Mechanochemical endovenous ablation in the treatment of varicose veins

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Chapter 9

Summary and future perspectives
Summary

The aim of the investigations described in this thesis is to assess the safety, clinical outcome and efficacy of MOCA using the ClariVein® system.

In chapter 2 we performed a review on all current endovenous treatment modalities for the treatment of varicose veins. The technique, mechanisms of action, outcome and complications of EVLA, RFA, UGFS, EVSA and also MOCA were extensively described. Prospective studies that reported on outcome were included in this review. All endovenous procedures can be performed in an outpatient setting without administration of antibiotics. Several advantages and disadvantages of endothermal and non-thermal techniques are summarized from the present literature.

In chapter 3 we present the first European pilot study that evaluates the feasibility and safety of MOCA. Thirty limbs in 25 patients with GSV insufficiency were treated with MOCA at two centers (Arnhem and Nieuwegein). Polidocanol, as the only sclerosant that is registered in the Netherlands was used in a solution of 1.5%. All treated veins showed occlusion on ultrasound directly after MOCA. Because MOCA does not use thermal energy, nerve injury or skinburn were not observed. Other potential complications of endovenous therapies, like deep venous thrombosis, pulmonary embolism, and hyperpigmentation were not determined. Localized hematoma and superficial thrombophlebitis were reported in respectively 30% and 13% of the treated patients. Six weeks after MOCA 26 of 30 veins (87%) were completely occluded. Three patients had a partial recanalization and 1 patient was diagnosed with an open GSV and required a successful redo-procedure. Patients were very satisfied with their treatment resulting in satisfaction score of 8.5 (0-10 scale). We concluded that MOCA is a safe and well-tolerated technique in short term, although further studies evaluating the efficacy of different sclerosant concentrations on outcome are indicated.

The ClariVein® system obtained the CE mark in 2010, allowing its use in Europe. We conducted a prospective series of MOCA procedures in 50 consecutive patients with SSV insufficiency. The results of this study are presented in chapter 4. Polidocanol 1.5% was used to treat the whole SSV segment in the first 15 patients. In the other 35 patients, the proximal SSV was treated with 2 mL polidocanol 2% and the distal SSV with polidocanol 1.5%. The protocol was altered because preliminary results showed improved occlusion rates in the treatment of GSV insufficiency. Six week after MOCA all treated SSV’s were occluded. No major complications were observed, especially no nerve injury. At 1 year, the
anatomic success rate was 94%. Interestingly, patients receiving high dose polidocanol had a superior occlusion rate compared to those with low dose polidocanol (97% versus 87%, \( P = 0.19 \)). The MOCA patients had a significant improvement in clinical outcome 1 year after treatment.

The outcomes of MOCA were also prospectively studied in 106 patients with GSV insufficiency and are described in chapter 5. The proximal GSV was treated with 2 mL polidocanol 2%, and the distal GSV with polidocanol 1.5%. Patients were evaluated with clinical examination and duplex ultrasonography at 6 weeks, 6 months, and 1 year after treatment. The clinical success after MOCA was high, whereas 93% of patients had improvement in VCSS after 1 year. The improvement in clinical outcome also resulted in a better disease-specific quality of life. At 1 year, 88.2% of the treated GSVs remained occluded as measured by duplex ultrasonography. Twelve patients had a recanalization, of which eight were partial. The median time to return to normal activities and time to return to work for employees was only 1 day. The fast recovery is supported by the low postprocedural pain that was observed. During the first 14 days after treatment the mean painscore was 7.5 mm per day on a 0 – 100 mm VAS.

One of the advantages of MOCA is the low postprocedural pain. As thermal ablation techniques for varicose veins carry a higher risk of postprocedural pain due to the heat that is used, a cohort study was performed simultaneously to the study in the previous chapter to address this issue. These results are described in chapter 6. Sixty-eight patients with unilateral GSV incompetence were treated with either RFA or MOCA to compare postprocedural pain and quality of life. Patients treated with MOCA reported significantly less postprocedural pain than patients treated with RFA during the first 14 days after treatment (4.8 mm versus 18.6 mm; \( P < 0.001 \)) (mean VAS over 14 days). The lower postoperative pain score was also associated with a significantly earlier return to normal activities (1.2 versus 2.4 days; \( P = 0.02 \)) and work resumption (3.3 versus 5.6 days, respectively; \( P = 0.02 \)). At 6 weeks, patients in both groups perceived an improved change in health status and an improved disease-specific quality of life.

