compared to UGFS (costing £3,640 per QALY gained), and generated a cost-saving (£206-£439) and QALY gain (0.078) compared to surgery. Applying a ceiling willingness to pay ratio of £20,000 per QALY gained, EVLA had the highest probability (78.7%) of being cost-effective.

Conclusions: The results suggest that for patients considered eligible for all three treatment options, EVLA has the highest probability of being cost-effective at accepted thresholds of willingness to pay per QALY.

Introduction

The treatment of patients with varicose veins results in a considerable workload and financial burden to the NHS.[1] Ultrasound guided foam sclerotherapy (UGFS) and endovenous laser ablation (EVLA) are now commonly used alternatives to surgery. Despite their widespread adoption uncertainty exists about their cost-effectiveness and about which method offers the best value for money.

To date there have been three published cost-utility analyses comparing these treatment modalities from a UK National Health Service (NHS) perspective, based on estimated treatment costs and outcomes, follow-up costs and five year recurrence rates. These have revealed differing results. One found EVLA and radiofrequency ablation (RFA) to be the most cost-effective[2], another found day-case EVLA to be cost-effective[3], whilst a third study found UGFS to be the most cost-effective[4].

CLASS is a multicentre randomised controlled trial which compared the clinical and cost effectiveness of three treatment modalities: UGFS; EVLA; and surgery.[5] Participant level cost and effect data were collected at six weeks and six months. A Markov decision model was developed to extrapolate the trial cost-effectiveness data over a 5 year time horizon. Results of these analyses are presented in this manuscript.

Materials and Methods

Seven hundred and ninety-eight participants were recruited from 11 centres in the United Kingdom from November 2008 to October 2012. All three treatment options were available in eight centres while three centres offered only UGFS and surgery: participants were randomised between the treatments with even allocation. This paper reports on the eight centres where all three treatment options were available. The allocation used a minimisation algorithm that included centre, age (<50 years, ≥50 years), sex, great saphenous vein (GSV) or small saphenous vein (SSV) reflux, and unilateral or bilateral veins. Inclusion criteria included: age over 18; primary unilateral or bilateral symptomatic varicose veins (Clinical Etiologic Anatomic Pathophysiological – CEAP - grade C2 or above)[5]; GSV and/or SSV involvement; and reflux > 1 second on duplex ultrasound. Exclusion

criteria included: current deep vein thrombosis; acute superficial vein thrombosis; a GSV or SSV diameter < 3mm or > 15mm; tortuous veins considered unsuitable for EVLA; and contraindications to UGFS or to general/regional anaesthesia which would be required for surgery. Further details of the trial are published elsewhere.[5]

Treatments

Surgery was performed under general anaesthetic. It consisted of proximal GSV/SSV ligation and stripping (all GSV) and concurrent phlebectomies. EVLA of truncal veins was performed under local anaesthetic in either an operating theatre (9.5% of patients) or treatment room (90.5% of patients). Further UGFS was administered to residual varicosities at six week follow-up if required, with the exception of one centre which performed concurrent phlebectomies. Foam was produced using the Tessari technique[6] at a ratio of 0.5ml sodium tetradecyl sulphate to 1.5ml air (3% STS for GSV/SSV truncal veins, 1% for varicosities, maximum of 12ml of foam per session).

Resource use and costs

Participant level resource use data were collected for each treatment modality and entered onto case report forms. Details of the following resource items were collected: location and time of treatment and recovery, and grade of surgeon and anaesthetist present. A separate survey of participating centres collected information on nursing and allied health professionals present for each procedure, and equipment and consumables used.

All resource inputs were costed in 2010/2011 unit prices (Table 1). The time of entering and time of leaving the operating theatre or treatment room was used to measure the total time requirement of staff present for the procedure. Staffing information and treatment/recovery duration times were combined with national unit cost data (PSSRU, 2011)[7] to estimate the total cost of staff time. Whilst the staff cost multipliers included an allocation for overheads and use of hospital space, these may not adequately capture the additional overhead costs associated with cases performed in theatre under general anaesthetic. Therefore, a secondary analysis was conducted whereby an estimate of theatre

overhead cost (£218 per hour)[8] was applied to cases carried out in this location. Capital equipment costs were amortised over the expected useful lifespan of the item, and allocated on a per patient basis using estimated annual clinical throughput obtained from sites. The majority of centres in CLASS reported receiving the laser generator for EVLA on loan but paying for laser fibres. Therefore, the generator costs were excluded from the base case analysis, but were included in a sensitivity analysis. A list of consumables required for each procedure was established and costed using unit prices obtained from participating centres.

