A Multi-Centre Randomised Controlled Trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – Final Results of the Venefit Versus Clarivein for Varicose Veins (VVCVV) Trial

<table>
<thead>
<tr>
<th>Journal:</th>
<th>Phlebology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID</td>
<td>PHLEB-16-055</td>
</tr>
<tr>
<td>Manuscript Type</td>
<td>Original Article</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>09-Apr-2016</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Lane, Tristan; Imperial College London, Academic Section of Vascular Surgery, Department of Surgery and Cancer Bootun, Roshan; Imperial College London, Department of Surgery and Cancer Dharmarajah, Brahman; Imperial College London, Academic Section of Vascular Surgery Lim, Chung; Imperial College, SORA Najem, Mojahid; London North West Hospitals NHS Trust, Department of Vascular Surgery Renton, Sophie; London North West Hospitals NHS Trust, Department of Vascular Surgery Srittharan, Kaji; Imperial College London, Academic Section of Vascular Surgery, Department of Surgery and Cancer Davies, Alun; Surgery;</td>
</tr>
<tr>
<td>Revised Keywords:</td>
<td>Venous reflux, Varicose veins, Endovenous technique, Endovenous thermal ablation, Endovascular treatment</td>
</tr>
</tbody>
</table>
A Multi-Centre Randomised Controlled Trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – Final Results of the Venefit Versus Clarivein for Varicose Veins (VVCVV) Trial

Tristan Lane 1,2,3, Roshan Bootun 1,2, Brahman Dharmarajah 1,2,3, Chung S Lim 1,2,3, Mojahid Najem 3, Sophie Renton 3, Kaji Sritharan 1,2, Alun H Davies 1,2.

1 Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London
2 Department of Vascular Surgery, Imperial College Healthcare NHS Trust
3 Department of Vascular Surgery, London North West Hospitals NHS Trust

Correspondence:
Tristan Lane, 4N13b, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF
E-Mail: Tristan.lane@imperial.ac.uk
Telephone: 020 3311 7320
Facsimile: 020 3311 7362

Keywords:
varicose veins, randomised controlled trial, endovenous ablation, mechanical occlusion chemically assisted ablation, radiofrequency ablation, pain.

Category:
Randomised Clinical Trial

Previously Presented:
Preliminary results have been presented at the Royal Society of Medicine Venous Forum, Charing Cross Symposium, Society for Academic and Research Surgery, the Controversies and Updates in Vascular Surgery Meeting and the American Venous Forum. A short report of early results has been published in Phlebolology.

Funding:
This study was supported by a research grant from the Clarivein® device manufacturer, Vascular Insights and an educational research grant from the Graham-Dixon Charitable Trust. Vascular Insights provided funding for Clarivein® devices, patient follow-up and duplex ultrasonography. Case funding was not used in this study. All trial particulars (design, data collection, analysis, discussion and data access) were performed independently of the funding bodies and the trial’s research sponsor was Imperial College London.

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health.
Previously Presented:

Preliminary results have been presented at the Royal Society of Medicine Venous Forum, Charing Cross Symposium, Society for Academic and Research Surgery, the Controversies and Updates in Vascular Surgery Meeting and the American Venous Forum. A short report of early results has been published in Phleboloy.

Word Count:
Total: 5089
Excluding Abstract and Legends: 4605
Excluding Abstract, Legends and References: 4071
Abstract

Background

Endovenous thermal ablation has revolutionised varicose vein treatment. New non-thermal techniques such as mechanical occlusion chemically assisted endovenous ablation (MOCA) allow treatment of entire trunks with single anaesthetic injections. Previous non-randomised work has shown reduced pain post-operatively with MOCA. This study presents a multi-centre randomised controlled trial assessing the difference in pain during truncal ablation using MOCA and radiofrequency endovenous ablation (RFA) with 6-months follow-up.

Methods

Patients undergoing local anaesthetic endovenous ablation for primary varicose veins were randomised to either MOCA or RFA. Pain scores using Visual Analogue Scale (VAS) and number scale (0-10) during truncal ablation were recorded. Adjunctive procedures were completed subsequently. Pain after phlebectomy was not assessed. Patients were reviewed at 1 and 6 months with clinical scores, quality of life scores and duplex ultrasound assessment of the treated leg.

Results

170 patients were recruited over a 21-month period from 240 screened. Patients in the MOCA group experienced significantly less maximum pain during the procedure by VAS (MOCA median 15mm (IQR 7-36mm) versus RFA 34mm (IQR 16-53mm), p=0.003) and number scale (MOCA median 3 (IQR 1-5) versus RFA 4 (IQR 3-6.5), p=0.002). “Average” pain scores were also significantly less in the MOCA group. 74% underwent simultaneous phlebectomy. Occlusion rates, clinical severity scores, disease specific and generic quality of life scores were similar between groups at 1 and 6 months. There were two deep vein thromboses, one in each group.

Conclusion

Pain secondary to truncal ablation is less painful with MOCA than RFA with similar short term technical, quality of life and safety outcomes.
A Multi-Centre Randomised Controlled Trial comparing radiofrequency and mechanical occlusion chemically assisted endovenous ablation ablation of varicose veins – Final Results of the Venefit Versus Clarivein for Varicose Veins (VVCVV) Trial

Tristan Lane 1,2,3, Roshan Bootun 1,2, Brahman Dharmarajah 1,2,3, Chung S Lim 1,2,3, Mojahid Najem 3, Sophie Renton 3, Kaji Sritharan 1,2, Alun H Davies 1,2.

