General discussion
ENDOVENOUS THERMAL ABLATION: WHICH TREATMENT SHOULD WE CHOOSE?

Since the beginning of this decennium, EVTA treatments have earned their way to the top, currently being the gold standard for treating incompetent saphenous veins. This thesis has verified this position for EVLA in particular. Choosing which type of EVTA to use, is not always easy and is dependent of many factors. Some considerations for instance can be efficacy, (minor) complications, costs, type of incompetent saphenous trunk (ST) (GSV or SSV), vein diameter, body mass index (BMI), signs of previous superficial vein thrombosis (SVT) in the ST lumen, patients’ experience with previous treatments, etc.

In terms of efficacy, EVLA and RFA are proven to be highly effective, with EVLA having slightly higher success rates than RFA after 5 years of follow-up (1). EVSA was a promising but not well studied method up to this thesis. Our first worldwide RCT with EVSA (chapter 4) has taught us that EVSA is an effective EVTA technique with a very favorable side effect profile, and is not inferior to EVLA (2). EVSA is not frequently used, but can definitely be suitable for some patients; for instance patients with multiple perforating veins along the ST or with incompetent perforating veins alone, patients who experienced minor complications (such as post-procedural pain) in a previous treatment with a different EVTA method, or patients with ulcers of extensive lipodermatosclerosis which restrict local surgical options (3).

If minor complications are an issue for your patient, RFA can be a preferred option of treatment as well, instead of EVLA, as RFA seems to have less post-procedural pain and bruising than short wavelength (810, 940 or 980 nm) EVLA (4). It is less clear however, whether RFA is also superior to long-wavelength EVLA; a study from Mese et al. (5) showed beneficial results for 1470 nm EVLA in comparison to RFA at this topic. As this thesis presented in chapter 5, in the first RCT comparing different wavelengths while all other EVLA variables were set equally, patients treated with 1470 nm EVLA showed significantly less post-procedural pain than patients treated with 940 nm EVLA (6). With this knowledge and the lack of evidence of RCTs on tolerability comparing RFA to long wavelength EVLA, no conclusion can be made on which of these procedures has the most patient friendly side effect profile.

Signs of previous SVT (for instance intraluminal trabeculae) in the ST you are opting to treat, may influence your choice of EVTA method as well. The RFA catheter is more rigid and thicker than the EVLA guidewire and fiber, and may therefore sometimes be more effective to puncture through intraluminal post-SVT trabeculae.

When the incompetent ST has a large diameter of more than 8-10 mm at some point along its course, EVLA may be the preferred treatment option, since you can alter the amount of emitted energy per cm vein. It seems rational that it requires more energy to occlude a vein with a relatively large diameter, than a vein with a small diameter; GSV...
diameter is found to be an independent predictor of recanalization after EVLA treatment (7). In RFA, you can alter the amount of RFA cycles, but you can never exactly administer a certain energy dose.

When it comes to costs, RFA is definitely the most expensive EVTA option, at least in the Netherlands. All EVLA devices have similar costs in the Netherlands, regardless wavelength and fiber type. A single EVSA is by far the least costly option, since it requires no guidewire or catheter. However, multiple EVSA sessions may be indicated and then the cost accumulate and may become comparable to the costs of EVLA.

In some cases, concomitant treatment of incompetent tributaries or perforating veins may be indicated. When there are large tributaries, post procedural SVT may be induced in these tributaries after EVTA treatment, causing pain and discomfort. Also, according to the ‘ascending pathophysiologic theory’, incompetent tributaries may render GSV incompetence and may therefore theoretically undo the treatment success of EVLA in time, with re-opening of the treated GSV or inducing incompetent neovascularization in the GSV compartment (8-10). Also, large incompetent perforating veins along the GSV course may theoretically induce GSV incompetence or neovascularization and may be opted to treat simultaneously with GSV treatment.

To our opinion, no EVTA treatment is superior; for each individual patient, it should be evaluated what the preferred method would be, keeping all above mentioned factors in mind. So personalized medicine also applies to phlebology.

**ENDOVENOUS LASER ABLATION: INFLUENCE OF MANUFACTURERS**

At the start of this millennium, several ideas and technical possibilities came together and created the EVLA procedure. Retrospectively, it is remarkable to observe the rapid development of this technique, especially since there was relatively little data of the ongoing processes during treatment. Compared to the year 2000 when the first case series of EVLA were published, our knowledge of the mechanisms of action of EVLA has now definitely increased, but several issues are still not well understood. Up until now, four possible mechanisms of action are proposed for EVLA (chapter 2): direct contact between fiber tip and vein wall (11), thermal interactions between the emitted laser light and the vein wall (12), the effects of steam bubbles including the ‘industrial heat pipe mechanism and the effects of the carbonized blood layer on the fiber tip (13, 14).