The results in the previous chapter demonstrate that MOCA is a safe and effective technique in the treatment of varicose veins. However, randomized studies are necessary to compare the effectiveness with endothermal techniques and define the definitive role of MOCA. In chapter 7, we present the outlines of a multicenter prospective randomized trial, the MARADONA trial that compares the outcome of MOCA with RFA. The primary endpoints are anatomic and clinical success at one-year follow-up and postprocedural
pain. Participating patients have scheduled follow-up until five years after treatment, so that long term outcome of MOCA can also be observed.

In chapter 8, the histological observations of a MOCA-treated vein, one year after treatment are discussed. Microscopic evaluation of the vein showed a circumferential disappearance of the endothelial layer and fibrosis of the vein. The media was considerably damaged with changes in collagen structure. These observations support the therapeutic effect of MOCA.

General discussion

Since the development of endovenous procedures in the end of the 1990’s, the landscape of varicose vein treatment changed dramatically. In a period of ten years, the ‘classic’ high saphenofemoral ligation with stripping of the GSV has practically been abandoned and is replaced by minimal invasive treatments. Endothermal techniques as EVLA and RFA appeared to be very effective with high short-term success\(^1,2\). Driven by the desire to reduce surgical trauma and to improve patient-related outcome parameters, these endovenous technologies were rapidly introduced in The Netherlands without a high level of evidence. Comparative evidence was not available until 2003, when the first randomized controlled trial that compared surgery with RFA was published\(^3\). This study showed less postoperative pain, fewer bruising and a faster return to work (4.7 versus 12.4 days) in favor of RFA. At 4 months, the occlusion rate was 90.5\% for RFA versus 100\% for surgery. Moreover, the first randomized controlled trial that compared EVLA with surgery was not published until 2007\(^4\). Since then a large number of retrospective, prospective case series, randomized controlled trials and reviews have been published. However, the number of studies with follow-up of more than 5 years is still sparse, as elaborated in chapter 2 of this thesis. A recent meta-analysis concluded that there is too little evidence to choose between endovenous techniques in terms of efficacy\(^5\). They advocated that more high quality RCTs and long term data are necessary, and reporting and measurement of outcome parameters in a standardized manner will facilitate future evaluation of results.

The occlusion rate is particularly presented as the dominant outcome parameter in evaluating success of endovenous treatment. However, there has been a large debate about defining ‘success’ in varicose vein treatment. In general, outcome parameters should be divided into clinical outcome, which is essential to the patient and broadens the perspective of treatment, and anatomical outcome. Clinical outcome assessment should
include standardized objective criteria that reflect patient symptoms, clinical signs, and general- and disease-specific quality of life. While the CEAP classification provides an accurate description of symptoms and signs, it is not very suitable to assess improvement after treatment. The VCSS facilitates evaluation of subtle changes in signs and symptoms over time, representing pain, the presence of varicose veins, edema, signs of CVI and venous ulcers. However, the VCSS offers no evaluation of the impact of venous disease on the quality of life of the patient, which is of utmost importance. Disease-specific quality of life questionnaires provide a more complete assessment of the total spectrum of venous disease, and have also been introduced as patient reported outcome measures (PROMs) in several countries. Because anatomical and hemodynamic findings on ultrasound poorly correspond with the clinical outcome in patients with varicose veins, the presence of anatomical reflux after endovenous treatment does not correlate with clinical disease. Therefore, the use of both clinical and technical outcome parameters probably is most suitable to assess the benefit of treatment.

Chronic venous insufficiency reflects a broad spectrum of symptoms. Increase of clinical severity of venous disease is associated with worse disease-specific quality of life. However, no appreciable difference exists between class C2, C3 and C4. The negative effect of uncomplicated varicose veins on quality of life is therefore comparable to veins with complications shortly before ulceration. This observation seems to be in contrast with the decision of insurance companies in The Netherlands to neglect reimbursement of C2 varicose veins. Clinical severity is also associated with generic quality of life impairment. For C2 varicose veins, deterioration in physical domains is observed, rather than psychological domains. Moreover cosmetic concerns are associated with mental health to a large extent. Where reimbursement should be determined by patients’ complaints, disease-specific quality of life questionnaires or a revised VCSS will be superior tools to identify whether symptoms are based on cosmetic concerns or physical complaints.