1 Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London
2 Department of Vascular Surgery, Imperial College Healthcare NHS Trust
3 Department of Vascular Surgery, London North West Hospitals NHS Trust

Introduction

Varicose veins are a common condition worldwide and cause significant quality of life impairments with consequent healthcare costs 1. Symptomatology is varied, as is progression to ulceration 2,3. Endovenous ablation with catheter based technology, using radiofrequency energy or laser energy to cause thermal damage to the vein leading to fibrosis and occlusion, has revolutionised modern varicose vein treatment. Now any superficial vein navigable by a soft hydrophilic guidewire can be treated in this manner. These developments have led to endovenous thermal ablation being recommended as first line treatment by the National Institute for Health and Care Excellence (NICE) 4,5. The aforementioned techniques however require the use of tumescent anaesthesia which involves multiple needle injections 6. In the past few years new techniques have been developed and older techniques extended to alleviate the need for tumescent anaesthesia, and improve the patient experience. One of the new techniques is mechanical occlusion chemically assisted endovenous ablation (MOCA), which uses a hybrid system of physical damage to the vein wall and liquid sclerotherapy to lead to scarring and fibrosis without the need for tumescent anaesthesia 7,8. The lack of requirement for multiple needle injections should in theory lead to reduced intra-operative and peri-operative pain. Recent work in a non-randomised study comparing RFA and MOCA has shown a reduced pain experience post-operatively for those patients undergoing MOCA 9. This study was designed to compare the pain levels encountered during the procedure between RFA (using the Medtronic Venefit RFA segmental catheter; Medtronic, Santa Rosa, California, USA) and MOCA (using the Vascular Insights Clarivein catheter; Vascular Insights, Quincy, Massachusetts, USA), with MOCA hypothesised to be less painful. Initial results of this study have previously been published 10.

Methods

The trial protocol and methodology have previously been reported 10, and is described in full below. The trial was registered with Current Controlled Trials and the ISRCTN registry (http://www.isrctn.com) (ISRCTN06552809). The trial protocol, inclusion and exclusion criteria are freely available at http://www.isrctn.com/ISRCTN06552809. Ethical approval was obtained from the United Kingdom National Research Ethics Service, London – Chelsea Committee (NRES) (Research Ethics Committee Reference: 12/LO/0570).
London were the trial sponsors (reference number JRCOH0431).

**Patients**

Patients with symptomatic primary varicose veins with either GSV or SSV incompetence (>0.5s reflux on colour duplex ultrasound) presenting to Charing Cross Hospital (Imperial College Healthcare NHS Trust) or Northwick Park Hospital (London North West Healthcare NHS Trust) in London, UK were assessed clinically by independent clinicians and listed for treatment. Clinical stage and symptom scores were recorded. Once listed for treatment they were screened trial inclusion and invited to participate in the Venefit Versus Clarivein for Varicose Veins (VVCVV) trial. Patients with recurrent varicose veins, current deep vein thrombosis, arterial disease (ankle brachial pressure index <0.8), veins <3mm in diameter or hypercoagulability were excluded from participation. Additionally, patients unable or unwilling to complete questionnaires or to participate were also excluded. Consenting participants were then randomised on the day of treatment to either MOCA (group one) or RFA (group two), using an online computerised randomisation software (SealedEnvelope, London, UK). In patients with bilateral disease the most symptomatic side was entered into the study. Patients completed generic and disease specific questionnaires prior to intervention.

**Interventions**

All procedures were carried out by trained vascular surgeons who were experienced in both techniques of endovenous ablation. No peri-operative analgesia or sedation was used. Standard distraction techniques were utilised with music and verbal distraction. Ultrasound guidance and local anaesthetic (and tumescent anaesthesia in the RFA group) were used in all procedures. Initial vein access (GSV or SSV) was performed under ultrasound guidance after injection of local anaesthetic (1% Lidocaine using a standard 3cm length 23 Gauge needle), targeting the most distal point of venous reflux where cannulation was possible. A standard 7Fr vascular sheath was placed (Medtronic, USA). The treatment catheter tip was positioned 2 cm distal to the sapheno-femoral junction or sapheno-popliteal junction, assessed in both longitudinal and transverse views on ultrasound.

The standard method was used for RFA (Venefit, Medtronic, USA), as described before. Concisely, cooled tumescent anaesthesia (either 360 ml Normal Saline with 40 ml 1% lignocaine with 1:200000 adrenaline; or 500ml normal saline with 20ml 1% lignocaine and 5ml 8.4% sodium bicarbonate, dependent on local protocol) was injected using a standard 4cm length 21 Gauge needle into the saphenous sheath using a Klein pump at 400mls per minute to create a “1cm halo” of tumescent along the vein to be treated (approximately 10mls per cm). Then RF segmental ablation was completed, with 20 seconds per treatment zone (7cm or 3cm dependent on catheter tip), and double treatment for the first segment.

MOCA (Clarivein, Vascular Insights, USA) was performed as previously described using 2% sodium tetradecyl sulphate (STS) (Fibrovein™, STD Pharmaceutical Products Ltd., Hereford, UK) (made by mixing equal volumes of 1% STS and 3% STS). Concisely, following cannulation and tip positioning under ultrasound guidance, the treatment tip was unsheathed and positioning rechecked. The sclerosant syringe was then attached. The device motor was engaged for 1-2 seconds to induce proximal vein spasm. Then, the activated catheter with rotating tip was steadily withdrawn by 1 cm every 7 seconds, whilst injecting sclerosant at a constant rate dependent on length of vein to be treated and volume of sclerosant. This sclerosant injection rates was calculated as per the manufacturer’s guidance.
Immediately after completion of the endovenous ablation, patients were asked to report their pain experience on a 0-100 mm Visual Analogue Scale and a 0-10 number scale.