Unlike pharmaceutical corporations, companies manufacturing endovenous devices do not spend a lot of financial resources on research, for the blunt reason that implementation of new endovenous devices does not need to meet strict requirements; the only requirement for implementation of a medical device in the Netherlands is a CE certification (15). Once this CE certificate is obtained, the device can be used in
patients. Several clinicians and physicists themselves have performed experimental and clinical research to explain the effectiveness of EVLA and its many different settings. Manufacturers obviously mainly benefit from new developments in EVLA treatments; introducing a new device/wavelength or fiber tip means an opportunity to increase sale and get more profit. Due to these constant and ongoing changes in EVLA possibilities, manufacturers made it almost impossible for clinicians to perform comparative registry based long-term research. It seems as if almost no device, setting or fiber tip (and definitely not a combination of these factors) lasts long enough to do a trial with a long follow up, let alone to perform a systematic review and meta-analysis; by the time the follow up has reached 2 years (or more), the device/setting/fiber has become old fashioned, and the outcomes of the trial clinically irrelevant. Similar issues are seen in other medical applications, such as breast implants, hip prostheses and lens implantations, where long-term safety is of even more importance than in EVLA. For us clinicians, it is therefore very important to keep the commercially origin of the alterations in EVLA procedures in mind while choosing an optimal EVLA treatment for our patients, and to stick to these settings, unless there is a valid - scientifically proven - reason to alter them.

ENDOVENOUS LASER ABLATION: THE EFFECT OF WAVELENGTH

The first EVLA devices had short wavelengths (810 nm), which was deliberately selected because it is targeting hemoglobin (Hb). Over the years, laser devices with longer wavelengths (1200 nm or more) were developed and shifted the theoretical chromophore from Hb to water. Devices with long wavelengths were thought to more specifically target the water in endothelial cells, and therefore to be more effective and have a more beneficial side effect profile. Temperature profiles of EVLA are independent of wavelength, as this thesis has shown in chapter 3 (16), which suggests that the working mechanism of EVLA is independent of wavelength and thus independent of the target (Hb or water) of laser light. Up until this thesis, all trials comparing short and long wavelengths also varied other parameters such as laser power or fiber tip making a true comparison impossible. To assess the impact of one variable (wavelength for instance), all other variables should be kept constant in the study, as we have done in our RCT included in this thesis (chapter 5) (6). In this trial, patients treated with long wavelength EVLA reported significantly less pain and had a shorter duration of analgesia use 1 week after treatment, than patients treated with short wavelength EVLA. As stated above, this difference cannot be explained by differences in temperature profiles, since they are similar. A possible explanation is that long wavelength EVLA has a better heat diffusion, as it generates more steam bubbles, compared to short wavelength EVLA, as we
observed in an experimental model (12). The heat generated in short wavelength EVLA seems to diffuse less, possibly causing more local tissue damage.

So in summary, all EVLA wavelengths are equally effective in getting optimal treatment results, but longer wavelengths (for instance 1470 nm) may have a more patient friendly side effect profile.

**ENDOVENOUS LASER ABLATION: OPTIMAL SETTINGS**

In EVLA, a lot of parameters can vary, such as wavelength, power, pullback speed and fiber tip. The EVLA procedure is far from standardized but has proven to be effective in many settings, as this thesis has confirmed (chapter 6). The administered amount of energy (J/cm), which is a result from power and pullback velocity, is currently a frequently used parameter to characterize the EVLA procedure in published EVLA studies. It is important to realize however that the thermal efficacy of EVLA is driven by laser power, not amount of energy; a 50 J/cm EVLA process produces an effective EVLA outcome when administered with 10 W laser power and a 2 mm/s pullback velocity, but it can equally be given as 0.1 W and 0.02 mm/s, with little possibility of an effective procedure (17). Therefore, it is essential to not only mention the administered energy when reporting on a procedure, but also the power and pullback velocity.

