A multicenter, randomized, dose-finding study of mechanochemical ablation using ClariVein and liquid polidocanol for great saphenous vein incompetence

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ABSTRACT

Background: The purpose of the present study was to identify the ideal polidocanol (POL) concentration for mechanochemical ablation (MOCA) of the great saphenous vein (GSV) using the ClariVein system (Merit Medical, South Jordan, Utah).

Methods: We performed a multicenter, randomized, controlled, single-blind trial with a follow-up period of 6 months. Patients with symptomatic primary truncal GSV incompetence were randomized to MOCA + 2% POL liquid (2% group) or MOCA + 3% POL liquid (3% group). The primary outcome was technical success (TS), defined as an open part of the treated vein segment of ≤10 cm in length. The secondary outcomes were alternative TS, defined as ≥85% occlusion of the treated vein segment, postoperative pain, venous clinical severity scores, Aberdeen varicose vein questionnaire scores, and short-form 36-item health survey questionnaire scores, and complications.

Results: From 2012 to 2018, 364 patients (375 limbs) were included, of which, 189 limbs were randomly allocated to the 2% group and 186 to the 3% group. The TS rate at 6 months was 69.8% in the 2% group vs 78.0% in the 3% group ($P = .027$). A higher overall TS rate was seen in GSVs of ≤5.9 mm compared with GSVs >5.9 mm (84.3% vs 59.5%, respectively; $P < .001$). The alternative TS rate at 6 months was 61.4% in the 2% group and 67.7% in the 3% group ($P = .028$). The venous clinical severity scores, Aberdeen varicose vein questionnaire scores, and most short-form 36-item health survey questionnaire domains had improved in both groups ($P < .002$). Postprocedural pain was low. Two pulmonary embolisms and two deep vein thromboses were seen. Superficial venous thrombosis had occurred more often in the 3% group (18 vs 8 in the 2% group; $P = .033$).

Conclusions: The results from the present study showed a higher success rate for MOCA with 3% POL liquid than for MOCA with 2% POL liquid at 6 months of follow-up. However, the difference in quality of life was not significant. Long-term follow-up studies are required to investigate whether these results will be sustained in the future. (J Vasc Surg Venous Lymphat Disord 2021;■:1-9.)

Keywords: ClariVein; Endovenous ablation; Great saphenous vein; Mechanochemical ablation; Polidocanol; Varicose veins

In the past decade, interest has been growing in nonthermal, nontumescent techniques for the treatment of saphenous truncal reflux. In 2010, mechanochemical ablation (MOCA) using the ClariVein system (Merit Medical, South Jordan, Utah) was introduced. This endovenous technique combines mechanical endothelial damage using a rotating wire with simultaneous infusion of polidocanol (POL) liquid or sodium tetradecyl sulfate (STS) liquid to chemically enhance damage to the vein wall, resulting in its occlusion. In the Netherlands, only POL has been licensed for use. The major benefit of MOCA is pain reduction during and after treatment, because no heat is used and tumescence anesthesia is not required.[1]

The safety and efficacy of MOCA have been extensively studied. Although many studies to date have reported high occlusion rates after short- and mid-term follow-up, very few studies have attempted to use different concentrations of POL to achieve higher occlusion rates.[2] At

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present, the manufacturer's instruction for use have recommended a variable dosage of 2 to 10 mL of 2% POL per cm of the vein to be treated, depending on the vein diameter. Thus, 5 mL of 2% POL has been advised for ablation of a 30-cm great saphenous vein (GSV) with a diameter of 6 mm.

When adhering to safe dosage levels, sclerosants with higher concentrations will potentially limit the extent of treatment. According to the toxicity, the amount of POL should not exceed 2 mg/kg/day. It has been demonstrated that this issue can be overcome by using POL as microfoam (MF).[3] Therefore, we aimed to identify the minimum POL concentration necessary to occlude the GSV using the ClariVein system. We previously reported the preliminary findings of a single-blind multicenter, three-arm randomized, controlled trial of 600 patients comparing MOCA +2% POL liquid, MOCA + 3% POL liquid, and MOCA + 1% POL MF for the treatment of GSV incompetence.[4] Because a disproportionally high number of failures was observed in the MOCA + 1% POL MF group, this arm was discontinued. It was not possible to alter the MF arm to a higher foam concentration or volume, because we had concluded that the ClariVein system was never meant to be suitable for MF delivery. Therefore, the study was changed to a two-arm study, and the ethical review board reviewed and approved the revised protocol. The primary and secondary endpoints could be maintained, and no revisions were necessary for the statistical analysis. The subsequent patients were only randomized to either MOCA + 2% POL liquid (2% group) or MOCA + 3% POL liquid (3% group), with these results described in the present report.

METHODS

Ethics statement. The present study was conducted in accordance with the principles of the Declaration of Helsinki, and the independent medical ethics committee of the Maastricht University Medical Center approved the study (project no., 11-2-064). An independent data safety monitoring committee oversaw the study and periodically reviewed the study conduct, progress, and participant safety. Eligible patients who had met the inclusion criteria were fully informed, and the included patients had provided written informed consent. The ethical review board reviewed and approved the revised protocol after the study had been changed to a two-arm design. The study was registered on September 1, 2011, at Netherlands Trial Register (NL2866).

Study design. The present study was designed as a multicenter, randomized, controlled, prospective, and single-blind trial. The study was performed at five centers in the Netherlands, each performing ~100 to 150 endovenous ablations annually, except for center E (Table I). Follow-up visits were performed at 6 weeks and 6 months postoperatively in the outpatient setting.