Details of secondary health care services use after treatment (hospital admissions and outpatient attendances) were collected at six weeks and six months. Use of primary care services was collected from a six month patient-completed questionnaire. All CLASS participants were invited to attend a six week and six month assessment appointment but only the six week assessment following UGFS or EVLA (to assess the need for further foam treatment) was considered potentially consistent with routine practice. Therefore, the cost of an outpatient appointment plus ultrasound scan was incorporated for patients attending this appointment following UGFS or EVLA. For patients in the EVLA or UGFS arms who underwent additional foam treatment at six weeks, the cost of the treatment, rather than the cost of follow-up assessment, was applied. The impact of applying the cost of an assessment visits prior to receiving top-up foam treatment was also assessed, as was the impact of removing all post-treatment assessment costs. National unit cost data were used to cost secondary and primary care contacts (Table 1).[7,9] The total cost to the health service (to six months) was computed for each participant by summing their treatment and follow-up costs.

Health outcomes

The EQ-5D-3L was completed by participants at baseline, six weeks and six months. A preference based utility score was derived for each participant's response to the EQ-5D using the UK population time trade-off tariff.[10] These scores represent the desirability of the different heath states defined by the EQ-5D on a scale where zero is equal to death and one is full health. Quality adjusted life years (QALYs) can be derived from responses to the EQ-5D by multiplying the time (in years) spent in

different states of health by the utility score associated with each state. The QALYs accrued to each participant at six months were calculated assuming that the change in utility between measures at adjacent time points followed a straight line.

Analysis of participant level cost and outcome data

Data were summarised and analysed by intention to treat using Stata[TM] version 12.1.[11] The mean incremental costs and QALYs associated with EVLA and UGFS versus surgery were estimated using generalised linear regression, with adjustment for minimisation variables and baseline values as appropriate. The method of recycled predictions[12] was used to recover the estimated mean cost and six-month utility estimates for surgery, and the mean utility and cost increments associated with UGFS and EVLA were used to recover the expected utilities and costs for patients receiving these treatments. This analysis was also repeated using a multiple imputation dataset generated using chained equations.[13]

Modelling of longer term cost-effectiveness

The cost and effect estimates from the trial data were used to populate the Markov model, developed in TreeAge Pro (TreeAge Software Inc, 2013)[14] to extrapolate cost-effectiveness over a 5 year time horizon. This is the duration to which the CLASS study follow-up will ultimately be extended, providing a validity check on initial model-based estimates of cost-effectiveness.

The model was constructed to simulate transitions between discrete health states on a six month time interval (Markov cycle), for a cohort of patients with mean age and sex matching that of trial participants (Figure 1). For the first six month cycle, the model was populated using the estimated mean cost and utility data obtained from the analysis of individual patient data. Beyond six months, monthly probabilities of clinical recurrence, derived from a network meta-analysis undertaken to inform the recent National Institute for Health and Care Excellence (NICE) guideline[2] (Table 1), were incorporated in the model. Clinical recurrence was assumed to result in a drop in health state utility to the mean baseline value observed across the treatment allocation groups in CLASS. Following

clinical recurrence, patients could either present for further treatment (surgery, UGFS or EVLA), and transit to the "post-treatment for recurrent varicose veins" state, or remain in the "clinical recurrence" state. In line with the modelling undertaken to inform the NICE guideline, it was assumed that 75% of patients experiencing a clinical recurrence would receive further treatment (42% UGFS, 12% surgery, and 46% EVLA), and prior to this treatment they would consult their GP twice and attend a vascular surgery outpatient appointment.[2] The initial treatment modality was assumed not to influence the method of treatment for clinical recurrence. For patients experiencing a second recurrence, a simplifying assumption was made that these patients would not proceed to further treatment. Modelled future costs and QALYs were discounted at the recommended rate of 3.5 per cent per annum[15].

Model based analysis

To characterise uncertainty each model input was assigned a distribution appropriate to the nature of the variable, and the model was analysed probabilistically. For treatment cost and utility parameters, distributions were derived from the analysis of patient level data. Beta distributions were applied to the probabilities of clinical recurrence based on reported mean values and standard errors.[2] The model was estimated 10,000 times, each time sampling a value for each parameter from its assigned distribution. The mean costs and effects from these 10,000 iterations are reported for each treatment option. To help identify the optimal approach to treatment, the net monetary benefit (NMB) framework was used, where the NMB for a given strategy is equal to the accrued QALYs multiplied by the ceiling ratio (Rc) of willingness to pay (WTP) per QALY, minus the strategy costs.

NMB = (QALYs x Rc) - Costs

The value of £20,000, which is typically used by NICE to inform judgements on cost-effectiveness, was placed on Rc.[15] The probability of each strategy generating the greatest NMB at this value of Rc is reported. Extensive deterministic sensitivity analysis was undertaken to assess the robustness of the findings to various parameter and structural assumptions applied in the base case analysis. This

included basing model input parameters on the analysis of multiple imputed patient data, to assess the sensitivity of findings to missing data.