If required (if symptomatic visible varicosities) and with patient consent, concomitant phlebectomies were then performed using standard Oesch hook technique with local tumescent anaesthesia. All patients received a single prophylactic dose of low molecular weight heparin at the completion of the procedure. Use of prophylactic antibiotics was left to the discretion of the treating surgeon.

Stockings were worn for two weeks post-procedure, and patients were advised to return to their work and normal activities as soon as they felt able to.

Patients were reviewed at 1 month and 6 months post procedure with clinical assessment, duplex ultrasound and asked to complete a questionnaire.

**Outcome Measures**

The primary outcome of the study was the degree of pain experience during endovenous ablation using a validated patient reported Visual Analogue Scale (VAS) and 0-10 number scale, prior to completion of any phlebectomies. Patients were also asked to describe the duration of the pain as lasting seconds, minutes or several minutes. The secondary outcomes were improvement in patient reported quality of life, both disease specific (Aberdeen Varicose Vein Questionnaire - AVVQ) and generic (Euroqol 5 Domain 3 Level - EQ-5D-3L and EuroQol VAS); clinical scores (Venous Clinical Severity Score - VCSS, Venous Disability Score - VDS and Clinical Etiology Anatomy Pathology score - CEAP) and time taken to return to normal activities and work. The primary outcome measure was assessed at the time of intervention. The secondary outcomes were assessed at 1 month and 6 months post operative follow-up. Technical success was also assessed at 1 month and 6 months with validated, blinded venous duplex ultrasound scanning. There were four possible scan classifications: complete occlusion of the saphenous vein, proximal occlusion (>5cm proximally occluded, with >5cm open distally), distal occlusion (>5cm distally occluded, with >5cm open proximally) and open. Patency in the first 3cm of the GSV was considered normal.

**Power Calculations**

Power calculations were based on the primary outcome of pain during the truncal ablation procedure as assessed by VAS. Detection of a 20-mm difference in maximum pain score with a standard deviation (SD) of pain score of 20 mm was considered a significant difference. The minimum target size was calculated to be 94 patients (47 per group) at 90% power and 5% significance. Allowing for loss to follow-up or protocol violations, an overall target recruitment of 170 legs (85 per group) was estimated.

**Statistical Analysis**

Data was recorded prospectively on a bespoke database and analysed using SPSS version 23 (IBM, Armonk, USA), STATA version 14 SE (Statscorp, College Station, Texas, USA), Wizard Pro version 1.7.14 (Evan Miller, Chicago, Illinois, USA) and Prism version 6 (GraphPad, La Jolla, California, USA). Data was analysed using parametric and non-
parametric statistical tests as dictated by distribution of data. Normally distributed data is reported as mean and standard deviation (SD), non-normal distributions are reported as median and interquartile range (IQR).

Results

170 patients were recruited between January 2013 and September 2014 from a potential 240 screened patients. 41% were male. 86% were GSV and 14% SSV. Baseline data is presented in Table 1, there were no significant differences between groups. 87 were randomised to receive MOCA and 83 to RFA. 83 of the 87 MOCA cases underwent MOCA and 82 of the 83 RFA cases underwent RFA. There was one crossover in each group. Analysis was performed on an intention to treat basis. Treatment data is presented in Table 2, there were no significant differences between procedural details, including number of patients having concomitant phlebectomies and number of phlebectomies performed. See Figure 1 for the Trial Consort Diagram. Proportion of patients completing follow-up at 1 month was 76% (n=129) and at 6 months 71% (n=121).

Primary Outcome

Maximum Pain experienced during truncal ablation (Figure 2)

Overall median maximum pain via VAS was 24mm (IQR 10-45) and 4 (2-5) by 0-10 number scale. Maximum pain experienced during endovenous ablation as measured on VAS was significantly less in the MOCA group with a median of 15mm (IQR 7-36mm) versus 34mm (16-53mm), p=0.003 (Mann-Whitney). As measured on a number scale of 0-10, median maximum pain experienced was also significantly less in the MOCA group - 3 (1-5) vs 4 (3-6.5), p=0.002 (Mann-Whitney). Post hoc power analysis demonstrated 91% power at 0.05% significance for the VAS and 94% power at 0.05% significance for the number scale. VAS and number scale showed a very strong correlation (Pearson’s r = 0.96, p<0.001).

86% of patients described the maximum pain as lasting seconds, and there was no difference in estimated duration of maximal pain duration between groups (90% seconds in MOCA group versus 82% seconds in RFA group, p=0.169).

“Average” Pain experienced during truncal ablation (Figure 3)

Overall median “average” pain experienced was 15mm (6-32) and 2.5 (1-4) by 0-10 number scale. “Average” pain experienced during endovenous ablation was also significantly less in the MOCA group with both VAS - median of 10mm (3-25mm) vs 19.5mm (9-38mm), p=0.003 (Mann-Whitney); and Number Scale - median of 2 (0.5-4) versus 3 (2-5), p=0.004 (Mann-Whitney). Post hoc power analysis demonstrated 55% power at 0.05% significance for the VAS and 74% power at 0.05% significance for the number scale. VAS and number scale showed a very strong correlation (Pearson’s r = 0.94, p<0.001).