Recommendations on the choice of treatment from a medical point of view must be based on well defined outcome parameters and patient emotions. Endovenous thermal ablative techniques have been proven for years to be very effective, with very low risk and minimal postprocedural pain. However, they do require the delivery of tumescent anesthesia. This adds overall time to the procedure and may cause discomfort to some patients. MOCA has several advantages with respect to endothermal techniques, including lower postprocedural pain, faster return to normal activities and work and is quicker to perform, as suggested in this thesis. Nevertheless, longer follow-up of MOCA-treated patients...
with focus on clinical and anatomical outcome, and randomized studies are needed to define their definitive position. There are multiple factors that will play a role in determining what the next standard treatment for varicose veins will be. An optimal balance between economics and patient outcomes will be decisive in this perspective. Ideally, high efficacy and patient outcomes would drive improved economics, but this, unfortunately, is not always the case when it comes to insurance companies. Additionally, medical device companies must have appropriate financial resources to continue to invest in developing and testing new technologies, with the goal of constantly improving health care while reducing costs.

**Future perspectives**

In thesis we have demonstrated that MOCA is a safe, feasible and effective treatment in abolishing saphenous reflux. These good experiences with MOCA, still leave various questions to be answered and concerns to be resolved in the near future. Most interesting will be to monitor long term outcomes to determine if the good short term results of MOCA translate to good long term results as well. The tight and fibrotic collagen structures that were observed in the treated segment of MOCA after 1 year, justifies the thought that recanalization this area will be very unlikely. On the other hand, treatment failures seem to increase over time with all endovenous procedures. Therefore, long term results of MOCA are necessary to definitively place the position of MOCA among treatment options for varicose veins. Our study group will soon analyze the outcome after 3 years of follow-up in the prospective registry study. In this study 106 legs (92 patients) were treated with GSV insufficiency.

When a new technology is introduced, development and standardization of the technique evolves over time. This is the case with RFA and EVLA, where catheters and tips are constantly perfected and adapted to new findings, and it will also be the case with MOCA. In MOCA there are several questions in standardization that need to be answered. The administration of the sclerosant dose is very pivotal. In our studies the dose of polidocanol was raised from 1.5% in the safety study to 3% in the proximal segment in the MARADONA study, to improve occlusion rates. The influences of different concentrations of sclerosant on outcome are studied in the ClariVein® dose finding trial (NTR3009), that randomizes patients with GSV insufficiency between treatment with polidocanol 2%, 3% and foam 1%. In a previous study we already
observed a higher anatomical success with polidocanol 2% compared with polidocanol 1.5% (97% versus 87%)\textsuperscript{19}. However, the difference between these was not statistically significant, probably because of the small number of patients.

In the hierarchy of research designs, the results of randomized controlled trials are considered to be evidence of the highest grade, whereas observational studies are viewed having less validity, because they might overestimate treatment effects. Therefore, we designed two multicenter randomized controlled trials (MARADONA trial, NCT01936168 and MESSI trial, NTR4613). The aim of both ongoing trials is twofold. First, it hypothesizes that anatomical success of MOCA is comparable with RFA in the treatment of GSV and SSV insufficiency. Secondly, it aims to demonstrate that MOCA is associated with less postprocedural pain than RFA. A cost analysis comparing MOCA with RFA will also be performed in the MARADONA study. In the background of increasing health resources, a rational cost analysis is necessary to determine the position of MOCA with other endovenous techniques. Nevertheless, the actual costs of treatment are influenced by several factors that should be encountered in the economic value of a new technique. For example, postprocedural pain leading to a longer recovery and delayed return to work; the shorter time to perform the procedure; long term clinical and anatomical success; and the number of re-interventions need to be evaluated as well. Our hypothesis, that adjunctive procedures are carried out less frequent after MOCA is an interesting point in terms of patient satisfaction and costs.

Also, a comparison in outcome between polidocanol and sotradecol would be very interesting to evaluate. Sotradecol is known to be a more potent sclerosant than polidocanol. Moreover, the outcome of MOCA with sotradecol appears to be slightly better than MOCA with polidocanol, as shown in chapter 2, but this observation is not evidence based. A randomized controlled trial that compares anatomical success of MOCA between patients treated with sotradecol versus polidocanol is an appropriate approach to study this issue. Unfortunately sotradecol is not registered in the Netherlands, and our study group is not able to design this study.

Histopathological outcomes are important in order to expose the mechanism of action of a technique and offers opportunities to improve the clinical results by adjusting details of the technique. There is only one study that has examined the effect of MOCA on the vein wall\textsuperscript{20}. We have commenced an animal study that evaluates the histological effects of MOCA, sclerotherapy and mechanical abrasion without infusion of a sclerosant. Analysis of the specimens will be performed directly and six weeks after the procedure.
References