To assess the sensitivity of findings to model structuring assumptions, an alternative model structure was developed using pre and post treatment health states defined by clinical severity, as assessed by the Venous Clinical Severity Score (VCSS).[16] In this model changes in quality of life were driven solely by transitions across four clinical severity states defined using the VCSS (0, 1-3, 4-6, >6). The patient data were then used to estimate the effects of the alternative treatments on transitions between these states from baseline to six months post treatment. The defined states were found to correlate reasonably with participants EQ-5D scores, which reflect participants' self-reported general health status and were used for estimating QALYs within this model.

Results

The mean estimates of resource use, costs and EQ-5D values are summarised in the supplementary Table 1. The cumulative mean time spent in treatment was considerably lower for those participants randomised to UGFS than it was for EVLA or surgery. Based on estimates of treatment duration, associated staff costs, consumable and equipment costs, the estimated total treatment costs were £245, £737 and £916 for participants randomised to UGFS, EVLA and surgery, respectively. Recovery time costs were highest for participants randomised to surgery. The cost of consumables was considerably higher in the EVLA group, on account of the high cost of the laser fibre (unit cost £256).

Total NHS costs at six months, incorporating routine follow-up (following EVLA and UGFS) and further unplanned use of health services, were £453, £951 and £1,113 for participants randomised to UGFS, EVLA and surgery, respectively. When an additional cost of theatre usage was included to reflect higher overhead costs, the corresponding costs increased to £465, £975 and £1,367, respectively.

The regression based estimates of the mean differences in cost and utility outcomes between treatment modalities, which were applied in the Markov model, are summarised in Table 2. Using multiple imputation data, the mean cost savings associated with UGFS and EVLA compared to surgery decreased somewhat (Table 2).

Model based Incremental cost-effectiveness analysis

The model based estimates of mean costs and QALYs at five years are presented in Table 3. EVLA was associated with increased costs and QALYs in comparison with UGFS, with an incremental cost per QALY gained of £3,640. Surgery was associated with increased costs compared with EVLA (£206), and on average produced slightly fewer QALYs (-0.078). This was driven by the slightly lower number of QALYs observed for surgery at six months compared to EVLA, and also the slightly higher clinical recurrence rate applied to surgery compared with EVLA. Applying a ceiling willingness to pay ratio of £20,000 per QALY gained, EVLA had the highest probability (78.7%) of being cost-effective.

The proportion of probabilistic iterations favouring each of the alternative strategies by increasing levels of willingness to pay per QALY gained is shown in Figure 2. This figure shows that as WTP increases beyond £30,000, EVLA has an ~80% chance of being the optimal strategy on grounds of cost-effectiveness.

Sensitivity analysis

The results of various analyses assessing the sensitivity of results to uncertainty surrounding several key input parameters and modelling assumptions are shown in supplementary Table 2. In general, the findings were robust to changes, including the cost of follow-up assessment in patients requiring further foam sclerotherapy treatment following EVLA and UGFS, the use of multiple imputation for missing data, and the inclusion of the annuitized cost of a laser generator. The application of additional theatre overhead costs, and the removal of all follow-up clinical assessment costs, increased the estimated cost savings associated with EVLA compared with surgery to £439 and £332

respectively. It was also noted that in some centres EVLA was carried out with a greater number of staff present than for UGFS. When all EVLA procedures were costed using the same nursing staffing profile as for UGFS, the cost saving with EVLA compared to surgery increased to £368.

When applying the assumption of equivalent QALYs between the strategies to six months, and equivalent EQ-5D values at six months (rather than the treatment specific mean estimates), UGFS had the highest probability of being cost-effective at five years (supplementary Table 2, scenario 13). However, the base case ordering of treatment modalities was restored when the time horizon for this analysis was extended to 10 years (supplementary Table 2, scenario 14).

The analysis of the alternative model structure, based on clinical severity states defined by the VCSS, predicted higher QALYs with EVLA compared to UGFS, and slightly higher QALYs with surgery compared to EVLA (supplementary Table 2, scenario 22). However, the probability of surgery being cost-effective remained lower than that for EVLA at the ceiling ratio of £20,000 per QALY.

Discussion

The results of this study suggest that, over a five year time horizon, EVLA is likely to be the preferred option on grounds of cost-effectiveness, costing £3,640 per QALY gained in comparison with UGFS, and costing less and producing slightly more QALYs than surgery. EVLA had a ~79% chance of being cost-effective at a ceiling willingness to pay ratio of £20,000 per QALY. These findings were generally found to be robust to uncertainty surrounding various model inputs and assumptions, including multiple imputation of missing data, and alternative model structuring assumptions.

