

## Early Outcomes after Polidocanol Endovenous Microfoam Therapy for Varicose Veins in Japan

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### ABSTRACT

**OBJECTIVES:** There has been substantial progress in the treatment of varicose veins. This study aims to examine the early outcomes in patients treated using polidocanol endovenous microfoam (PEM) (Varithena®, BTG plc., London, United Kingdom) therapy.

**METHODS:** We retrospectively reviewed and analyzed the early clinical course of 50 patients with refractory varicose veins who underwent PEM therapy in 2018. Data relating to patient characteristics, disease etiology and post-operative outcome were collected.

**RESULTS:** Etiology of varicose veins in 50 patients consisted of five primary diseases; valve impairment of saphenofemoral junction (7 patients), post-operative stasis dermatitis (10 patients), post-operative residual veins (30 patients), veins with significant tortuosity (2 patients) and recurrence due to neovascularization (1 patient).

Initial PEM therapy success rate was 86.3%. No 30-day mortality and no severe complications were noted.

**CONCLUSION:** PEM therapy could help to shed light on the treatment of refractory varicose veins with various backgrounds.

**Key words:** Foam sclerotherapy; Non-thermal non-tumescent; Varicose vein; Polidocanol endovenous microfoam therapy

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### INTRODUCTION

Before 1990 the mainstay of surgical treatment for varicose veins in the lower limbs in Japan was stripping and varicectomy. These procedures were associated with post-operative complications such as subcutaneous hemorrhage, neuropathy, and pain. As alternatives, minimally invasive surgical treatments, endovenous thermal ablation (ETA)<sup>[1,2]</sup>, and non-thermal non-tumescent treatment (NTNT)<sup>[3,4]</sup> were developed. However, although minimally invasive, ETA still produced intra- and post-operative pain as a result of ablation under local anesthesia. NTNT on the other hand is thought to be less likely to result in such complications. Since Tessari's method was published in 2001<sup>[5]</sup>, foam sclerotherapy has been performed, providing higher rates of complete occlusion and lower rates of recurrence. Moreover in 2013, polidocanol endovenous microfoam (PEM) therapy with Varithena (BTG plc., London, United Kingdom) was approved by the Food and Drug Administration. Current standard treatments for varicose veins typically require multiple procedures for optimal outcomes (e.g. supplementary phlebectomy or sclerotherapy). PEM treatment demonstrates effectiveness in occluding all veins and varicose tributaries. By virtue of having remarkably small foam particles (< 500 µm), which provide a large surface area in contact with the vascular endothelium it also achieves high levels of vessel occlusion. This report describes the early outcomes of PEM therapy for refractory varicose veins with various backgrounds at a single center in Japan.

## MATERIALS AND METHODS

### Study design

We retrospectively analyzed 50 patients who underwent PEM therapy with Varithena at the Morisue Clinic between February and November 2018. All patients gave informed consent, and the study protocol was approved by the ethics committee of the Morisue Clinic. All patients were assessed before treatment by transthoracic or transesophageal echocardiogram to exclude the existence of cardiac shunts such as atrial septal defect.

### Surgical technique and post-operative management

The above-knee great saphenous vein (GSV) trunk was cannulated in the direction of saphenofemoral junction (SFJ) and the below-knee GSV was done in the distal direction. PEM consisted of 1% Polidocanol and a gas mixture of Oxygen: Carbon Dioxide (35:65). PEM was injected after confirmation of leg vein collapse following raising of the lower limbs to an angle of 40 degrees. When injected PEM reached the SFJ, the SFJ was manually compressed and PEM allowed to flow to the peripheral saphenous veins and the lateral branches. Compression of the SFJ was released after injected PEM was not detectable in the SFJ by ultrasonography. After verification that PEM had expanded throughout the lower limb, compression bandages and stockings were applied. The lower limbs were then lowered from their raised position 10 minutes after the last injection of PEM. Compression bandages were removed on the 2<sup>nd</sup> post-operative day. Compression stockings remained in situ until the 12<sup>th</sup> post-operative day. The primary endpoint measured was vessel retraction of target varicose veins on the 30<sup>th</sup> day after the operation. In cases in which we deemed initial PEM therapy to have produced insufficient vessel retraction, additional PEM therapy was conducted.

### Study variables and operative outcomes

Information pertaining to patient-specific characteristics and primary disease was collected for all 50 patients (Table 1). Post-operative outcomes including overall success and complication rates were obtained from clinical records held at our institution (Table 2).