ARTICLE HIGHLIGHTS

- **Type of Research:** A multicenter, prospective, randomized, controlled, single-blind trial
- **Key Findings:** A total of 364 patients with symptomatic primary truncal great saphenous vein incompetence were randomized to mechanochemical ablation (MOCA) + 2% polidocanol liquid or MOCA + 3% polidocanol liquid, with a technical success rate at 6 months of 69.8% and 78.0% ($P = .027$), respectively. The venous clinical severity score and quality of life had improved in both groups ($P < .002$).
- **Take Home Message:** The results from the present study showed greater success with MOCA using 3% polidocanol liquid compared with MOCA with 2% polidocanol liquid at 6 months of follow-up. However, the difference in quality of life was not significant.

Patients. The inclusion criterion was symptomatic primary truncal GSV incompetence, defined as retrograde flow lasting >0.5 seconds measured in an upright position using duplex ultrasound (DUS). The exclusion criteria were age <18 years, previous surgery of the ipsilateral GSV, a GSV diameter of >12.0 mm, obstruction of the deep venous system, a body mass index >40 kg/m^2, C5 and C6 of the CEAP (clinical, etiologic, anatomic, pathophysiologic) classification,[5] a known allergy or contraindication to POL, pregnancy, and a life expectancy of <6 months. The GSV diameter was measured using DUS at seven different levels above the knee with the patient in the standing position: at the ostium of the saphenofemoral junction and every 5 cm below the ostium for a length of 30 cm. If focal dilatation was present, measurement was performed just above or below it. All GSV perforators and tributaries were noted as side branches. The patients were randomized using computer block randomization, stratified by center, to undergo MOCA + 2% POL or MOCA + 3% POL. For patients with two affected limbs, each limb was randomized individually. The other limb was treated 4 weeks to 11 months after the first treatment.

Primary endpoints. The primary outcome was technical success (TS), defined as an open part of the treated vein segment of ≤10 cm in length assessed using DUS at 6 months.

Secondary endpoints. The clinical outcome was measured using the venous clinical severity score (VCSS).[6] Quality of life was measured using the Aberdeen varicose vein questionnaire (AVVQ) and the short-form 36-item health survey questionnaire (SF-36).[7,8]

Table I. Baseline characteristics of patients (n = 364) and treated limbs (n = 375)

Characteristic	2% POL (n = 189)	3% POL (n = 186)	Total (n = 375)	*P* value[a]
Treatment center				.841
A	17 (9.0)	19 (10.2)	36 (9.6)	
B	13 (6.9)	14 (7.5)	27 (7.2)	
C	51 (27.0)	58 (31.2)	109 (29.1)	
D	12 (6.3)	11 (5.9)	23 (6.1)	
E	96 (50.8)	84 (45.2)	180 (48.0)	
Age, years	52.0 ± 14.7 (18.7-85.3)	53.3 ± 15.0 (18.8-87.4)	52.7 ± 14.8 (18.7-87.4)	.571
Female sex	114 (61.6)	129 (72.1)	243 (66.8)	.080
Weight, kg	80.9 ± 13.4 (43.5-125.0)	79.6 ± 13.2 (52.0-125.0)	80.3 ± 3.3 (43.5-125.0)	.160
Treated GSV diameter, mm	5.8 ± 1.4 (3.2-12.2)	5.7 ± 1.6 (2.5-12.9)	5.7 ± 1.5 (2.5-12.9)	.506
Treated GSV length, cm	27.3 ± 8.4 (15-31)	28.7 ± 6.0 (15-31)	28.0 ± 7.3 (15-31)	.425
POL dosage, mL	4.5 ± 1.2	4.7 ± 0.8	4.6 ± 1.0	.106
Side branches	2.5 (2.0)	3.0 (1.9)	2.7 (1.9)	.008
CEAP class[b]				.431
C1	0 (0.0)	1 (0.6)	1 (0.3)	
C2	17 (9.4)	20 (11.4)	37 (10.4)	
C3	130 (71.8)	119 (67.6)	249 (69.7)	
C4	34 (18.8)	36 (20.5)	70 (19.6)	

CEAP, Clinical, etiologic, anatomic, pathophysiologic; *GSV*, great saphenous vein; *POL*, polidocanol.
Data presented as number (%), mean ± standard deviation (range), or median (interquartile range).
[a]For difference between treatment groups.
[b]CEAP data were missing for 4.8% patients.

Daily pain scores were recorded using a numeric rating scale, ranging from 0 (no pain) to 10 (worst pain ever) by patients for 2 weeks after their treatment.[9] Alternative technical success (aTS) was defined as ≥85% occlusion of the treated vein segment assessed using DUS. The reported complications were categorized and registered as minor or major complications in accordance with the guidelines of the Society of Interventional Radiology Standards of Practice Committee.[10] The secondary endpoints were measured at 6 weeks and 6 months, except for the pain scores.

Treatment. All physicians had been trained at their local center by the coordinating investigator until they had passed the learning curve. Before the procedure, the area to be treated was disinfected, and sterile drapes were applied with the patient in the supine position. Under ultrasound guidance, the GSV was punctured at knee level below the 30-cm incompetent segment. The ClariVein catheter was placed through a 4F introducer sheath, and the ball tip of the wire was positioned 2 cm distally from the ostium of the saphenofemoral junction. After the motor handle unit was assembled onto the rotating wire catheter, the device was activated at a setting of 3500 rotations/min held stationary for 3 seconds before withdrawal at a steady pullback rate of 1 cm/6 s, with simultaneous infusion of a maximum dosage of 5 mL of 2% POL or 3% POL for 30 cm. No concomitant ambulatory phlebectomy was performed. No thrombosis prophylaxis was given. After the procedure, the patients were advised to wear a class 2 thigh stocking continuously for 48 hours, followed by 2 weeks during the day. Moreover, the patients were advised to remain mobile without extreme exertion. If the patients had had symptomatic incompetent recanalization of the treated vein or new varicosities of the treated limb at the 6-month follow-up, reintervention was offered.

