Title: Radiofrequency Ablation vs Laser Ablation of the Incompetent Small Saphenous Vein

PI: Malcolm Sydnor, MD

NCT #: 02248740

Unique Protocol ID: HM11844

Document approval date: 1/16/2014

Document Type: Protocol/SAP

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Chronic venous insufficiency (CVI) is estimated to affect 25 million Americans. This condition leads to aching, fatigue, swelling, ulcerations, and bleeding in the lower extremities. The **second** most common refluxing or incompetent **Small** Saphenous Vein (**S**SV). This condition results in pooling of deoxygena lower extremities rather than successful transport of the blood back to the heart and lungs. The historica been to surgically remove or 'strip' the GSV so that blood is rerouted through the healthier deep veins. treatment option, Endovenous Thermal Ablation, has emerged over the last decade and has virtually rep This involves advancing a catheter under ultrasound guidance through the SSV and then advancing a las radiofrequency probe through the catheter. These devices then produce the energy to destroy the vein as slowly pulled back. While both radiofrequency ablation and laser ablation are accepted treatments, neit been definitively proved to have fewer complications or superior results. This is in part because very fe the ability to make a head to head comparison between the two technologies and must choose one or the financial constraints. The aim of this study is to perform a randomized prospective trial comparing the t that more definitive information to evaluate complications and outcome can be obtained and then recom which, if either, technology is superior can be made.

VI. SPECIFIC AIMS

1. To prospectively compare the outcome as measured by ultrasound examination and lack of recurre symptoms of Radiofrequency ablation of the SSV to laser ablation of the SSV at 1 week, 6 weeks, and yearly thereafter.

2. To prospectively compare the incidence of acute complications between radiofrequency ablation of ablation of the SSV including deep vein thrombosis (DVT), skin burns, hyperpigmentation, parasth development of new spider veins.

3. To prospectively compare between radiofrequency ablation and laser ablation of the SSV the level during the procedure and postoperative period as determined by pain and postoperative bruising.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Chronic venous insufficiency (CVI) is estimated to cause symptoms in 25 million Americans, making it vascular disease in this country (1). Symptoms include lower extremity pain, fatigue, aching, throbbing physical findings can include varicose veins, pigmentation changes, edema, and ulcerations. Venous ins caused by poorly functioning venous valves, which permit deoxygenated blood to reflux towards the fee efficiently toward the heart and lungs. The **second** most common form of CVI in symptomatic patients **Small** Saphenous Vein (**S**SV) (2-3). The previous gold standard for treatment of a refluxing **S**SV was s However, this has been largely supplanted by a less invasive technique, Endovenous Thermal Ablation last decade. EVTA is a catheter-based technique that uses electromagnetic energy to obliterate the GSV procedure. Several studies have shown EVTA to be equal to or better than Surgical Ligation and Stripp **venous** reflux (4-8). In addition, EVTA is performed on an outpatient basis and patients can immediate normal daily activities. Surgical ligation and stripping is performed under general anesthesia and requir recovery period (9).

There are two types of electromagnetic energy currently in use to perform EVTA: radiofrequency heat and laser heat. During the EVTA procedure, a catheter is advanced from the level of the knee through the SSV to the level of the groin. The surrounding tissues are then protected by injecting tumescent anesthesia around the vein all the way up the leg. A la fiber or radiofrequency probe is advanced through the catheter and just beyond so the device is exposed in the vein. The device and catheter is then turned on and withdrawn as it destroys the vein. The Radiofrequency probe is operated at a temperature between 85 and 95 degrees and the energy is delivered at the vein wall causing shrinkage of the collagen fibers, venous spasm, and decreased subsequent thrombus within the occluded vein (10). The laser fiber is heated to temperatures of >100 degrees C which causes boiling of the blood resulting in endothelial injury from steam bubbles and increased subsequent thrombus within the vein (11-12). Both device types have been independently studied and found t have excellent results with 4 to 17% recanalization rates for up to 4 years out for Radiofrequency Ablation (6,8,13-17) a 0-10% recanalization rates for up to 1 year out for Laser Ablation (4,16,18-20). These same studies have proven both technologies to be safe with a reported DVT rate of 1% or less in all but one study (15), and only 2 pulmonary emboli w reported in over 2500 limbs treated. Minor complications including skin burns, parasthesias, and phlebitis were reported more in the Radiofrequency groups than the Laser groups. However, it has also been suggested that laser procedures res in more vein perforations (11) as well as more post procedure bruising and associated pain (19).

