Laser and Radiofrequency Ablation Study (LARA study): A Randomised Study Comparing Radiofrequency Ablation and Endovenous Laser Ablation (810 nm)

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Abstract
Objectives: There have been few randomised studies comparing Radiofrequency Ablation (RFA) with other endovenous techniques. The primary aim of this study was to determine whether RFA of the great saphenous vein (GSV) was associated with less pain and bruising than endovenous laser ablation (EVLA).

Materials and methods: This trial had two cohorts: patients with bilateral GSV incompetence causing varicose veins (VV) and those with unilateral GSV VVs. In total 87 legs were treated in this study. Limbs in the bilateral group were treated with RFA in one leg and EVLA in the other. In the unilateral group limbs were randomised to RFA or EVLA. RFA was performed using the Celon RFITT system (Teltow, Germany). EVLA was performed using an 810 nm Laser (Biolitec AG, Germany). Phlebectomies were performed as required. Primary endpoints were patient assessed pain and bruising measured by visual analogue scale (VAS). Secondary endpoints were patency assessed by duplex ultrasound at 6 weeks and 6 months.

Results: In the bilateral group, RFA resulted in significantly less pain than EVLA on days 2–11 postoperatively. RFA also resulted in significantly less bruising than EVLA on days 3–9. There were no significant differences in mean post operative pain, bruising and activity scores in the unilateral group. Both RFA and EVLA resulted in occlusion rates of 95% at 10 days postoperatively.

Conclusions: RFA was less painful for patients than EVLA and produced less bruising in the postoperative period with comparable success rates but there was no difference in the unilateral group.

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Introduction

The development of minimally invasive procedures for the treatment of varicose veins has been led by a desire to reduce operative trauma and bruising associated with standard surgical techniques. Currently there are two major thermal endovenous treatments available; Endovenous Laser Ablation (EVLA) and Radiofrequency Ablation (RFA). Randomised clinical trials comparing EVLA with surgery have shown EVLA to be an equally effective treatment, while producing less pain and bruising and a significantly better quality of life. Randomised studies comparing RFA and open surgery showed that RFA caused less pain, bruising and fewer complications with less time off work.

At the time of designing our study, the comparative advantages of RFA and EVLA with an 810 nm laser had not been assessed. The primary aim of this study was to determine whether RFA of the GSV was associated with less pain and bruising than EVLA. The secondary aims were to assess efficacy of vein ablation and quality of life following these procedures.

Methods

Patients who presented at the Department of Vascular and Endovascular Surgery at University Hospital Nottingham with bilateral or unilateral varicose veins between March 2006 and December 2007 were considered for inclusion in this study. Each patient had a pre-operative duplex ultrasound examination to identify the site of reflux and suitability for endovenous ablation. Ultrasonography was performed by two vascular technologists using GE Logic 9 scanners (General Electric ultrasound, Milwaukee, USA). Two cohorts of patients were studied: patients with bilateral varicose veins (BLARA study) and patients with unilateral varicose veins (ULARA study). All participants gave written informed consent, and the study was approved by the hospital research and development department and the Research Ethics Committee.

Inclusion and exclusion criteria

Guidelines for inclusion on duplex criteria included a GSV without significant tortuosity or with a diameter less than 12 mm lying in the saphenous compartment and not a more superficial tributary. Veins had to be free of current or previous thrombophlebitis. Patients who were on anticoagulants, who had pacemakers, concomitant peripheral artery disease or serious systemic disease were excluded. All patients had to have venous disease which was Clinical grades 2–6, primary (Ep), Superficial (As) and reflux only (Pr).