Statistical analysis. According to the power calculation, detecting a 10% difference in success rate between both treatment groups considered clinically significant, 188 patients were required in each group ($\alpha = 0.05$; $\beta = 0.20$; power, 80%). To allow for the loss of patients to follow-up, 200 patients per group were required. Statistical analyses were performed using the SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY). Normality was tested using the Shapiro-Wilk test.

The primary endpoint, TS at 6 months, was reported as frequencies and proportions in the intention-to-treat population. The predictors for TS, including age, gender, center, patient weight, mean GSV diameter, total length of GSV reflux, number of side branches, CEAP class, VCSS, and POL concentration were analyzed using logistic regression. Testing each predictor by the change in −2 log-likelihood χ^2, a final best-fitting model was sought

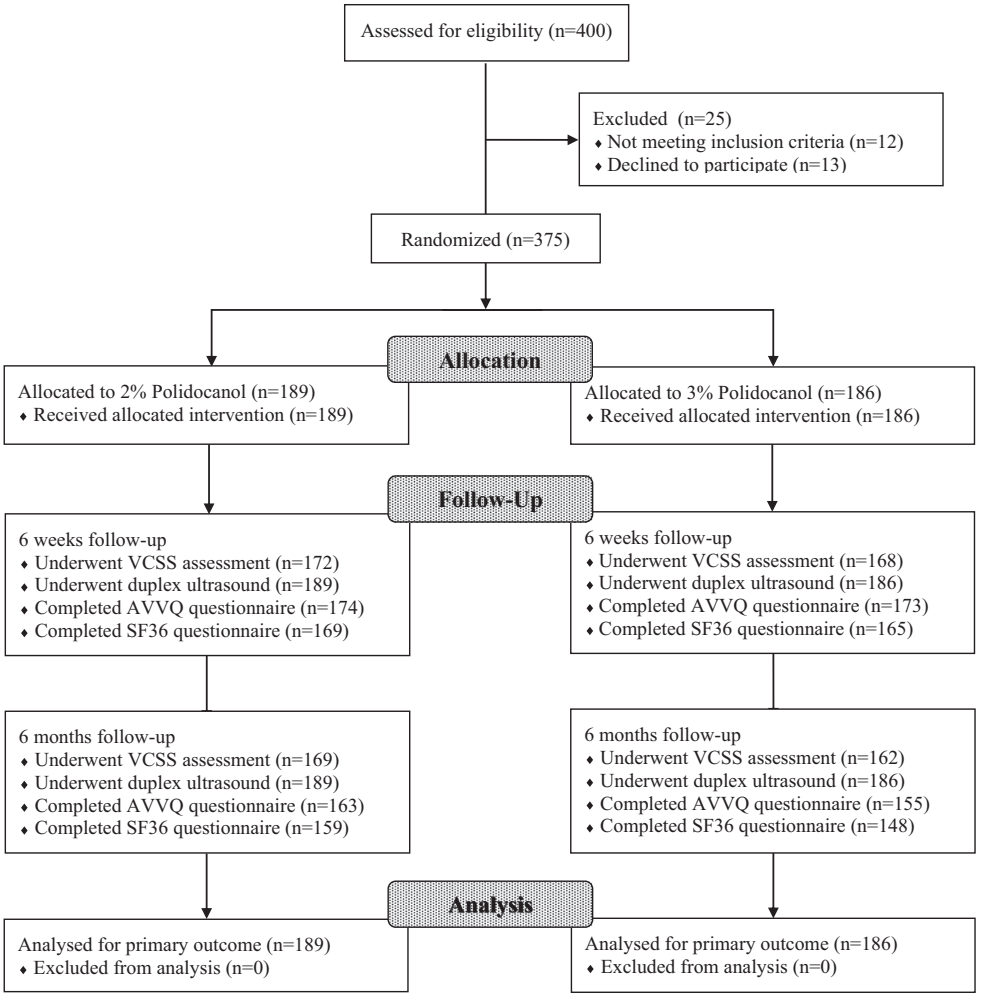

Fig 1. CONSORT (consolidated standards of reporting trials) flow diagram showing trial recruitment, randomization, treatment allocation, and follow-up in limbs. *AVVQ*, Aberdeen varicose vein questionnaire; *SF36*, short-form 36-item health survey questionnaire; *VCSS*, venous clinical severity score.

that would contain only statistically significant effects of predictors. All first order interaction effects between significant direct effects were also tested. The GSV diameters are reported as mean values obtained from the seven different measurement levels and were equally categorized into five groups: <4.6, 4.6 to 5.3, 5.3 to 6.0, 6.0 to 6.9, and >6.9 mm.

The AVVQ scores, SF-36 scores, CEAP class, VCSS, and pain scores were analyzed using repeated measure analysis of covariance and are reported as the mean ± standard deviation for normally distributed data and as the median and interquartile range (IQR) for a non-normal distribution. A P value < .05 was considered statistically significant. For missing data, data imputation was performed using the last observation (DUS) from 6 weeks carried forward to 6 months, with multiple imputation used to impute additional missing data.