Only 2 retrospective studies have compared the two technologies and they compared cohorts from different time periods **and both of these groups studies the greater saphenous vein rather than the small saphenous vein**. Puggioni (21) compared 53 limbs treated with RFA to 77 limbs treated with EVLA. This group found 94% GSV occlusion for the lase group and 91% GSV occlusion for the RF group at 1 month only with 20% complications in the laser group compared to 8% in the RF group. Almeida (22) retrospectively compared Laser ablation in 819 limbs with RF in 128 limbs and foun closure rate at 500 days of 85% for RF and 92% for EVL. This group reported minimal complications. To our knowled no study has been performed comparing Radiofrequency Ablation to Laser Ablation during the same retrospective time period and no prospective studies have been performed. There is widespread debate on which technology is better suited to perform EVTA based on outcomes and complications. Industry and cost factors continue to have influence on which device is used and there is widespread use of both competing technologies. Therefore, this study is designed to evaluate which device is more effective and which device results in more complications in a randomized prospective manner.

References:

1. McLafferty RB, Lobr JM, Caprini JA, et al. Results of the national pilot screening program for venous disease b the American Venous Forum. J Vasc Surg 2007;45:142-8.
2. Labropoulos N, Giannoukas AD, Delis K, et al. Where does venous reflux start? J Vasc Surg 1997; 26:736–742
3. Evan CI, Allan PL, Lee AI, Bradbury AW, Ruckley CV, Fowkes PG. Prevalence of venous reflux in the general population on duplex scanning: the Edinburgh Vein Study. J Vasc Surg 1998;28:767-776
4. Min RJ, Khilnani N and Zimmet SE, Endovenous laser treatment of saphenous vein reflux: long-term results, *J Vasc Interv Radiol* **14** (2003), pp. 991–996.
5. Weiss RA, Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radio frequency cathete under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. Dermatol Surg 2002;28:38-42.
6. Rautio T, Ohinmaa A, Perälä J, Ohtonen P, Heikkinen T and Wiik H *et al.*, Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of costs, *J Vasc Surg* **35** (2002), pp. 958–965.
7. Stolter L, Schaaf I, Bockelbrink A. Comparative outcomes of radiofrequency endoluminal ablation, invagination stripping, and cryostripping in the treatment of great saphenous vein insufficiency. Phlebology 2006;21:60-5.
8. Lurie F, Creton D, Eklof B, et al. Prospective randomized study of endovenous radiofrequency obliteration (Closure) versus ligation and stripping in a selected patient population (EVOLVES study). J Vasc Surg 2005;38:207-14.
9. Vaislic C, Clerc PCG, Dan J, de Tilly I, Escalard JM, Gosselin J *et al.* [Return to work after surgical treatment o varicosities of the lower limb.] *Phlebology* 1992; **45**: 159-165.

