Original Article

Outcomes of Ultrasound-guided Catheter-directed Foam Sclerotherapy with or without Perivenous Tumescent Enhancement in the Treatment of Great Saphenous Vein Reflux

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Background: Great saphenous reflux is widely managed by endovenous methods as first line treatment. Sclerotherapy is a recommendation when other endovenous treatments are not. Ultrasound-guided catheter-directed foam sclerotherapy appears to be attractive and suitable. Tumescent anesthesia is used in other endovenous thermal treatments to help with vein compression around the catheter for better contact and prevent heat damage. In developing countries like Thailand, the costs of the standardized instruments such as radiofrequency ablation or endovenous laser are costly. Not many patients can afford such treatments alternative of a minimally invasive treatment in truncal vein reflux. But it is inferior in terms of closure rate.

Objective: In general, foam sclerotherapy has an closure rate of only about 70% in 3 years. The compressive effect of tumescent anesthesia can be applied to help increase the effectiveness of sclerotherapy as it can compress the vein and empty the blood. Therefore, better contact of the sclerosant to the vein wall and the concentration of the sclerosant is not dissipated by the blood.

Perivenous tumescent injection together with ultrasound-guided catheter-directed foam sclerotherapy was proposed. Reviewed literature showed lower costs and acceptable satisfaction.

Materials and Methods: Randomization of 31 patients with 38 treated legs in total. 16 patients with 20 treated legs were enrolled in the tumescent group and 15 patients with 18 treated legs in the non-tumescent group. 1% aethoxysklerol was used as sclerosant. Tumescent solution was comprised of 1% xylocaine, ketorolac, 0.9% NSS, and dexamethasone. Patients were treated as ambulatory cases with light sedation in the operating room. Patients were followed-up at 2-week, 1-month, 3-month and 6-month intervals with duplex ultrasonography performed by vascular fellows. Primary outcome was closure rates between the two groups. Secondary outcomes were VCSS, incidence of DVT or symptomatic PE, any other adverse events and satisfaction score.

Results: Both groups were not statistically significant in terms of occlusion rate by the Kaplan-Meier curve (p = 0.891). Occlusion rates at 90 days were 93.75% in the tumescent group and 100% in the non-tumescent group, at 150 days were 81.2% in the tumescent group and 78.1% in the non-tumescent group. DVT or PE 0%. Adverse events were ecchymosis in two patients and cord like tenderness in one. Mean satisfaction score at last follow-up was 4 out of 5. Reduction in the VCSS at the end of follow-up period compared to pre-operatively was not statistically different between the two groups.

Conclusion: Perivenous tumescent enhanced ultrasound-guided foam sclerotherapy solution did not demonstrate improvement in occlusion rate. But it could be performed as an outpatient setting with no major adverse events.

Keywords: Chronic venous disease, Great saphenous vein, Reflux, Foam sclerotherapy, Ultrasound, Tumescent anesthesia

J Med Assoc Thai 2019;102(Suppl.2): S1-8
Website: http://www.jmatonline.com

Great saphenous reflux is widely managed by endovenous methods as first line treatment. The National Institute for Health and Care Excellence (NICE) recommended treatment for patients with truncal venous reflux in 2013. They stated that if endothermal ablation is unsuitable, offer ultrasound-guided foam sclerotherapy[1].

Sclerotherapy is also a recommendation by the European guidelines for sclerotherapy in chronic venous disorders in 2013 in the treatment of incompetent saphenous veins with the level of evidence grade 1A, and in the treatment of varicose veins in the proximity of the leg ulcer with the level of evidence grade 1B[2]. Foam sclerotherapy was also

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How to cite this article: Prayoonhong P, Horsirimanont S, Tirapanich W, Jirasiritum S, Leela-Udomlipi S, Pootracool P, Kittitirapong N, Pornwaragorn C. Outcomes of Ultrasound-guided Catheter-directed Foam Sclerotherapy with or without Perivenous Tumescent Enhancement in the Treatment of Great Saphenous Vein Reflux. J Med Assoc Thai 2019;102;Suppl.2: S1-8.

shown to have low rate of major complications[3].