The base case estimated reduction in cost (£206) associated with EVLA compared to surgery, is likely to be a conservative estimate that does not fully capture the increased overhead costs associated with day case admission and use of theatre required for surgery. When a separate estimate of theatre overhead costs (per hour) was factored into the analysis, the cost saving associated with EVLA increased to £439. This additional overhead cost was omitted from the base case analysis because it

was only available for one recruiting centre and it may also double count some of the overhead costs included in the staff time unit cost multipliers. However, even when excluding this cost, sensitivity analysis indicated that the cost savings associated with EVLA would increase to £336 if performed using a similar staff profile to UGFS, and that further savings would also be realised if patients with a good outcome following initial EVLA treatment were not followed up at six weeks in routine practice.

Strengths and limitations

The model was populated, where possible, using estimates of the mean differences in costs and effects derived from the analysis of prospectively collected individual patient data on resource use. Therefore, the results are internally valid and generalisable across settings in the UK.

In the absence of data on long-term clinical recurrence for the CLASS cohort, the risk of clinical recurrence was modelled using data derived from an existing network meta-analysis of trials reporting clinical recurrence of varicose veins as an outcome.[2] While this provides the best current source of evidence on recurrence, the quality of included trials varied and follow-up generally extended to only 12 or 24 months. Further, definitions of clinical recurrence were not always well defined and varied between studies. Uncertainty remains regarding the applicability of these recurrence rates to patients in the CLASS trial (and more generally), and also regarding the risks of recurrence beyond 24 months. This underlines the importance of collecting further data on clinical recurrence and its impact on generic HRQoL via the extended follow-up of CLASS participants which is currently in progress, with expected results in 2018.

Comparison with other cost effectiveness studies

In general, the modelling approach used in this paper is consistent with that used in previous economic modelling studies of treatments for varicose veins. The structure and assumptions applied in our primary analysis are in line with those used in the model developed to inform the recent NICE Clinical Guideline 168 on (Varicose veins in the legs: the diagnosis and management of varicose

veins)[2] which also found that endothermal treatment (EVLA or RFA) had the highest probability of being cost-effective under most scenarios assessed.

However, the cost and utility inputs applied in our model were based on prospectively collected data from randomised patients. Consequently, based on our 'bottom-up' costing approach, we estimated a somewhat narrower difference in cost between EVLA and surgery compared with the estimates used in the NICE guideline model. This was due to differences in our estimated mean treatment durations, and the reported staffing profiles for the different procedures, compared to those used in the NICE model. Our estimates are more likely to be representative of current practice because they were derived using time and staffing data collected prospectively alongside the CLASS trial. Furthermore, rather than assuming equivalent utility values following the different treatment modalities at six months (as was done in the NICE guideline model), we applied the estimated six month mean incremental differences between UGFS and surgery and between EVLA and surgery.

Gohel *et al*[3] similarly developed a Markov model to assess the cost-effectiveness of conservative management, UGFS, EVLA, RFA and surgery. Based on their model, Gohel and colleagues estimated that EVLA carried out under local anaesthetic would have the highest chance of being cost-effective at a ceiling ratio of £20,000 per QALY. In contrast to our findings they reported that surgery (on a day case basis) had the next highest probability of being cost-effective, followed by RFA and UGFS.[3]

Our findings appear inconsistent with those of a recently conducted modelling study which concluded UGFS would be more cost-effective than surgery, EVLA and RFA, based it having the lowest cost whilst generating similar clinical outcomes. Within this modelling study, Carroll and colleagues used data from two single centre UK trials to assess the relative cost differences between UGFS, RFA, EVLA and surgery.[17, 18] Based on these data, the cost of EVLA was estimated to be 2.02 times that of surgery. However, this multiplier was derived from cost data collected for 88 patients randomised between surgery and RFA,[17] and in this particular study RFA was performed under general anaesthesia and took 30 minutes longer than surgery. The staff and theatre costs were thus higher for

RFA than surgery. By contrast in CLASS, all EVLA procedures were performed under local anaesthetic; the majority (90.5%) were carried out in a clinic treatment room rather than an operating theatre; and the measured procedure time was lower for EVLA than for surgery. This information was collected prospectively for patients recruited to CLASS from multiple treatment centres, and so should be generalisable to standard NHS practice. This explains our lower estimate for the cost of EVLA compared with surgery, and also helps explain why we found EVLA to be cost-effective in comparison with UGFS.

Conclusions

In conclusion our modelling suggests that for patients with primary varicose veins, in whom all three of the investigated treatment modalities offer a clinically viable option, EVLA performed under local anaesthetic has the highest probability of being cost-effective at accepted thresholds of willingness to pay per QALY. This finding is consistent with the results of recent modelling undertaken to inform the NICE clinical guideline on the management of varicose veins. In the interests of cost-effectiveness, EVLA should be performed where possible in a clinic treatment room and the levels of nursing support required should be carefully considered.

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