That being said, a certain energy threshold is probably needed to get effective EVLA treatment. In energy dosing studies by Proebstle et al. (18, 19), a threshold of around 50 J/cm was suggested. Chapter 6 in this thesis however revealed that there are no significant differences in success rates between EVLA RCT’s with energy of more or less than 50 J/cm. A temperature of around 50°C is assumed to be the threshold for collagen denaturation, needed to cause irreversible damage to the vein wall. As shown in chapter 2 of this thesis (16), EVLA procedures with 30 J/cm energy (with a power of 12 W) still generate temperatures of around 70°C, implicating that a threshold of 30 J/cm is sufficient to occlude an incompetent vein. In addition to the energy related variables, there are physical characteristics of the laser fiber that may affect treatment outcome and occurrence of adverse events. During treatment, bare laser fibers have more direct contact with the vein wall, than alternative fibers such as a tulip tip, radial or NeverTouch fibers, which all have a sort of protective coating placed around the fiber tip. Some of the minor complications of EVLA can be explained by direct contact of the fiber tip with the vein wall, resulting in ulcerations and perforation of the vein wall. In RCTs, bare fibers have proven to have more post-procedural minor complications, such as pain and ecchymosis, than the other fibers (20, 21). Also, in an experimental setting described in this thesis (chapter 3), bare fibers had significantly higher peak temperatures than radial fibers. These findings indicate that bare fibers are less patient friendly than other laser fibers.
After carefully having studied the available evidence of the different parameters in EVLA we propose the following standard settings: use a long wavelength EVLA device (for instance 1470 nm) and do not use a bare fiber for the ideal side effect profile, use a functional power setting (for instance 10 W) and administer at least 30 J/cm energy (increase to 50 J/cm when the vein diameter is more than 8mm (7)) to get the intended anatomical effect.

OUTCOME MEASURES FOR ENDOVENOUS TREATMENTS

Since EVTA treatments have proven to be highly effective, attention in clinical practice is shifting from efficacy to patient reported outcome measures (PROMs, the experience of the patient with treatment results), and patient reported experience measures (PREMs, the experience of the patient with health care provision). Especially PROMs are now a main focus of health care providers in phlebology and can be measured with disease specific HRQOL tools such as AVVQ and CIVIC, or generic HRQOL questionnaires such as SF-36, EQ-SD or EQ-VAS, but also with NRS and VAS (pain, patient satisfaction). In addition, symptoms and signs of CVD can be well evaluated with the VCSS. However, in studies concerning EVTA treatments, DUS measured occlusion or reflux are unfortunately often still the primary study endpoints and PROMs are considered a secondary outcome.

In time, and with progression of venous disease, different kinds of recurrent varicose veins can be present after EVLA, either with or without clinical symptoms. There can be recurrence in the saphenofemoral junction (SFJ), along the GSV or AASV course, or as tributaries. To explain recurrence after EVLA, the focus has been on recanalization of a previously obliterated trunk; it is now well known that such recanalization occurs more frequently after ultrasound guided foam sclerotherapy (UGFS) than after EVLA (22). The incidence of neovascularization at the SFJ is much lower after EVLA than after surgical procedures (22). Progression of the disease cannot be avoided and is an important contributory factor in pathophysiology of recurrence in the long-term (23). Apart from genetic factors, other patient related factors (BMI > 30, pregnancy after intervention) have been claimed to be responsible for this progression.

In the end, the ultimate goal of EVLA should be to improve the patients’ quality of life and to prevent complications, not to improve anatomic and hemodynamic outcomes (24). As is presented in previous studies, presence of reflux does not essentially relate to evolution of clinical disease (25, 26), or decrease in HRQOL (27). This seems counterintuitive and is quite difficult to comprehend for treating physicians. Therefore, we should evaluate the treatment outcome carefully and expand beyond the control US and include patients’ perspectives.
FUTURE

As the position of EVTA/EVLA as the gold standard for incompetent STs is further established with this thesis, focus of future research on EVTA should be on patient reported complications. There is still a knowledge gap in post procedural patient reported outcomes of long wavelength EVLA versus RFA. Also, the benefits of additional and/or combination treatments, such as complementary phlebectomies or UGFS treating incompetent tributaries simultaneously to EVTA treatment, have not been well studied, even though these simultaneous treatments are widely used clinically. In order to ensure that these treatments remain financially compensated for by health care providers in the Netherlands, more scientific evidence is needed to confirm the medical significance of these additional of combined treatments, especially for ambulatory phlebectomies. At the Erasmus MC in Rotterdam, the Netherlands, a large RCT is currently ongoing, studying the effects of solely ambulatory phlebectomy of tributaries on incompetence of the GSV (SAPTAP trial; NTR number NTR4821, www.trialregister.nl).

In the present time, with rapid health technology improvement and ongoing cost-effectiveness analyses, treatment related costs will remain an important issue in phlebologic management strategies. The past few years we have noticed the growing influence of health care providers in the Netherlands, indicating that in the years to come, treatment costs may even become a more pressing issue than physicians wish them to be. The remaining challenge is to choose the most appropriate therapy for each individual patient, and thereby reducing unnecessary therapies and costs and providing the best possible care for our patients.

It is important to define and record your opted treatment goal in advance, distinguishing globally between one of these four groups: 1. Cosmetic, 2. Symptom reduction, 3. Prevent disease progression to clinically relevant stages such as C4+, 4. Reverse clinically relevant C4+ disease or increase healing speed and rate of venous ulcers. Defining these groups and communicating them with our patients is important for interpreting treatment outcomes, in both clinical and research settings, and to be able to justify the treatments costs in the future.
REFERENCES