68% of patients described the “average” pain as lasting seconds, and there was a significant difference in estimated duration of “average” pain duration (76% seconds in MOCA versus 60% seconds in RFA group, p=0.021).

Secondary Outcomes

Disease Specific Quality of Life - AVVQ (Figure 4)

Overall AVVQ significantly improved from baseline to 1-month post treatment (19.3 (13.2-28.7) to 12.8 (7.3-20.7), p<0.001) and this continued to be significant at 6 months (10.8 (4.3-
20.5), p<0.001 (Friedman)). Between groups, there was no significant difference at baseline, 1-month or 6-month - 12.1 (7.3-21.2) for MOCA versus 12.9 (6.6-20.4) for RFA at 1 month (p=0.799); and 11.8 (7.2-20.5) for MOCA versus 9.4 (3.6-21.4) for RFA at 6 months (p=0.511), Figure 4.

**General Quality of Life - EQ-5D QOL and EQ-5D VAS**

Overall, EQ-5D QOL and EQ-5D VAS showed no significant change from baseline to 6 months (Median 0.761 (0.690-0.796) at baseline, 0.761 (0.690-1.000) at 1 month and 0.761 (0.659-1.000) at 6 months, p=0.060, Friedman). Between groups, there was no significant difference in EQ-5D QOL at 1 month (MOCA - 0.761 (0.659-1.000) versus RFA - 0.761 (0.690-1), p=0.939) or at 6 months (MOCA 0.761 (0.690-1.000) versus RFA 0.761 (0.486-1.000), p=0.125).

EQ-5D VAS was also not significantly different at either timepoint – at 1 month 85 (60-95) for MOCA versus 87 (80-90) for RFA (p=0.227) and at 6 months 85 (60-93) versus 89 (70-95) (p=0.302).

**Clinical Severity Scoring - VCSS and VDS (Figure 5)**

Overall, VCSS significantly improved from baseline to 1 month (5 (4-7) versus 2 (1-5)) as did VDS (1 (1-2) versus 0 (0-1)), and both VCSS and VDS preserved this change at 6 months (p<0.001, Friedman). Between groups, there was no significant difference for VCSS at either 1 month (MOCA 2 (1-4) versus RFA 3 (1-5), p=0.096) or 6 months (MOCA 2 (1-4) versus RFA 2 (1-5), p=0.536) (Figure 5).

VDS also showed no significant difference between groups at 1 month or 6 months.

**Return to Work and Return to Normal Activities**

Overall, participants returned to work at a median of 2 days (IQR 2-7) and to normal activities at a median of 2 days (IQR 1-6). There was no significant difference between groups for either return to work (MOCA Median 3, IQR 1-7 versus RFA Median 2, IQR 2-7, ns) or return to normal activities (MOCA Median 2, IQR 1-4 versus RFA Median 2, IQR 1-7, ns).

**Technical Success of truncal ablation**

Overall complete or proximal occlusion rates were 92% at 1 month and 90% at 6 months. MOCA showed 93% complete or proximal occlusion at 1 month, compared to 92% in RFA. At 6 months the rates were 87% for MOCA versus 93% for RFA. There was no significant difference in occlusion rates at 1 month or 6 months (p=0.403 and p=0.483). Occlusion status had no significant effect on clinical or quality of life scores.

**Complications**

There were 3 cases of minor phlebitis along the treated vein in the MOCA group and 2 in the RFA group. 2 deep vein thromboses (DVTs) occurred (1.2%) - 1 in each group. The MOCA DVT was a tongue of thrombus into the common femoral vein occluding <50% of the vein diameter (corresponding to Endovascular Treatment Induced Thrombosis stage 2), and the RFA DVT was a calf vein thrombus. Neither DVT had had avulsions performed. There were no patient reported cases of sensory disturbance at either clinical follow-up. No further procedures were required after initial treatment at 6 months of follow-up. No difference in cosmetic appearance or satisfaction was reported by patients at clinical follow-up. There were no significant differences in complications between groups.
Discussion

Varicose veins and chronic venous disease is a benign but progressive and pervasive disease. The treatment options have been transformed with endovenous ablation, allowing movement from the operating theatre to the outpatient suite. Recently clinicians have begun searching for fine point percentage benefits in treatment. This study shows that tumescentless treatment using MOCA for truncal veins has a reduced pain profile for truncal procedure, whilst retaining similar 6 month occlusion rates, as compared to RFA. Patients improved similarly in both groups with respect to disease specific clinical scoring and disease specific quality of life values at all time points. The MOCA group did show a significantly larger improvement in AVVQ from baseline to 6-months, despite no significant difference in baseline or 6-month follow-up group values. This difference of 3.3 AVVQ points falls below the clinically significant threshold of 5 points used for previous studies. On simple group comparison, patients in the MOCA group also had an improved generic quality of life outcomes (EQ-5D QOL) at 6 months, despite similar post-operative complication rates. However, once corrected via linear regression for baseline differences there was no significant difference. No significant improvement was found from baseline to 6 months due to multiple testing correction (6 month data was significantly improved from baseline when assessed directly) and loss to follow-up. This study was not prospectively powered to assess generic or disease QOL. It may also be possible that due to the severity of disease treated in this cohort, the reversibility of QOL detriment is limited.