Randomisation was performed preoperatively using random number generator. For the BLARA study the left leg was randomised to one treatment with their right leg assigned to the other. Patients presenting with unilateral varicose veins were randomised to either RFA or EVLA for the affected limb (ULARA study). Patients were not advised of the treatment allocation so ensure that this trial was carried out in a blinded fashion, as far as was possible. All operations for the BLARA study were carried out in the Day Surgery Unit, City Hospital, Nottingham and were performed under general anaesthetic by the same surgeon. History and consent were taken from the patient and the veins marked with a pen. The CEAP classification was assigned by a surgeon skilled in the management of venous disease. Patients were asked to complete the Aberdeen Varicose Vein Questionnaire (AVVQ) preoperatively. This has been shown to be a valid measure of quality of life for patients with varicose veins. Treatment was carried out under general anaesthetic. For RFA, under ultrasound guidance a 6F sheath was introduced into the vein at an appropriate point near or below the knee crease using a Seldinger technique. The RFA applicator was passed through the sheath and into the GSV under ultrasound control. A laser sheath was inserted in a similar way for patients undergoing EVLA. The RF catheter or laser sheath was inserted and the tip positioned to approximately 2 cm below the saphenofemoral junction or just distal to a competent tributary of the GSV under ultrasound guidance. For EVLA the BioLITEC (Biolitec AG, Germany) and for RFA Olympus Celon RFITT (Teltow, Germany) systems were used.

Tumescent fluid (0.9% saline without local anaesthetic) was injected into the saphenous compartment of all patients who had EVLA (mean volume 467 ml). The laser fibre was then inserted and the treatment commenced. The laser fibre was inserted into the sheath after tumescence in order to avoid inadvertent damage to the laser fibre by the needle used to infiltrate fluid. The Biolitec Laser generator was used to provide laser energy (810 nm emission wavelength). Pullback rates were set in order to deliver at least 80 J/cm of energy to the vein.

In patients undergoing RFA tumescent fluid infiltration was not used routinely. However, in 11 limbs the vein was less than 1 cm from the skin. Saline was infiltrated subcutaneously in these patients to reduce the risk of skin burn (mean volume 52 ml). An Eschmarch bandage was used to compress the limb during treatment. The generator was set to deliver a power of 23 W. The RFA catheter withdrawn at approximately 0.8 cm per second during treatment using audio feedback provided by the RFITT system. Treatment stopped when the catheter entered the sheath so the vein containing the sheath was not treated.

Immediately following treatment of the GSV with RFA and EVLA, intraoperative ultrasound imaging was used to confirm shrinkage of the vein and to identify an increase in echogenicity of the vein wall. Varices were treated by phlebectomy under the same anaesthetic. The time taken to complete each phase of the treatment was recorded including the time taken to cannulate, position the catheter, inject tumescent fluid, and complete the endovenous procedure. A record was made of length of vein treated and the number of avulsions above and below the knee. All patients received a standard postoperative regimen; dressings were placed over the wounds and crepe bandages wrapped around both legs. Patients were instructed to remove all dressings on the first postoperative day, to shower and then to apply class II full length compression hosiery for 2 weeks. Patients were asked to complete post-operative assessment data sheets for 14 days assessing for pain, bruising, return to activity and any
analgesia taken. A 10 cm visual analogue scale (VAS) was used for self-assessment of pain and bruising with patients filling out a VAS for each leg treated. Scores were measured in centimetres. Patients were asked to remove the stockings on a daily basis to evaluate bruising. They were asked to return to normal activity as soon as they wished and return to activity VAS was scored as to how inactive patients were on scale of 1–10.

Duplex ultrasound scans were repeated seven to fourteen days after the operation looking for successful treatment and whether there was any residual flow in the GSV. The technologist performing the scan was not aware of the treatment allocation of any limb in the study. Patients returned to the clinic at least 6 months later. A second post-operative duplex scan was performed and patients completed a further AVVQ. Further follow-up is planned after 2 and 5 years to assess the long term outcome.

**Statistical analysis**

Statistical calculations were performed using the Statistical Package for Social Sciences (SPSS version 15.0; SPSS, Chicago, IL) software. The distribution of the demographic data was assessed and then analysed using the Student’s t tests and Mann–Whitney U tests for parametric and nonparametric data respectively. Normally distributed data were expressed as mean and SD and non normally distributed data were expressed as median and interquartile range for the purposes of this study. Analysis of the pain and bruising scores was performed using repeated measures design for the bilateral cohort including length of vein as covariate supervised by statistician. For the unilateral cohort a univariate analysis was performed including length of vein as a covariate. A P value of less than 0.05 was considered significant and a VAS score of less than one was considered normal.

**Pre-calculation of sample size**

A sample size of 20 for the BLARA study and 40 for the ULARA study had been calculated based on the assumption that there would be a 50% difference between the mean pain score for both procedures, with significance at the 5% level and a 90% power.