RESULTS

Patient characteristics

From 2012 to 2018, 364 patients were enrolled in the present study. Of these patients, 314 patients had been enrolled during the first 2.5 years. After computerized block randomization, 185 patients (189 limbs) were assigned to the 2% group and 179 patients (186 limbs) to the 3% group (Fig 1). Eleven patients had undergone treatment of both limbs. The POL concentration was almost evenly randomized among the five participating centers (P = .841). The mean POL volume was 4.6 ± 1.0 mL. The mean age of the patients was 52.7 ± 14.8 years (IQR, 18.7-87.4 years), and 243 were women (66.8%) and 121 were men (P = .034). The CEAP class for most patients was C3 or C4. The mean GSV diameter was 5.7 ± 1.5 mm (IQR, 2.5-12.0 mm), and the mean treated GSV length was 28.0 ± 7.3 cm (IQR, 15-30.0 cm). The number of side

Table II. TS (<10 cm) and aTS (>85%) of treated GSV after 6 weeks and 6 months of follow-up in 2% POL (n = 189) and 3% POL (n = 186) groups

	TS, %			aTS, %		
Follow-up	2% POL	3% POL	*P* value[a]	2% POL	3% POL	*P* value[a]
6 Weeks	88.9	83.9	.103	80.4	80.6	.530
6 Months	69.8	78.0	.027	61.4	67.7	.028

aTS, Alternative technical success; *GSV*, great saphenous vein; *POL*, polidocanol; *TS*, technical success.
[a]Difference between treatment groups corrected for treatment center, treated GSV diameter, and patient weight at both follow-up points.

branches was significantly higher in the 3% group ($P = .008$; Table I).

Primary outcome

Data imputation was performed for 26 cases using the last observation (DUS) carried forward and for 17 cases using multiple regression analysis. The overall TS rate was 86.4% (324 of 375 limbs) at 6 weeks and 73.9% (277 of 375 limbs) at 6 months.

The TS rate at 6 weeks was 88.9% (168 of 189) in the 2% group and 83.9% (156 of 186) in the 3% group ($P = .103$). The TS at 6 months was 69.8% (132 of 189) in the 2% group and 78.0% (145 of 186) in the 3% group ($P = .027$; Table II). The TS was 1.791 times greater for the 3% group compared with the 2% group (95% confidence interval [CI], 1.062-3.019; $P = .027$). At 6 months, the TS rate was affected by the treatment center ($P < .001$) and the mean GSV diameter ($P = .001$). Age, gender, patient weight, total length of GSV reflux, number of side branches, CEAP class, and VCSS did not affect the failure rate. Center E had had a higher TS rate compared with the other centers (Fig 2) and had reported significantly smaller preoperative vein diameters than the other centers ($P = .002$). Supplementary Fig 1 (online only) shows the distribution of the GSV diameters at each clinic. The GSV diameter measurements were missing for 4.5% of the patients.

Secondary outcomes

Vein diameter. The overall TS rate was associated with the mean GSV diameter; thus, the larger the mean GSV diameter, the lower the success rate (odds ratio, 0.728; 95% confidence interval [CI], 0.624-0.850; $P < .001$). A higher overall TS rate was seen for the GSVs of ≤5.9 mm compared with the GSVs with a larger diameter (84.3% [n = 177] vs 59.5% [n = 88], respectively; $P < .001$). No statistically significant difference was found between the two groups (Table III).

Venous clinical severity score. The overall mean VCSS had improved after 6 months ($P < .001$). The mean change in the VCSS from baseline to 6 months was −1.3 in the 2% group and −1.2 in the 3% group ($P = .671$; Fig 3).

AVVQ scores. The overall mean AVVQ score had improved after 6 months ($P < .001$). The mean change in the AVVQ scores from baseline to 6 months was −8.9 in the 2% group and −7.6 in the 3% group ($P = .585$; Supplementary Fig 2, online only).

SF-36 scores. The overall physical functioning, role physical, and bodily pain domains were improved at 6 months, with statistical significance ($P = .001$, $P = .002$, and $P < .001$, respectively). The change in the remaining SF-36 domains did not differ significantly between the two groups (Supplementary Table, online only).

Pain. All the patients tolerated the procedures well. The mean intraprocedural pain score was 2.51 ± 1.88. The postprocedural pain scores were 1.82 ± 1.96, 1.06 ± 1.69, and 0.86 ± 1.65 at days 1, 7, and 14, respectively. No statistically significant differences were found between the two groups.

aTS rate. The overall aTS rate was 80.5% (302 of 375 limbs) at 6 weeks and 64.5% (242 of 375 limbs) at 6 months. The aTS rate at 6 weeks was 80.4% (152 of 189) in the 2% group and 80.6% (150 of 186) in the 3% group ($P = .530$). The aTS rate at 6 months was 61.4% (116 of 189) in the 2% group and 67.7% (126 of 186) in the 3% group ($P = .028$; Table II). The aTS rate was 1.721 times greater for the 3% group compared with the 2% group (95% CI, 1.055-2.808; $P = .028$).

Complications. Major adverse events caused by venous thromboembolism (VTE) occurred in three patients (0.82%). Of these, two patients in the 2% group, who had presented with chest pain and acute shortness of breath, had had pulmonary embolism detected by computed tomography pulmonary angiography on days 5 and 45. One of these two patients also had had a thrombus extension into the common femoral vein found on DUS. One patient in the 3% group had an asymptomatic deep vein thrombosis (DVT) in the ipsilateral femoral vein detected at 6 weeks. All the patients had recovered after hospitalization and anticoagulant therapy. Other major adverse events were one myocardial infarction in the 2% group in one patient with a history of cardiac disease and multiple myocardial infarctions at day 5. In the 3% group, one patient experienced anaphylactic shock after the POL injection. All the patients recovered after treatment.