10. Weiss RA. Comparison of endovenous radiofrequency versus 810 nm diode laser occlusion of large veins in an animal model. Dermatol Surg 2002;28:56-61
11. Proebstle TM, Lehr HA, Kargl A, Espinola-Klein C, Rother W and Bethge S *et al.*, Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles, *J Vasc Surg* **35** (2002), pp. 729–736.
12. Proebstle TM, Sandhofer M, Kargl A, Gul D, Rother W, Knop J *et al.* Thermal damage of the inner vein wall during endovenous laser treatment; key role of energy absorption by intravascular blood. *Dermatol Surg* 2002; 2 596-600.
13. Weiss RA, Weiss MA. Controlled radiofrequency endovenous occlusion using a unique radio frequency cathete under duplex guidance to eliminate saphenous varicose vein reflux: a 2-year follow-up. Dermatol Surg 2002;28:38-42
14. Merchant RF, DePalma RG, Kabnick LS. Endovascular obliteration of saphenous reflux (a multicenter study). J Vasc Surg. 2002;35:1190–1196.
15. Hingorani AP, Ascher E, Markevich N, Schutzer RW, Kallakuri S, Hou A, et al. Deep venous thrombosis after radiofrequency ablation of greater saphenous vein (a word of caution). Vasc Surg. 2004;40:500–504.
16. Almeida JI. Radiofrequency ablation versus laser ablation in the treatment of varicose veins: value and limitatio Vascular 2004;12:S57
17. Merchant RF, Pichot O, Myers KA. Four-year follow-up on endovascular radiofrequency obliteration of great saphenous reflux. Dermatol Surg 2005;31:129-134
18. Navarro L, Min RJ, Bone C. Endovenous laser: a new minimally invasive method of treatment for varicose vein preliminary observations using an 810 nm diode laser. Dermatol Surg 2001;27:117-122
19. Proebstle TM, Gul D, Lehr HA, Kargl A and Knop J, Infrequent early recanalization of greater saphenous vein after endovenous laser treatment, *J Vasc Surg* **38** (2003), pp. 511–516.
20. Perkowski P, Ravi R, Gowda RC, et al. Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single-center experience. J Endovasc Ther 2004;11:13 138
21. Puggioni, M. Kalra, M. Carmo, G. Mozes and P. Gloviczki, Endovenous laser therapy and radiofrequency ablati of the great saphenous vein: analysis of early efficacy and complications, *J Vasc Surg* **42** (2005), pp. 488–493.
22. Almeida J.I. and Raines J.K. Radiofrequency ablation and laser ablation in the treatment of varicose veins. Ann Vasc Surg 2006; 20:547-552.

VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

Not applicable.

IX. RESEARCH METHOD AND DESIGN

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

All new patients with symptoms of chronic venous insufficiency are initially evaluated with a color flow examination with a high resolution linear probe (7 to 12 MHz). Patients in whom endovenous thermal al indicated will be considered for enrollment. Specifically, patients will be included if they:

1) have undergone at least 6 weeks of conservative treatment with compression stockings (unless t ulcers, recurrent phlebitis, or bleeding varices)
2) have venous disease that meets CEAP clinical class 2 through 6

3) have symptoms secondary to Small Saphenous Vein insufficiency defined as reverse flow in the saphenous vein than 0.5 seconds after calf compression or while standing.

Patients will be excluded if they

1) have previously undergone surgery, EVTA, or phlebectomy in that extremity (exclusive of spider vein injections or other cosmetic surface procedure.
2) have a history of DVT.
3) have a history of hypercoaguability disorder.
4) are pregnant or breastfeeding.
5) are nonambulatory.

Patients will be randomized to one of the two EVTA techniques (radiofrequency ablation or laser ablation) and will undergo the procedure and associated follow-up according to standard clinical practice. Patients will be seen in follow-u at 4 days, 6 weeks, and 6 months post-procedure. Ultrasounds of the treated leg will be obtained at each visit to ensure tl the vein remains closed. If the SSV remains closed and the patient has not developed new refluxing veins in the same area, the procedure will be considered successful. If the SSV is open or new refluxing veins appear in the same area, the procedure will be considered a failure.

At 1 year and yearly thereafter, the patient will be telephoned and asked if there are recurrent clinical symptoms. If No, the procedure will be considered successful at that time. If yes, the patient will be asked to come in for an ultrasound examination to determine if the clinical symptoms are a result of recurrence of the original treated vein or a new problen and based on this, will be categorized as success or failure at that time period.