**Results**

The flow of patients through the two parts of this study are shown in the CONSORT diagram (Fig. 1). One-hundred and thirty five patients were considered for entry into the study. From this group 66 patients were included in the studies or a total of 87 legs. Twenty-one patients in the BLARA study and 45 patients in the ULARA study. The details of patients included in the BLARA cohort is summarised in Table 1. Table 2 summarises the details of patients from the ULARA cohort.

A greater length of vein was treated in the EVLA limbs than in the RFA limbs. The median dose per cm was 91.4 J/cm in the EVLA group. RFA was quicker to perform. The median pullback rate was 0.5 cm/s. A similar number of avulsions were performed in the RFA and EVLA limbs.

**Pain and bruising**

In patients in the BLARA cohort, pain caused by RFA was lower than that caused by EVLA. The peak pain score was day 1 for RFA and day 5 for EVLA. Pain scores were significantly different on days 2–11, with RFA being less painful than EVLA (Fig. 2). The bruising score for RFA was lower than that of EVLA, being significant on days 3, and 5–9 (Fig. 3). The peak score for RFA was day 3 and for EVLA day 5. In the ULARA cohort peak pain score for both RFA and EVLA was on day 1. Both the bruising and the pain scores were similar in the RFA and EVLA groups during the postoperative period (Fig. 4).

**Quality of life**

In the BLARA cohort out of 17 patients who had bilateral treatments 14 completed questionnaires were returned. There was no statistical differences on preoperative AVVSS scores between legs randomised to receive EVLA(14 patients, right leg 6 and left leg 8, mean AVVSS 3.95) and EVLA(14 patients, right leg 8 and left leg 6, mean 3.99; P = 0.96). In the patients who completed AVVSS questionnaires 6 months after their surgery, there was no statistically significant difference in AVVSS between patients who had EVLA (mean 3.78) and those who had RFA (mean 3.55; P = 0.74).

**Return to activity**

Assessment of return to normal activity following treatment with EVLA or RFA was only possible in patients from the ULARA cohort. There were no statistical significant differences between the two treatments (Fig. 5).

**Postoperative scans**

The results of post-operative ultrasound imaging are summarised in Table 3. 96% of patients returned at a median of 10 days after treatment for their first scan and 79% of patients returned a median of 237 days postoperatively for the second scan. Similar rates of occlusion were observed in the EVLA and RFA groups.

**Complications**

Two patients developed phlebectomy wound inflammation which was treated with antibiotics by their primary care physician. The cause of inflammation was not established. One patient developed a transient area of numbness caused by a phlebectomy. There were no long term complications.

**Discussion**

This study showed that resistive RFA of the GSV using the CELON RFiTT system caused less pain and bruising in the postoperative period than EVLA using the Biolitec 810 nm Laser. The study was designed so that patients and observers were blinded to the assigned treatment. Only the surgeons knew how limbs had been treated and they were not responsible for outcome assessment. In the bilateral
study, patients received both treatment modalities and were therefore able to make objective comparisons with respect to levels of pain and bruising for each different treatment modality. This type of study design where patients act as their own 'controls' has been reported previously. This was a small study conducted by one surgeon in a single institution. The results are supported by a larger multicentre study. The difference between the study designs is that the multicentre study compared segmental conductive, rather than resistive radiofrequency ablation, with EVLA using 980 nm laser.

Several other studies have been performed to assess pain and bruising following RFA and EVLA treatments. The results of these studies also support our findings, when EVLA treatment bruise scores ranged from 1.3 to 46% and significant postoperative pain was experienced by 3.9–67% of patients. This compares with only 10.8% of patients experiencing limb pain on day 3 in a recent series of 194 patients treated with RFA. In the same study 6.4% of

Figure 1 The CONSORT diagram for the BLARA and ULARA studies.