The occlusion rates at 6 months are equivalent for both modalities, however, both the RFA and MOCA groups had lower rates of occlusion than expected from the published literature. In the most recent study of long-term follow-up, a total or proximal occlusion rate of 92.7% at 5 years post RFA has been reported. However, a recent study comparing open surgery to endovenous laser ablation found a 41% recurrence rate at 5 years. The findings of this study may be secondary to detailed and independent post-operative duplex scanning or it may represent real world efficacy of these treatment types. The vascular scientists performing the follow-up scans were experienced in the post-operative appearances of both techniques. It is unlikely that these rates are due to poor technique, due to extensive experience in all operators prior to commencement of the study (there was no “roll-in” period). Longer follow-up is needed to give detailed evidence of the robustness of the techniques. The total number of patients without successful occlusion at 1 month was 11 and at 6 months was 12, which limits the inferences that can be drawn from such occlusion rates.

Thus this study supports the hypothesis that MOCA is an effective treatment for truncal vein incompetence and subjects the patient to a less painful ablative procedure. Additionally, this study provides evidence that MOCA with simultaneous phlebectomy is safe and effective in the short term.

The study was powered at 90% power and 5% significance to detect a 20mm difference in mean pain scores on VAS, with the observed difference in medians found being 19mm. This protocol power calculation required 47 patients per treatment group. However, target recruitment was inflated to 170 patients to compensate for expected 50% loss to follow-up. 121 patients (71%) attended 6-month follow-up. The study treated 165 patients, and post hoc power calculations with this data show that the for pain scores, the study had 91% power at
0.05% significance criterion.

The use of both a VAS and a number scale has provided evidence of their equivalence.

The full study showed no significant reduction in pain scores from the initial report suggesting that there was no time dependent decrease in pain score to indicate a learning curve during the study.

This study was limited by lack of treatment blinding for the patients and interventional clinicians. This was due to the technical differences between devices i.e. tumescent injections in the RFA group and device vibration in the MOCA group. Follow-up appointments and ultrasound scanning were treatment blind.

A further limitation of this study is the lack of long term follow-up - only short term occlusion rates are assessed in this study, with the primary outcome obtained at the time of procedure. Operating time was not recorded in this study, however all cases were performed in standardized theatre sessions in single slots with 1 surgeon performing all tasks, and 74% of patients also underwent simultaneous phlebectomy.

A major limitation of all tumescentless techniques is how to treat varicosities left after truncal ablation, with level 1 evidence now supporting combined treatment with phlebectomies. This study was designed and commenced prior to the completion of latest trial, but took into consideration the fact that phlebectomies cause pain, and so pain scores taken after truncal ablation but before any phlebectomies were completed. This therefore represents a significant limitation to the outcomes of this trial, as the pain scores reported above do not assess the complete treatment, except for those patients who did not undergo phlebectomy.

However, similar numbers of patients underwent phlebectomies in both treatment groups. In the context of tumescentless truncal ablation, the use of phlebectomies requires the use of additional local or tumescent anaesthesia, so further injections are not avoided. Indeed, the phlebectomies may be the over-riding cause of pain. However, tumescentless techniques still obviate the need for injections in the proximal thigh and groin which may be more painful than distal injection in the leg. This would require further study to delineate. Additionally, volume of tumescent anaesthesia used was not formally documented.

This study did not assess pain scores after phlebectomy or after the periprocedural period.

Treatment of the varicosities with foam sclerotherapy in combination with truncal ablation is an alternative technique but has yet to be assessed formally in an appropriately powered randomised study, however previous work has supported its use in principle. MOCA presents a dilemma due to sclerosant dose limitations, with European consensus guidelines advocating a maximum dose of 10ml of <3% concentration liquid sodium tetradecyl sulphate sclerosant or 2mg/kg polidocanol sclerosant and 10ml of foam sclerosant. Additionally the treatment techniques leads to a variable dosage of scleroant per cm treated, dependent on vein diameter, and governed by the Vascular Insights MOCA sclerosant guidance and instructions for use. Alternative tumescentless devices do not have such dose limitations, but published data is lacking. Studies examining volume limits would be beneficial to help guide both MOCA and pure sclerotherapy techniques.

Further studies examining pain experienced during combined phlebectomy and truncal ablation procedures would be of great benefit to ascertain the difference treatment devices make in simultaneous therapy – for assessment of the whole treatment.
Conclusion

Mechanochemical truncal ablation offers patients reduced intra-procedural pain with equivalent technical success compared to radiofrequency truncal ablation at 6 months. Patients have equivalent disease specific quality of life and clinical outcomes, and returned to work and normal activities at similar times.

Further work with larger studies and extended follow-up are needed to assess long term outcomes and recurrence rates.

Conflict of Interest

All procedures, data collection, analysis and presentation were performed independently of the funding bodies.

Contribution

TRAL, AHD conceived and setup the study. TRAL, RB, BD, CSL, MN, SR, KS and AHD performed the procedures and collated the data. TRAL and RB performed the data-analysis. TRAL wrote the first draft of the manuscript. TRAL, RB, BD, CSL, MN, SR, KS and AHD critically appraised, edited and approved the final manuscript. AHD is the guarantor.

Funding:

This study was supported by a research grant from the Clarivein® device manufacturer, Vascular Insights and an educational research grant from the Graham-Dixon Charitable Trust. Vascular Insights provided funding for Clarivein® devices, patient follow-up and duplex ultrasonography. Case funding was not used in this study. All trial particulars (design, data collection, analysis, discussion and data access) were performed independently of the funding bodies and the trial’s research sponsor was Imperial College London.