X. Plan for Control of Investigational Drugs (If the VCUHS Investigational Drug Pharmacy is not used), Devices, and Biologics

Describe your plans for the control of investigational products including: (1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s); (2) plan for storing the investigational product(s) as specified by the sponsor (if any) and in accordance with applicable regulatory requirements; (3) plan for ensuring that the investigational product(s) are used only in accordance with the approved protocol; and (4) how you will ensure that each subject understands the correct use of the investigational product(s) (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

Not applicable.

XI. Data Analysis Plan

For investigator–initiated studies.

Patients that are found to have Smaller Saphenous Vein (SSV) insufficiency and elect to enroll in the stu randomized into either the radiofrequency ablation (RA) or laser ablation (LA) group by a statistician in 2, 4 and 6. Neither the patients nor the investigators will be blinded as to the randomized treatment the

The success of the randomization procedure will be evaluated by comparing the two treatment groups fo demographic information and pre-treatment Venous Clinical Severity Score (VCSS). Categorical demo

will be tested via a Chi-Square analysis, while continuous demographic variables and pre-treatment VCSS will be tested using a t-test.

Specific Aim 1 will be evaluated in two ways. First, short term success will be defined as the SSV remaining closed and the patient does not develop any new refluxing veins in the same area during the first 6 months post-treatment. The two groups will be compared using a Chi-Square test to see if they are significantly different. In addition, short term success will be evaluated using a binary logistic regression model (Hosmer and Lemshow, 1989) that includes demographic and pre-treatment VCSS covariates. PROC FREQ and PROC LOGISTIC in SAS® (SAS Institute Inc. Cary, NC) will be used to carry out this short term success analysis.

Overall success will be evaluated using survival models. As it was for the short term success analysis, failure will be defined as the SSV failing to remain closed or the patient develops new refluxing veins in the same area. Survival curves for the two groups will be computed using Kaplan-Meier estimates (Kaplan and Meier, 1958) and the equality of these curves will be evaluated using both the Log-Rank and Wilcoxon test statistics. The Wilcoxon test gives greater weight to early observation when sample sizes are larger while the Log-Rank test is more sensitive to late events when fewer patients remain in the study. A multivariate Cox Proportional Hazards Model (Cox, 1972) will be used to analyze the impact of demographic variables and VCSS. PROC LIFETEST and PROC PHREG in SAS® (SAS Institute Inc. Cary, NC) will be used to carry out this overall success analysis.

Specific Aim 2 will be evaluated using Chi-square tests to compare the two groups for presence or absence of DVT, skin burns, hyperpigmentation, parathesias and the development of new spider veins.

Finally, Specific Aim 3 will be evaluated using a non-parametric Mann-Whitney U test (Wilcoxon Rank-Sum test) (Conover, 1999) on the subjective pain and bruising score provided by the patients at the 1 week follow-up visit.

All tests will be two-sided at the $\alpha = .05$ level of significance. Effects will be reported with a point estimate and 95% confidence intervals in addition to p-values. We will examine the distributions of all measures and identify possible outliers. Outliers will be thoroughly checked for collection or data entry errors before being used in the analysis.

References

Kaplan, E.L. and Meier, P. (1958), "Non-parametric estimation from incomplete observations." *Journal of the American Statistical Society,* 53, 457-481.

Cox, D.R. (1972), "Regression Models and Life-Tables (with Discussion)," *Journal of the Royal Statistical Society, Series B*, 34, 187-220.

Hosmer, D.W., Jr. and Lemeshow, S.(1989) *Applied Logistic Regression*, New York: John Wiley and Sons, Inc.

Conover, W.J. (1999), *Practical Nonparametric Statistics*, Third Edition, New York: John Wiley and Sons, Inc.