| Table 1 Demographic and treatment details of patients in BLARA cohort. |
|-----------------|-----------|-----------|
|                  | Laser     | RF        | P value |
| Age              | 47 ± 12   | 47 ± 11   | 1       |
| Sex              |           |           |         |
| Male             | 2         | 2         | 1       |
| Female           | 15        | 15        |         |
| Cannulation time (min)<sup>a</sup> | 1 (IQR 1–2.75) | 1 (IQR 1–3.75) | 0.615 |
| Positioning time (min) | 3.8 ± 2.6 | 3 ± 1.7 | 0.338 |
| Volume tumescence (ml)<sup>a</sup> | 467 (IQR 412–550) | 52 (IQR 0–100) | 0.0001 |
| Tumescence time (min) | 7.4 ± 2.1 | 1.9 ± 1.3 | 0.0001 |
| Length of procedure (min)<sup>a</sup> | 4.5 (IQR 3.25–5) | 2 (IQR 2–3) | 0.0001 |
| Lower leg avulsions | 7 ± 5 | 9 ± 5 | 0.255 |
| Upper leg avulsions<sup>a</sup> | 1 (IQR 0–2.75) | 0 (IQR 0–6.75) | 0.822 |
| Total no avulsions | 14 ± 7 | 15 ± 6 | 0.493 |
| Time for avulsions (min) | 15 ± 9 | 19 ± 7 | 0.341 |
| Length of vein treated (cm)<sup>a</sup> | 46 (IQR 44–49) | 37 (IQR 31–43) | 0.0001 |
| Diameter of vein (cm) | 7.5 ± 2.5 | 8.1 ± 2.6 | 0.51 |
| Joules/cm for EVLA | 91.4 | N/A |         |

<sup>a</sup> Data were not normally distributed and therefore nonparametric statistic test was used — Mann Whitney U test. Remaining significance values were calculated using a paired t test.
patients suffered bruising whilst only 1.6% had ultrasound proven haematoma. A recent publication by Almeida et al showed less pain and improved QOL following RF versus EVLA treatment in a randomised trial.19

Our findings may be explained by differences in the mechanism of action of RFA and EVLA to deliver energy to the vein wall.16 The generally accepted mechanisms of action of endovenous thermal treatment of varicose veins is by protein denaturation and destruction of cell structure which ultimately leads to collagen contraction,20,21 confirmed by histological studies.22,23 Another mechanism that has been proposed is that EVLA causes permanent vein closure through a high-temperature photothermolytic process at the point of contact between the vein and the laser.24 Schmedt et al.25 showed that endovenous treatment with RFA resulted histologically in reproducible and complete circular thermal alteration of vein wall. When they looked at vein wall alteration following EVLA they found changes ranging from localised tissue ablation in certain quadrants of vein wall up to complete transmural ablation and multiple perforations. The extent of vein perforation caused by EVLA may account for the increased pain and bruising experienced by patients.

The vascular technologists who performed the preoperative and postoperative duplex scans were blinded to the treatments assigned to each limb. Differences in the appearance of vein segments treated by RFA and EVLA were apparent at the time of the first postoperative duplex scan. The veins treated with RFA tended to be small in diameter whilst those treated with EVLA were large and had evidence of oedema, vein wall perforations and large amounts of haematoma in the soft tissues. These observations in ‘paired’ limbs may further support the view that higher levels of pain and bruising observed in limbs treated with EVLA are due to thermal damage of perivenous tissues and vein perforation. Previous studies have also demonstrated a higher incidence of painful thrombophlebitis with EVLA which may again explain the higher pain scores observed for EVLA in the presented study.26,27

For those included in the BLARA cohort, it could be argued that bilateral treatments might lead to unreliable assessments of pain due to distracting painful stimuli from

| Table 2 | Demographic and treatment details of patients in ULARA cohort. |
|----------------|------------------|----------------|
|               | LASER            | RF             | P value   |
| Age           | 48 ± 11.6        | 45 ± 9.3       | 0.38      |
| Sex           |                  |                |           |
| Male          | 7                | 8              | 0.513     |
| Female        | 15               | 15             |           |
| Positioning time (min) | 2 ± 0.8        | 3 ± 1          | 0.83      |
| Tumescence time (min) | 8.7 ± 3.4      | 6 ± 2          | 0.32      |
| Lower leg avulsions | 10 ± 7         | 8 ± 3.5        | 0.75      |
| Total no avulsions | 13 ± 8.3       | 10 ± 1.3       | 0.51      |
| Time for avulsions (min) | 11 ± 5.6       | 13 ± 6         | 0.70      |
| Length of vein treated (cm)a | 44 (IQR 39–48) | 35 (IQR 33–39) | 0.286     |
| Diameter of vein (cm) | 11 ± 2.3       | 8.5 ± 2.5      | 0.09      |
| Joules/cm for EVLA | 92.67 ± 20     | n/a            |           |
| a Data were not normally distributed and therefore nonparametric statistic test was used — Mann Whitney U test. Remaining significance values were calculated using a paired t-test.