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed are those of the authors and not necessarily those of the NHS, NIHR, or the Department of Health.

References


13 Carradice D, Mekako AI, Hatfield J, Chetter IC. Randomized clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. BJS. 2009 Apr; 96: 369–375.


19 Kabnick LS, Ombrellino M, Agis H, Mortiz M. Endovenous heat induced thrombus (EHIT) at the...


Figure Legends

Figure 1:
VVCVV Consort Diagram

Figure 2:
Maximum Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale, (b) – Number Scale.

Figure 3:
Average Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale, (b) – Number Scale.

Figure 4:
Aberdeen Varicose Vein Questionnaire scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).

Figure 5:
Venous Clinical Severity Score (VCSS) scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).
Table Legends

Table 1: Patient Demographics - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).

Table 2: Treatment Characteristics - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>MOCA</th>
<th>RFA</th>
<th>Difference?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>170</td>
<td>87</td>
<td>83</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>70 (41.2%)</td>
<td>37 (42.5%)</td>
<td>33 (39.8%)</td>
<td>ns (0.714)</td>
</tr>
<tr>
<td>Age Median</td>
<td>50</td>
<td>54.5</td>
<td>48</td>
<td>ns (0.099)</td>
</tr>
<tr>
<td>GSV</td>
<td>147 (86.5%)</td>
<td>77 (88.5%)</td>
<td>70 (84.3%)</td>
<td>ns (0.427)</td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>20 (13.4%)</td>
<td>13 (16.7%)</td>
<td>7 (9.9%)</td>
<td>ns (0.223)</td>
</tr>
<tr>
<td>CEAP Median</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>ns (0.627)</td>
</tr>
<tr>
<td>VCSS Median</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>ns (0.112)</td>
</tr>
<tr>
<td>VDS Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>ns (0.135)</td>
</tr>
<tr>
<td>AVVQ</td>
<td>19.303</td>
<td>19.546</td>
<td>18.888</td>
<td>ns (0.592)</td>
</tr>
<tr>
<td>EQ5D QOL Median</td>
<td>0.761</td>
<td>0.761</td>
<td>0.730</td>
<td>ns (0.989)</td>
</tr>
<tr>
<td>EQ5D VAS Median</td>
<td>81.0</td>
<td>84.5</td>
<td>80.0</td>
<td>ns (0.050)</td>
</tr>
</tbody>
</table>

Table 1 Patient Demographics
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>MOCA</th>
<th>RFA</th>
<th>Difference?</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>165</td>
<td>83</td>
<td>82</td>
<td>ns</td>
</tr>
<tr>
<td>Length of vein treated (GSV) mm</td>
<td>364</td>
<td>359</td>
<td>373</td>
<td>ns</td>
</tr>
<tr>
<td>Length of vein treated (SSV) mm</td>
<td>205</td>
<td>227</td>
<td>166</td>
<td>ns</td>
</tr>
<tr>
<td>Concomitant Avulsions</td>
<td>74%</td>
<td>68%</td>
<td>76%</td>
<td>ns</td>
</tr>
<tr>
<td>Median Number of Avulsions</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>Median Vein Diameter mm</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>ns</td>
</tr>
</tbody>
</table>
Screening n=240

Recruitment n=170

Randomisation n=170

Allocated to MOCA n=87

Received MOCA n=83 (95%)

Attended 1 month Follow-Up n=69 (79%)

Attended 6 month Follow-Up n=62 (71%)

Did Not Receive MOCA n=4 (5%)

Allocated to RFA n=83

Received RFA n=82 (99%)

Attended 1 month Follow-Up n=60 (72%)

Attended 6 month Follow-Up n=59 (71%)

Excluded n=170

Refused participation

Did not meet inclusion criteria
Figure Legends

Figure 1:
VVCVV Consort Diagram

Figure 2:
Maximum Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale, (b) – Number Scale.

Figure 3:
Average Pain Score during procedure for Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA) (a) – Visual Analogue Scale, (b) – Number Scale.

Figure 4:
Aberdeen Varicose Vein Questionnaire scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).

Figure 5:
Venous Clinical Severity Score (VCSS) scores at baseline, 1 month and 6 months follow-up - by treatment group - Mechanochemical Ablation group (MOCA) and Radiofrequency Ablation (RFA).
Table 1:
Patient Demographics - Mechanochemical Ablation group (MOCA) and
Radiofrequency Ablation (RFA).

Table 2:
Treatment Characteristics - Mechanochemical Ablation group (MOCA) and
Radiofrequency Ablation (RFA).
JOURNAL CONTRIBUTOR'S PUBLISHING AGREEMENT

To be completed by the owner of copyright in the Contribution

<table>
<thead>
<tr>
<th>TITLE OF CONTRIBUTION:</th>
<th>A Multi-Centre Randomised Controlled Trial comparing radiofrequency and mechanical occlusion chemically assisted ablation of varicose veins – Final Results of the Venefit Versus Clarivein for Varicose Veins (VVCVV) Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTENDED FOR PUBLICATION IN:</td>
<td>Phlebology</td>
</tr>
<tr>
<td>AUTHOR NAME(S):</td>
<td>Tristan Lane, Lane, Bootun, Dharmarajah, Lim, Najem, Renton, Sritharan, Davies</td>
</tr>
<tr>
<td>CORRESPONDING AUTHOR:</td>
<td>Section of Vascular Surgery, Imperial College London, 4N13b, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF</td>
</tr>
</tbody>
</table>