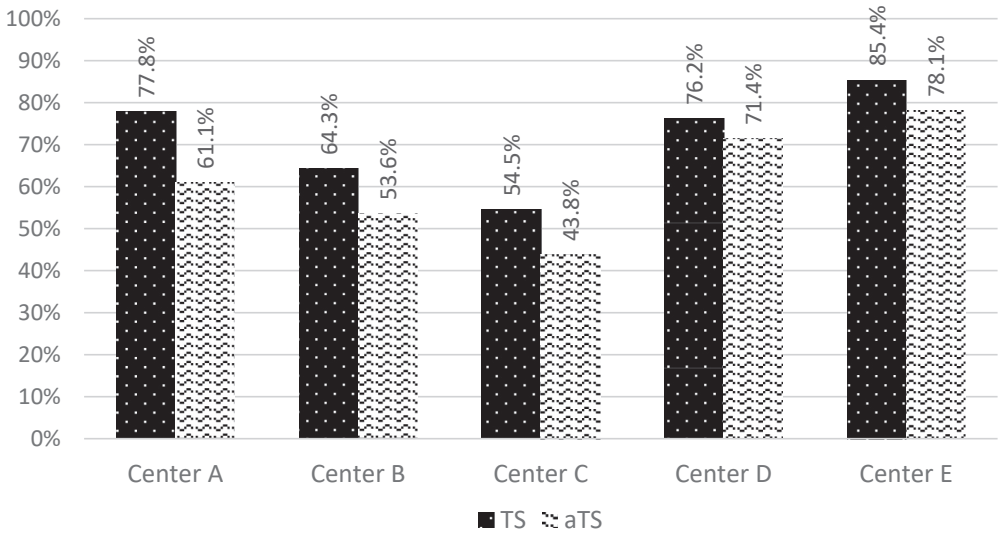

Fig 2. Differences in overall technical success (TS; <10 cm) and alternative technical success (*aTS*; >85%) of the treated great saphenous vein (GSV) after 6 months between centers ($P < .001$).

Table III. TS (<10 cm) and aTS (>85%) of treated GSV after 6 months of follow-up in 2% POL (n = 176) and 3% POL (n = 182) groups

	TS, %			aTS, %		
GSV diameter,[a] mm	2% POL	3% POL	*P* value[b]	2% POL	3% POL	*P* value[b]
<4.6	87.9	92.7	.378	75.8	78.0	.516
4.6-5.3	81.1	70.6	.225	73.0	67.6	.408
5.3-6.0	77.5	87.8	.176	57.5	80.5	.032
6.0-6.9	55.9	68.8	.205	47.1	50.0	.503
>6.9	43.8	64.7	.072	40.6	52.9	.225
Total	69.9	78.0	.051	59.1	67.0	.074

aTS, Alternative technical success; *GSV*, great saphenous vein; *POL*, polidocanol; *TS*, technical success.
[a]GSV diameter missing for 4.5% patients.
[b]Difference between treatment groups stratified by different diameter groups.

The minor complication of superficial venous thrombosis (SVT) occurred in 7.6% of patients, more often in the 3% group (18 vs 8 in the 2% group; $P = .033$). These patients received enhanced surveillance and, if necessary, anticoagulant therapy was offered to prevent progression to DVT.[11] In general, their complaints were mild, self-limiting, and resolved fully. In the 2% group, 1 case of skin induration, 3 cases of skin infection, and 14 cases of hyperpigmentation of the skin had occurred. In the 3% group, 3 cases of skin induration, 1 case of skin infection, and 14 cases of hyperpigmentation of the skin had occurred. The hyperpigmentation had resolved on its own in 9 cases, with 8 and 11 cases remaining in the 2% and 3% groups, respectively.

DISCUSSION

In the present study, MOCA + 2% POL liquid was compared with MOCA + 3% POL liquid to find the minimum dosage necessary to occlude the GSV and adhere to safe dosage levels. At 6 months, the TS rate was higher after treatment with MOCA + 3% POL liquid than after MOCA + 2% POL liquid.

This difference could have been because 3% POL is a stronger sclerosant and could result in better successful treatment outcomes. A strong relationship between the liquid sclerosant effects and the concentration has been reported.[12,13] Few data on MOCA and the POL concentration have been reported. Two studies investigated hybrid combinations in which a higher concentration of POL was used to treat the proximal 10 cm of GSV, followed by a lower concentration for the remaining segment of the vein to optimize the results of MOCA.[2,14] The overall TS and aTS rates at 6 months were 73.9% and 64.5%, respectively. Vos et al[15] reported a higher pooled TS rate of 94.7% after MOCA with a follow-up time of 6 months. Although in two of the five included studies, STS had been used.