### Ethical approval

All subjects enrolled in this research gave their informed consent, which alongside the described protocol, has been approved by the institutional committee on human research at the Morisue Clinic.

## RESULTS

22 male and 28 female patients, with an average age of 67.7 ± 13.0 years (range: 34-91 years) were included in the study. 21 patients had varicose veins on the right lower limb, 28 patients on the left, and 1 patient on both lower limbs (Table 1). The etiology of varicose veins in the cohort consisted of five primary diseases: valve impairment of SFJ (7 patients, Group I), post-operative stasis dermatitis (10 patients, Group II), post-operative residual veins (30 patients, Group III), veins with significant tortuosity (2 patients, Group IV; Figure 1A) and recurrence due to neovascularization (1 patient, Group V; Figure 1B) (Table 1). The initial PEM therapy success rate was 86.3% (Table 2). Of the seven patients in Group I, five demonstrated insufficient retraction of varicose veins and two of the five had local pigmentation in the lower limbs. In these patients however, additional PEM therapy produced a significant retraction the above-knee with no recanalization. Nine out of ten patients in Group II experienced reduced pain after PEM therapy. However, additional percutaneous

ablation of perforators was required in one patient who had a large incompetent perforating vein and continued to experience pain after PEM therapy. For patients in Group III, PEM therapy showed good occlusion rates in the below-knee GSV trunk and saphenous vein branch (85.7% and 87.5%, respectively). Although PEM therapy for one of two patients in Group IV did not show sufficient retraction of small saphenous veins in the lower limb, additional PEM therapy induced complete occlusion of varicose veins and improved symptoms such as pain and edema. In Group V, complete occlusion of recurrent varicose veins was achieved and was associated with improvement in symptoms such as pain and edema in the lower

**Table 1** Patient characteristics and surgical procedures.

	n = 50
Age, y, mean (±SD)	67.7 (±13.0)
Female gender, n (%)	28 (56.0)
<b>Affected side, n (%)</b>	
Right	21 (42.0)
Left	28 (56.0)
Both	1(2.0)
<b>Primary disease, n (%)</b>	
Valve impairment of saphenofemoral junction (Group I)	7 (14.0)
Postoperative stasis dermatitis (Group II)	10 (20.0)
GSV ablation	6 (60.0)
GSV stripping + GSV ablation	1 (10.0)
GSV stripping + SSV ablation	1 (10.0)
GSV ablation + SSV ablation	2 (20.0)
Postoperative residual veins (Group III)	30 (60.0)
Meandering vessels (Group IV)	2 (4.0)
Recurrence due to neovascularization (Group V)	1 (2.0)
<b>The amount of PEM use, mean (±SD)</b>	
Valve impairment of saphenofemoral junction (Group I)	13.7 (±1.4)
Postoperative stasis dermatitis (Group II)	5.6 (±2.6)
Postoperative residual veins (Group III)	4.3 (±2.2)
Meandering vessels (Group IV)	9.5 (±5.0)
Recurrence due to neovascularization (Group V)	15

Abbreviations: GSV, great saphenous vein; PEM, polidocanol endovenous microfoam; SD, standard deviation; SSV, small saphenous vein.

**Table 2** Clinical outcomes.

	n = 51
Initial PEM therapy success, n (%)	44 (86.3)
Additional PEM therapy, n (%)	6 (11.8)
Valve impairment of saphenofemoral junction (Group I)	5 (83.3)
Postoperative stasis dermatitis (Group II)	0 (0.0)
Postoperative residual veins (Group III)	0 (0.0)
Meandering vessels (Group IV)	1 (16.7)
Recurrence due to neovascularization (Group V)	0 (0.0)
Additional PAPs, n (%)	1(2.0)
Complications, n (%)	4 (7.8)
Thrombophlebitis	2 (50.0)
Infection	0 (0.0)
Postoperative pain	1 (25.0)
Stiff skin	0 (0.0)
Skin induration	0 (0.0)
Pigmentation	1 (25.0)

Abbreviations: PAPs, percutaneous ablation of perforators; PEM, polidocanol endovenous microfoam.