Please read the notes attached, then complete, sign and return this form (using BLOCK LETTERS) to: phlebeditorial@sagepub.co.uk

SOLE AND EXCLUSIVE LICENSE TO PUBLISH

I represent that the Contribution is owned by me unless the following is checked:

☐ Work made for hire by employer – The Contribution was prepared by me at the request of my employer and within the scope of my employment and copyright in the Contribution is owned by my employer. (Both the Contributor and an authorized representative of the Contributor’s employer shall sign this Agreement.) Employer name: ____________________________________________

☐ U.S. Government Work – I am an employee of the United States Government and prepared the Contribution as part of my official duties. (If the Contribution was not prepared as part of the Contributor’s official duties, it is not a U.S. Government work. If the Contribution was jointly authored, all the co-authors must have been U.S. Government employees at the time they prepared the Contribution in order for it to be a U.S. Government work; if any co-author was not a U.S. Government employee, then the Contribution is not a U.S. Government work. If the Contribution was prepared under a U.S. Government contract or grant, it is not a U.S. Government work - in such case, copyright is usually owned by the contractor or grantee.)

In consideration for publication in the above Journal, of the above Contribution, I hereby grant to Sage Publications Ltd (‘SAGE’) the sole and exclusive right and license to produce, publish and make available and to further sub-license the Contribution and the abstract prepared by me to accompany the Contribution for the full legal term of copyright and any renewals thereof throughout the world in all languages and in all formats, and through any medium of communication now known or later conceived or developed.

If you or your funder wish your article to be freely available online to non-subscribers immediately upon publication (gold open access), you can opt for it to be included in SAGE Choice, subject to payment of a publication fee. For further information, please visit SAGE Choice.

In the event I provide Supplemental Material to SAGE, I hereby grant to SAGE the non-exclusive right and license to produce, publish and make available and to further sub-license the material, in whole or in part, for the full legal term of copyright and any renewals thereof throughout the world in all languages and in all formats, and through any medium of communication now known or later conceived or developed.

By signing this Contributor Agreement I agree both to the above provisions and to the terms of the agreement attached below.

Contributor
Signed: ___________________________ Date: ________________

The author who has signed above warrants that he/she is authorized to sign on behalf of him/herself and, in the case of a multi-authored Contribution, on behalf of all other authors of the Contribution.

Authorised Representative of Employer (if Work made for hire/done in the course of employment box is checked)
Signed: ___________________________ Date: ________________

SAGE Publications Ltd

Terms of the Agreement page 1 of 5
This Agreement may be signed and executed in the following ways:

- Traditional hard copy – please sign and return the Agreement.
- By fax – please sign and fax a copy of the Agreement.
- By e-mail – a scanned hard copy of the Agreement with your signature on it or a digital original copy with your electronic signature are equally acceptable.

Further
- One contributor may sign on behalf of any co-authors if authorized to do so by the co-authors.
- All parties may sign one document OR
- Individual parties may sign separate copies of the same agreement (using any of the methods described above) and return them individually.

TERMS OF THE AGREEMENT

Copyright

While copyright remains mine as the author, I hereby authorise SAGE to act on my behalf to defend my copyright should it be infringed and to retain half of any damages awarded, after deducting costs.

Warranties

I warrant to SAGE that the Contribution is my original work, that I have the full power and authority to enter into this Agreement and to convey the rights granted herein to SAGE and to submit the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, either in printed or electronic form, that I have obtained and enclose all necessary permissions for the reproduction of any copyright works not owned by me (including artistic works, e.g. illustrations, photographs, charts, maps, other visual material, etc.) contained in the Contribution and any Supplemental Material I provide and that I have acknowledged the source(s), that the Contribution and any Supplemental Material I provide contain no violation of any existing copyright, other third party rights or any libellous or untrue statements and do not infringe any rights of others, and I agree to indemnify, defend and hold harmless SAGE against any claims in respect of the above warranties. I further agree to be bound by the Conditions of Publication provided herein as part of this Agreement which outline the circumstances under which work may be reused.

Declaration of Conflicting Interests

I certify that:
1. All forms of financial support, including pharmaceutical company support, are acknowledged in the Contribution
2. Any commercial or financial involvements that might present an appearance of a conflict of interest related to the Contribution are disclosed in the covering letter accompanying the Contribution and all such potential conflicts of interest will be discussed with the Editor as to whether disclosure of this information with the published Contribution is to be made in the Journal.
3. I have not signed an agreement with any sponsor of the research reported in the Contribution that prevents me from publishing both positive and negative results or that forbids me from publishing this research without the prior approval of the sponsor.
4. I have checked in the manuscript submission guidelines whether this Journal requires a Declaration of Conflicting Interests and complied with the requirements specified where such a policy exists.
It is not expected that the details of financial arrangements should be disclosed. If the Journal does require a Declaration of Conflicting Interests and no conflicts of interest are declared, the following will be printed with your article: ‘None Declared’.

**Supplemental Material**

Supplemental Material includes all material related to the Contribution, but not considered part of the Contribution, provided to SAGE by you as the Contributor. Supplemental Material may include but is not limited to datasets, audio-visual interviews including podcasts (audio only) and vodcasts (audio and visual), appendices, and additional text, charts, figures, illustrations, photographs, computer graphics, and film footage. Your grant of a non-exclusive right and license for these materials to SAGE in no way restricts re-publication of Supplemental Material by you or anyone authorized by you.