Figure 2  The mean pain scores (error bars: standard deviation) for each treatment over the 2-week study period.
the contralateral limb in accordance with the gate control theory of pain.\[^28\] However, this strategy showed clearly that the EVLA group was scored as more painful than the RFA limb. Interestingly in unilateral patients there was no difference between RFA and EVLA patients. This may have been because the sample size was too small to demonstrate this small difference.

The length of vein treated was longer in the EVLA legs and it is possible that this might be the reason for higher pain scores in that group. The reason for a difference in treatment lengths was the Laser treated the GSV to the point of entry while the RF treated the GSV to the tip of the indwelling sheath. Once withdrawn into the sheath, the applicator was not in contact with the vein wall and there was no treatment. This was a technique used to reduce the risk of skin damage and to allow repeated passage of the RF applicator if required. Since the study was finished, the senior author now removes the sheath and treats the GSV to the point of entry. The reported pain scores in subsequent patients treated with RFA have remained the same as those in this study so it is unlikely that the length of vein treated affected the pain score.

More recent work has shown that the use of wavelengths longer than 810 nm laser result in less post-operative pain.\[^29\] Our study used the standard wavelength available when the trial commenced (810 nm). We acknowledge that there may be advantages in using newer lasers operating at longer wavelengths.

Patients in this study underwent phlebectomy for varices associated with truncal saphenous incompetence in the same session as saphenous ablation. There was no difference in the number of phlebectomies performed between EVLA and RFA limbs in the number of phlebectomies performed, so this will not have influenced the outcome of this study.

**Figure 3** The mean bruising scores (error bars: standard deviation) for each treatment over the 2-week study period.

**Figure 4** The mean pain scores (error bars: standard deviation) for each treatment over the 2-week study period for both BLARA(B) and ULARA(U) studies.
The success of RFA and EVLA as determined by postoperative duplex ultrasound 1 week post-operatively was 95%. These results are similar to rates reported for immediate postoperative occlusion in other studies. A recent meta-analysis of EVLA reported occlusion rates ranging from 87.9-100%. At 6 months follow up we found little difference between the 2 techniques, however only a small number of patients returned for their second scan. The actual occlusion rates were a little disappointing. The senior author was experienced in endovenous ablation and the effects of a learning curve are unlikely to have affected the results. All the EVLA procedures used a LEED of 80 J/cm of energy or more to minimise recanalisation. It is not clear why the observed success rate of EVLA was lower than more recent studies. Previous non-randomised studies have demonstrated slightly higher efficacy of EVLA compared with RFA in terms of immediate treatment success and also less recanalisation at follow up. The 74% 6-month occlusion rate of veins treated with RFA in our study might be related to the energy delivered through the vein wall. At the time of the study, the manufacturers had suggested a generator setting of between 20 and 25 W following previous successful pilot studies. A pullback rate of 1 cm/s would give a LEED of about 25 J/cm for RFA, however the mechanism of transmural resistive heating requires less energy to produce heating to 80 °C than a laser does to heat tissue to several hundred centigrade. Our practice has been revised since this study; power is now set to 10–18 W with a pullback rate of 0.5 cm/s resulting in occlusion rates of 98%. We no longer use an Esmarch bandage and employ tumescent infiltration in all patients.

In conclusion, this study showed that RFA produced less pain and bruising than EVLA using an 810 nm Biolitec system. Success of treatment, quality of life and return to activity were not affected by treatment modality.

Table 3 Summary of occlusion rates.

<table>
<thead>
<tr>
<th>Post op duplex</th>
<th>LASER</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Days</td>
<td>95% (37/39)</td>
<td>95% (38/40)</td>
</tr>
<tr>
<td>9 Month</td>
<td>78% (25/32)</td>
<td>74% (25/34)</td>
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</tbody>
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Conflict of Interest

None.

Funding

Celon supplied all Catheters without charge and have paid a fee per patient treated which contributed to but did not cover the costs of additional ultrasound scans.

BB has received fees from Celon for presenting results of studies at international meetings. These fees have also been used to pay for the ultrasound scans.

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References