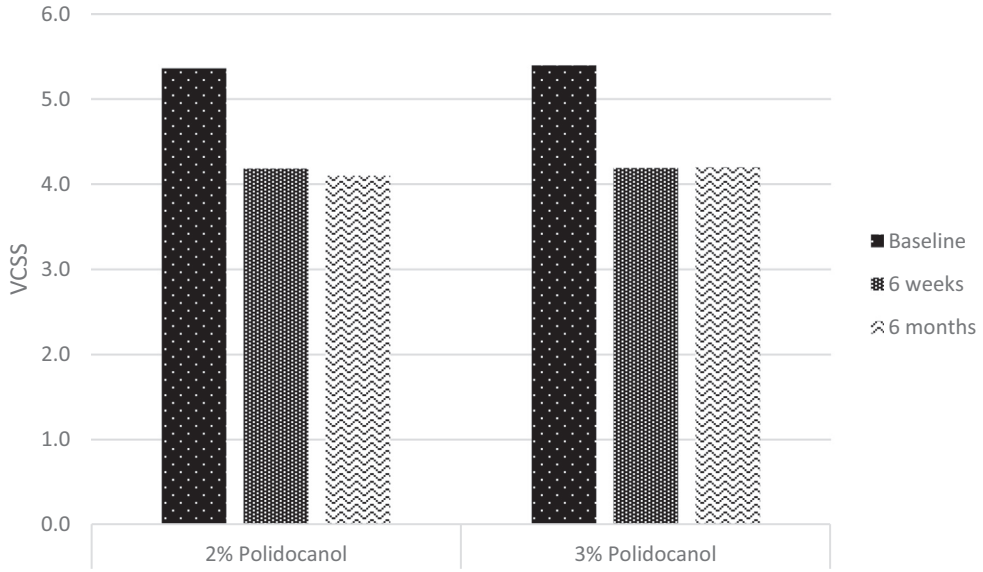

Fig 3. Mean venous clinical severity score (VCSS) at baseline (5.4 ± 2.4 vs 5.4 ± 2.3) and after 6 weeks (4.2 ± 2.8 vs 4.2 ± 2.8) and 6 months (4.1 ± 2.7 vs 4.2 ± 2.8) of follow-up in 2% polidocanol (POL) and 3% POL group, respectively. The difference between both groups was not statistically significant ($P = .671$).

In the present study, TS, which was defined as an open part of the treated vein segment of ≤10 cm in length, was used to allow for comparisons with previous studies using endovenous laser ablation and radiofrequency ablation. Previously, the TS definition had been used by other studies comparing different endovenous modalities, including MOCA of the small saphenous vein. Compared with endovenous laser ablation and radiofrequency ablation, the TS of MOCA in the present study was lower. However, the clinical results were comparable.[16,17] Several potential explanations exist for the lower TS rate in our study. First, the previous studies had reported on different types, concentrations, and dosages of sclerosant.[15] These differences made it difficult to compare their results with the results from the present study. In addition, the aTS was defined as ≥85% occlusion of the treated vein segment. Because the present study was a technology assessment study to find the optimal POL concentration, we not only adopted the outcome assessments as proposed in the joint statement of the American Venous Forum[16] but also added the aTS as a potentially better tool to assess the technical outcome. We believe that the aTS is a comprehensive quantitative measurement of occlusion and more objective for a dose-finding study. However, we acknowledge the use of the standardized definition of success. Additionally, we adopted secondary endpoints to report the clinical outcomes. Another explanation for the overall higher rate of failure in the present study could have been because most of the limbs were classified as C3 and C4 (69.7% vs 19.6%). The limbs with clinical class C3 to C6, defined as chronic venous disease, will develop higher venous pressures and are, therefore, more prone to remodeling of the venous wall. Thickening of the vein wall can result in less effective transmural damage with subsequent recanalization of the vein after endovenous thermal ablation.[18-20] It seems possible that this mechanism could also apply to MOCA, resulting in less effective transmural damage. Therefore, patients with class C5 and C6 disease were excluded from the present study. Third, the extent of treatment was limited by the maximum POL dosage of 2 mg/kg/d. Thus, a refluxing distal GSV could have been left, which could have promoted recanalization and reflux.[21]

Surprisingly, two centers had had an overall success rate that was higher than that of the other centers. This result was likely related to the small GSV diameter that were treated at these clinics (Supplementary Fig 1, online only). Another possible explanation for this might be the suggestion that MOCA could be operator dependent and could have influenced the overall success rate. A significant contributory factor is the challenge of pulling back the catheter with simultaneous sclerosant injection and remaining alert for any signs of the tip becoming caught in the valves. However, all treatments were performed by experienced vascular surgeons, who had been required to have treated ≥10 patients to become fully assimilated with MOCA. Moreover, the more treatments performed by the surgeon, the more familiar the surgeon became with the technique. Furthermore, GSV occlusion measurements per 1 cm using DUS are highly operator dependent, which could also affect the anatomic and technical success.

The present study, including a sufficient sample size, has shown that a larger GSV diameter will be associated with more failure. At 6 months, more recanalization was seen in veins >5.9 mm, regardless of the sclerosant concentration used. Thus, the larger the vein, the lower the success. In accordance with these results, an earlier study also reported an association between the GSV diameter and recanalization, although STS 1.5% was used.[22] Some other studies had not reported an association between GSV diameter and recanalization, which had mainly resulted from the use of STS and a small sample size.[23-25] Our results have indicated that MOCA is a treatment option for small diameter GSVs or SSVs (<5.9 mm) with reasonable success rates and that the GSVs with a diameter of >5.9 mm will have lower success rates and alternative treatment options should be considered. Nevertheless, the POL concentration used with MOCA remains poorly understood, and it will be necessary to continue to investigate the relationship between the saphenous vein diameters and MOCA and, in particular, the POL concentration. We suggest uniformity in the method of measuring the diameters and documentation of the treated vein lengths in future studies to allow for pooling the results in larger meta-analyses.