**Termination**

SAGE, in its sole, absolute discretion, may determine that the Contribution should not be published in the Journal. If in the rare circumstance the decision is made not to publish the Contribution after accepting it for publication, then all rights in the Contribution granted to SAGE shall revert to you and this Agreement shall be of no further force and effect, and neither you nor SAGE will have any obligation to the other with respect to the Contribution.

**Counterparts; Facsimile**

This Agreement may be executed in counterparts each of which shall be deemed the original, all of which together shall constitute one and the same Agreement. A faxed copy or other electronic copy shall be deemed as an original.

**Electronic Signature Authorization**

This transaction may be conducted by electronic means and the parties authorize that their electronic signatures act as their legal signatures of this Agreement. This Agreement will be considered signed by a party when his/her/its electronic signature is transmitted. Such signature shall be treated in all respects as having the same effect as an original handwritten signature. (You are not required to conduct this transaction by electronic means or use an electronic signature, but if you do so, then you hereby give your authorization pursuant to this paragraph.)

**Modification; Entire Agreement; Severability**

No amendment or modification of any provision of this Agreement shall be valid or binding unless made in writing and signed by all parties. This Agreement constitutes the entire agreement between the parties with respect to its subject matter, and supersedes all prior and contemporaneous agreements, understandings and representations. The invalidity or unenforceability of any particular provision of this Agreement shall not affect the other provisions, and this Agreement shall be construed in all respects as if any invalid or unenforceable provision were omitted.

**Governing Law; Arbitration**

This Agreement shall be deemed to be a contract made in England and shall be construed and applied in all respects in accordance with English law and the parties submit and agree to the jurisdiction of the English courts.

If any difference shall arise between you and SAGE touching the meaning of this Agreement or the rights and liabilities of the parties thereto, the same shall be referred to the arbitration of two persons (one to be named by each party) or their mutually agreed umpire, in accordance with the provision of the England Arbitration Act 1996 or any amending or substituted statute for the time being in force.
Your rights as author

- You retain copyright in your work.
- You may do whatever you wish with the version of the article you submitted to the journal – version 1.
- Once the article has been accepted for publication, you may post the accepted version (version 2) of the article on your own personal website, your department’s website or the repository of your institution without any restrictions.
- You may not post the accepted version (version 2) of the article in any repository other than those listed above (i.e. you may not deposit in the repository of another institution or a subject repository) until 12 months after first publication of the article in the journal.
- You may use the published article (version 3) for your own teaching needs or to supply on an individual basis to research colleagues, provided that such supply is not for commercial purposes.
- You may use the article (version 3) in a book you write or edit any time after publication in the journal.
- You may not post the published article (version 3) on any website or in any repository without permission from SAGE.
- When posting or re-using the article please provide a link to the appropriate DOI for the published version of the article on SAGE Journals (http://online.sagepub.com).

All commercial or any other re-use of the published article should be referred to SAGE. More information can be found at: http://www.sagepub.co.uk/journalsPermissions.nav

When posting or re-using the article, you should provide a link/URL from the article posted to the SAGE Journals Online site where the article is published: http://online.sagepub.com and please make the following acknowledgment: ‘The final, definitive version of this paper has been published in <journal>, Vol/Issue, Month/Year by SAGE Publications Ltd, All rights reserved. © [The Author(s)]

SAGE’s use of the work

Although you have retained the copyright in your article, you have granted SAGE an exclusive license to use it. This helps us to ensure adequate protection against infringement of copyright protected material through breach of copyright or piracy anywhere in the world. It also ensures that requests by third parties to reprint or reproduce a contribution, or part of it in any format, are handled efficiently in accordance with our general policy which encourages dissemination of knowledge inside the framework of copyright.

Where practicable, we advise third parties inform you of their requests to re-use your material. This does not apply to blanket arrangements covering the Journal as a whole. Please keep our mailing list up to date with your institutional or business address changes to help us to do this. Inadvertent failure to inform you will not constitute a material breach of this Agreement.
Your responsibilities as author: inclusion of other copyright material

SAGE is sympathetic to the needs of scholars to include other copyright material, and is happy to provide guidance on this. Responsibility for obtaining permission to use any other copyright material rests with you as the author of the Contribution.

If your Contribution includes material which is not your copyright, you are responsible for submitting with your manuscript the written permission from those who control copyright in that material to include it and reproduce it within your Contribution. In most cases this will be the publisher of the work. As the Journal is available in both print and electronic media and may be translated or archived, this permission needs to be for all media in all languages in perpetuity. You are responsible for the payment of any permission fees.

Fair Dealing information for your reference:

Fair Dealing provisions under UK copyright law and/or the Fair Use provisions under US law for use of material in review, and/or other International Copyright Laws allow for the limited use of third party copyright materials in particular circumstances, without the requirement to obtain permission as above.

The term ‘fair dealing’ is not defined in UK legislation itself but should be viewed from a qualitative as well as a quantitative perspective. There are no set rules which cover what is or is not fair dealing. For guidance:

- Fair dealing can only apply to material used for specific purposes including those of criticism and review and news reporting and incidental use.
- Permission should always be sought where reproduction could reasonably be construed as competing with the sale of the original source and/or where the amount of copying is substantial.
- Whether you are including material with permission, or on the basis that it falls under ‘fair dealing’ or ‘fair use’, you must include acknowledgement of the copyright holder and original publication of the material.

If you are in doubt, please ask for advice from SAGE or the journal editor.