**Figure 1** Representative pictures and illustrations of varicose veins with marked tortuosity from the posterior surface of the thigh to below the knee (A) and varicose veins with neovascularization below the left saphenofemoral junction (B).

limb. Follow-up was completed in all cases with a mean follow-up time of 295.8 days. No 30-day mortality, pulmonary embolisms, and cerebrovascular or neurological events were noted. There were four minor post-operative complications: two cases of thrombophlebitis in Group I, one case of post-operative pain in Group IV, and one case of local pigmentation in Group IV. Additional PEM therapy for two patients with thrombophlebitis in Group I was not performed because post-operative ultrasonography showed sufficient retraction of targeting vessels in each patient. These patients continued with compression stockings and did not develop any symptoms or experience recurrence of varicose veins. Post-operative pain and local pigmentation in Group IV gradually resolved.

## DISCUSSION

There are currently more reliable minimally invasive treatments for varicose veins. In particular, ETA, such as endovenous laser ablation (EVLA) and radiofrequency ablation, is the preferred method for various veins. Numerous studies have demonstrated superiority of EVT in terms of surgical outcomes such as expedited recovery<sup>[6-8]</sup>. Notwithstanding these benefits of EVTA, tumescent local anesthesia (TLA) which is key to the success of ETA was the main cause of patient-reported discomfort<sup>[9,10]</sup>. Further researches into improved treatments without thermal ablation and TLA are expected to improve patient-reported outcomes such as quality of life. PEM therapy, a minimally invasive and non-surgical procedure, is highly regarded due to its lower incidence of post-operative complications.

Several centers have shown PEM therapy to be an effective treatment for varicose veins<sup>[11,12]</sup>. In this study, we investigated early outcomes following the use of PEM therapy to treat refractory varicose veins of various etiologies. In the 50 patients included in our study, the etiologies included; SFJ valve impairment, post-operative stasis dermatitis, post-operative residual veins, veins with significant tortuosity, and recurrence due to neovascularization. The overall initial success rate of PEM therapy was 86.3%, which was

satisfactory compared with a recent published study<sup>[11]</sup>. Patients with post-operative stasis dermatitis, post-operative residual veins, and venous tortuosity did not need additional treatment. As demonstrated in previous studies<sup>[13,14]</sup>, post-operative stasis dermatitis in particular may be a good indication for treatment because PEM therapy has the capacity to produce significant improvements for patients with ulcers or other related complaints in the lower limbs. Unfortunately, five patients in Group I did not experience sufficient retraction of varicose veins. Although the average diameter of GSV in Group I was  $6.2 \pm 1.3$ mm, which was within the range of indication for PEM therapy (less than 8mm), patients in Group I required more PEM than those in other groups, except Group V (Table 1). A previously published study addresses a similar issue, in which PEM injection from varicose tributaries may result in insufficient intimal damage around the SFJ<sup>[15]</sup>. In our patients in Group I, inflammatory changes in the intima of varicose veins and consequently sclerosis of the vascular wall may have made the initial PEM therapy difficult. Further consideration regarding the adequate surgical indication and effective use of PEM therapy for patients in Group I is recommended. Although a direct comparison cannot be made between operation success rates in this study and previous studies, this study demonstrated significant and clinically satisfactory patient benefit following PEM therapy in patients with refractory varicose veins. It is worth bearing in mind however that vascular conditions in each case may reduce the success rate of PEM therapy.

In this study, we did not experience any major complications related to PEM therapy however, there were four cases of minor post-operative complications: two cases of thrombophlebitis (3.9%) and one case of extremity pain (2.0%). Judging from previous studies in which thrombophlebitis and extremity pain accounted for 5 to 12% and 10 to 19%, respectively<sup>[11,16]</sup>, the complication rates noted in this study may be satisfactory. At the time of writing, all complications have resolved without sequelae. Additionally, there were no complications such as visual impairment, chest discomfort, and dizziness caused by the gas (air or carbon dioxide) used to make

the microfoam. Injection of microfoam over 30ml should be avoided to prevent unnecessary complications since one report demonstrated that deep venous thrombosis occurred at the rate of 2.5% when 30 to 60 ml of microfoam mixed with carbon dioxide was used<sup>[17]</sup>. Overall, the incidence of complications due to PEM therapy in this study was considered to be lower than that in other studies despite the varied disease background in our study participants.

## CONCLUSION

PEM therapy could help to shed light on the treatment of refractory varicose veins of various etiologies.

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### Contributorship

Dr. Atsushi Morisue had full access to all of the data in this study and takes responsibility for this integrity of the data and the accuracy of the data analysis. Study concept and design: Atsushi Morisue. Acquisition, analysis, or interpretation of data: Atsushi Morisue. Drafting of the manuscript: Atsushi Morisue.

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