The clinical results showed significant improvements in the patient symptoms as measured using the AVVQ, VCSS, and SF-36 questionnaire in the short term. The VCSS were significantly improved statistically; however, this might not be of clinical relevance. The limited improvement in the VCSS might have been because no concomitant ambulatory phlebectomy was performed, the high proportion of C3 and C4 limbs, and the reasonable success rates. In addition, intra- and postprocedural pain scores were similar between the groups. All these results corresponded with those from previous reports.[26-30]

In the present study, the occurrence of major adverse events was rare in both groups. DVT and pulmonary embolism had occurred in both groups. However, none of these patients had clinical risk factors. The use of MOCA involves a small, but definite, risk of VTE and our reported VTE rate was in line with MF studies and other MOCA studies.[29,31-33] However, thromboprophylaxis could be considered for specific patients with predisposing factors. The more frequently reported adverse events were self-limiting, including SVT and hyperpigmentation of the skin. Twenty-six cases of SVT (7.6%) were reported, again in line with the results from other studies.[4,24,27] However, more cases of SVT were noted in the 3% group, probably owing to higher dosage of POL that permeated through a higher number of side branches to the varicosities of GSV.[2]

The strength of the present prospective study was that the patients and DUS were blinded to the treatment concentration. The surgeons were not kept unaware because the study had been initiated with MF as one of the treatment arms.

The present study had several limitations. The temporary recruitment of patients was suspended twice in the present study. The first time was because the MOCA + 1% POL MF treatment success was unexpectedly inferior, and the second because of reimbursement issues. In the first 2.5 years of the study, 314 patients were enrolled. Subsequently, only centers C and E were enrolling patients. Therefore, the reduced number of recruiting centers influenced the recruitment tempo. In addition, the results from the present study must be carefully interpreted, because only POL was used and no STS. The use of STS might result in better occlusion rates because it causes more endothelial damage than does POL.[34] Further investigation using a head-to-head study of MOCA + STS vs MOCA + POL is needed. Furthermore, some patients were lost to follow-up, and data imputation was required. The number of reinterventions was not analyzed. However, this did not influence the primary outcome at 6 months, because for the patients who had undergone reintervention, the last observation (DUS) from 6 weeks was carried forward to 6 months. Finally, the present trial did not reflect all patients in real-world practice, because of the heterogenicity of the inclusion and exclusion criteria, which occurs in most studies. Because we focused on the adequate determination of an open or closed vein in this technology assessment study, the follow-up time was limited to 6 months of follow-up. However, perhaps these results will not be sustained in the future, and the number of reinterventions will increase at later follow-up points. Therefore, a long-term follow-up study is needed.

CONCLUSIONS

The results from the present study showed a greater success rate with MOCA + 3% POL liquid compared with MOCA + 2% POL liquid at 6 months of follow-up. However, the difference in quality of life was not significant. Long-term follow-up studies are required to investigate whether these results will be sustained in the future.

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AUTHOR CONTRIBUTIONS

Conception and design: YL, MS, AS, AV, IN, JL, FN, CW
Analysis and interpretation: YL, TA
Data collection: YL, MS, AS, AV, IN, JL, FN, CW
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Critical revision of the article: YL, TA, MS, AS, AV, IN, JL, FN, CW
Final approval of the article: YL, TA, MS, AS, AV, IN, JL, FN, CW
Statistical analysis: YL, TA

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YL and TA contributed equally to this article and share co-first authorship.

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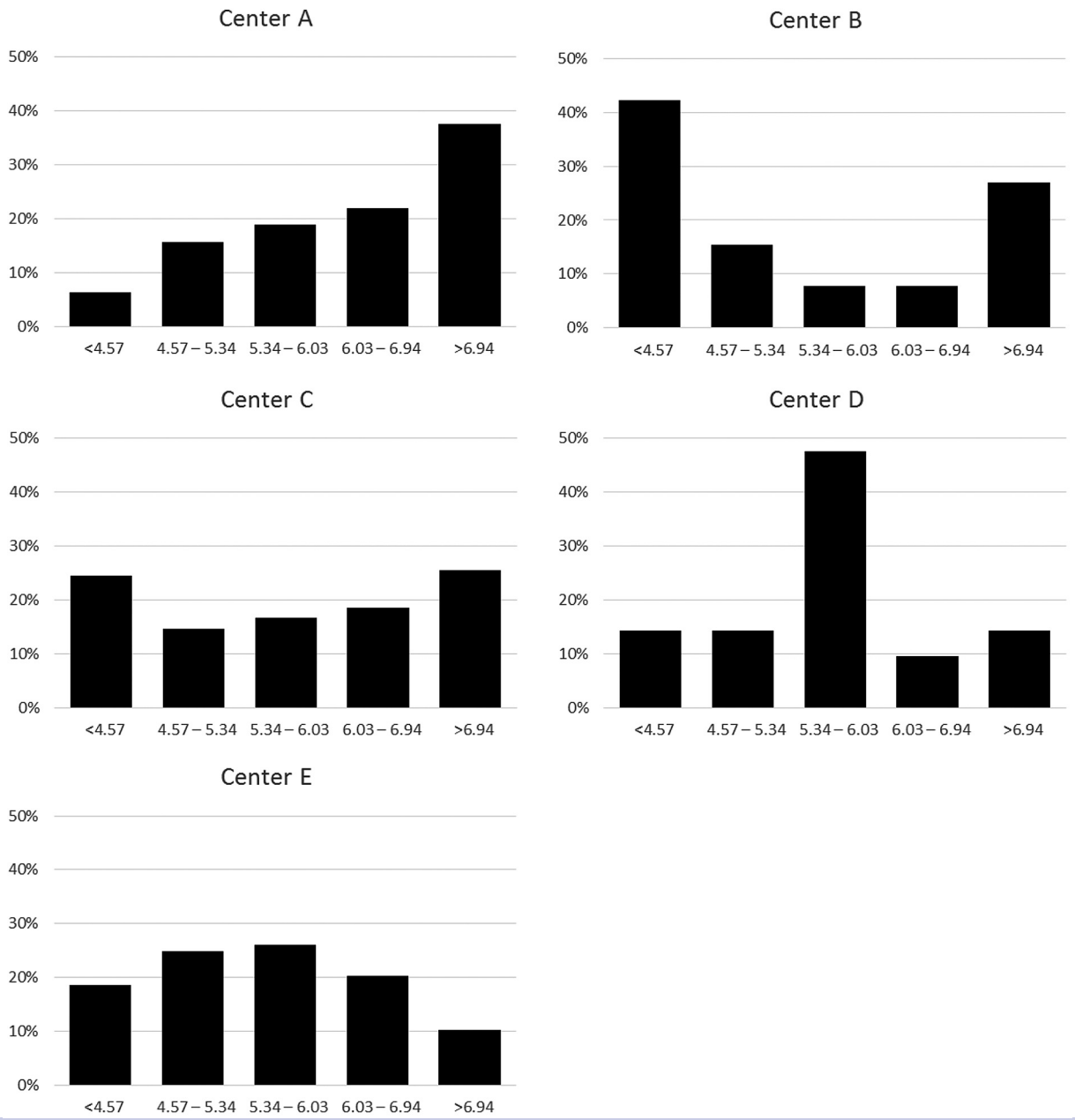
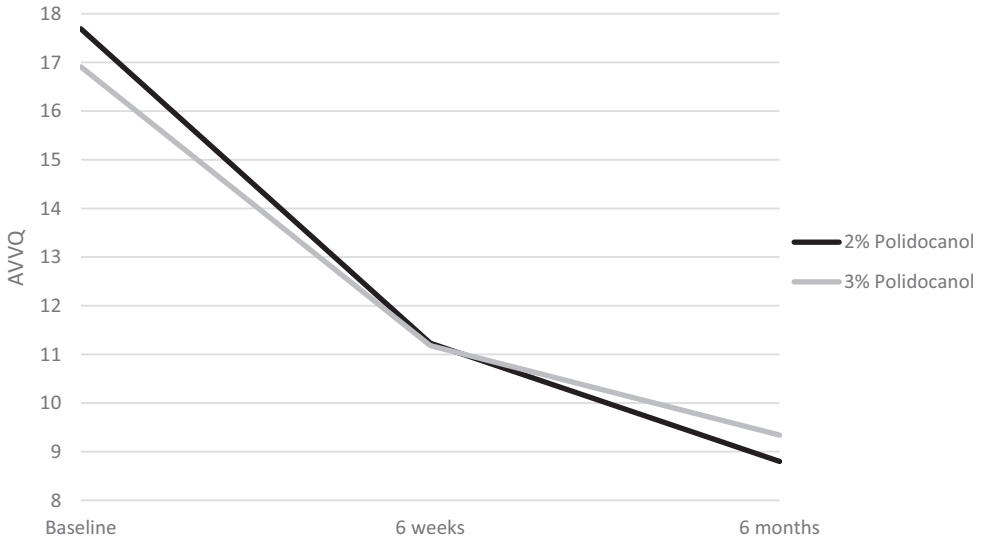
Appendix



Supplementary Fig 1 (online only). Great saphenous vein (GSV) diameter distribution per center ($P < .001$).



Supplementary Fig 2 (online only). Mean Aberdeen varicose vein questionnaire (AVVQ) at baseline (17.7 ± 12.6 vs 16.9 ± 12.4) and after 6 weeks (11.2 ± 8.7 vs 11.2 ± 9.8) and 6 months (8.8 ± 9.1 vs 9.3 ± 9.6) of follow-up for 2% polidocanol (POL) and 3% POL group, respectively. The difference between the two groups was not significant ($P = .585$).

Supplementary Table (online only). Mean scores for SF-36 domains at baseline and after 6 weeks and 6 months of follow-up in both treatment groups

	2% POL			3% POL			
Domain	Baseline	6 Weeks	6 Months	Baseline	6 Weeks	6 Months	*P* value[a]
PF	77.95 ± 21.92	80.79 ± 23.23	80.94 ± 24.70	78.37 ± 22.63	81.13 ± 22.36	83.34 ± 23.11	.539
RP	73.18 ± 26.00	77.17 ± 25.69	76.34 ± 26.46	73.82 ± 27.91	75.15 ± 27.81	79.73 ± 24.28	.680
BP	71.33 ± 20.50	76.59 ± 20.83	79.86 ± 22.79	72.79 ± 20.22	79.29 ± 20.46	81.80 ± 19.40	.542
GH	69.61 ± 19.81	70.48 ± 19.82	69.47 ± 22.68	72.09 ± 21.22	72.28 ± 20.06	74.14 ± 19.59	.393
VT	64.50 ± 18.92	65.59 ± 19.83	66.02 ± 20.81	65.18 ± 19.03	67.35 ± 18.22	68.59 ± 19.00	.630
SF	83.59 ± 21.41	85.21 ± 21.50	82.12 ± 25.53	83.14 ± 21.86	85.23 ± 21.13	86.39 ± 20.53	.381
RE	80.93 ± 23.66	83.33 ± 22.72	81.75 ± 25.95	80.46 ± 26.87	82.32 ± 23.40	83.78 ± 23.32	.343
MH	76.46 ± 17.12	78.26 ± 16.95	76.14 ± 20.06	75.85 ± 17.45	78.07 ± 15.58	77.62 ± 18.13	.464

BP, Bodily pain; *GH,* general health; *MH,* mental health; *PF,* physical functioning; *POL,* polidocanol; *RE,* role emotional; *RP,* role physical; *SF,* social functioning; *VT,* vitality.
Data presented as mean ± standard deviation.
[a]Difference between baseline and 6 months of follow-up in both treatment groups.