It is known that, foam sclerotherapy has a closure rate of only about 70% in 3 years[4-7]. Hence, inferior closure rates compared to standard treatments such as surgery, radiofrequency ablation and endovenous laser treatment. Tumescent anesthesia is used in other endovenous thermal treatments to help with vein compression around the catheter for better contact and prevent heat damage[4].

The primary limitation of sclerotherapy is the vein diameter, as the chemical needs to be directly in contact with the vein wall could cause endothelial damage and subsequent fibrosis[8].

Tumescent anesthesia would help in compressing the vein and empty the blood, therefore, reduce the vein diameter and less dissipation of the sclerosant concentration, allowing higher concentration and better contact to the vein wall[9].

In developing countries like Thailand, the costs of the standardized instruments are expensive. Not many patients can afford such treatments. Nevertheless, some do not accept the idea of having a surgical wound from an open surgery. Thus, ultrasound-guided catheter-directed foam sclerotherapy appeared to be an attractive alternative, minimally invasive treatment of the great saphenous vein reflux (GSV) as it appeared to be cost-effective compared to surgery[10].

Perivenous tumescent injection together with ultrasound-guided catheter-directed foam sclerotherapy was proposed.

Materials and Methods

Study design

This study was designed as a controlled, single-center, double-blinded, prospective, randomized trial. Subjects were enrolled between May 2016 and December 2017. Approval was obtained from the medical ethics committee of Ramathibodi hospital. The primary outcome was the closure rate of the great saphenous vein after the procedure. The secondary outcomes were Venous Clinical Severity Score, satisfaction score, incidence of DVT or symptomatic PE and any other adverse events.

Patient selection

Male or female patients who were eligible for the study and aged between 18 to 85 years. All patients were diagnosed with chronic venous insufficiency from clinical findings together with duplex ultrasound findings.

The patients were excluded if the great saphenous veins were less than 3 mm or greater than 8 mm in diameter or severely tortuous. History of patent ductus arteriosus. Known allergy to sclerosant. Active infection at the needle puncture site. Pregnancy.

Interventions

Patients were randomized in 1: 1 ratio by block 4 randomization whether to receive perivenous tumescent injection or not. A total of 31 patients were enrolled. A total of 38 treated legs. They were randomized into two groups. One being treated with perivenous tumescent enhanced ultrasound-guided catheter-directed foam sclerotherapy and the other being treated with ultrasound-guided catheter-directed foam sclerotherapy alone. 16 patients with 20 treated legs were enrolled in the tumescent group and 15 patients with 18 treated legs in the non tumescent group.

Before the procedure the Venous Clinical Severity Score and diameter of the great saphenous vein at thigh level were recorded for each patient. And the results of the duplex ultrasonography done by radiologists were reviewed.

The procedure was performed in the operating room by vascular fellows. The patients were put under light sedation. Ultrasonography was performed to scout the overall characteristics of the great saphenous vein, saphenofemoral junction (SFJ) and the common femoral vein.

Puncture was done at the ankle level with an 18G cannula. 5 Fr x 5.5 cm (Cordis) was then inserted. Hydrophillic guide wire 0.035" 260 cm (Terumo) was introduced and advanced to 2 cm from the SFJ (Figure 1).

Then Glide catheter 5 Fr x 100 cm (Terumo) was advanced to the same point and the guide wire removed (Figure 2).

If the perivenous tumescent solution was to be injected, a combination of 0.9% normal saline 500 ml, ketorolac 1 ampule, 1% xylocaine 30 ml, 7.5% sodium bicarbonate 20 ml was made. The tumescent solution was injected into the saphenous compartment via an injector (Nouvag dispenser DP 30) under ultrasound guidance (Figure 3).

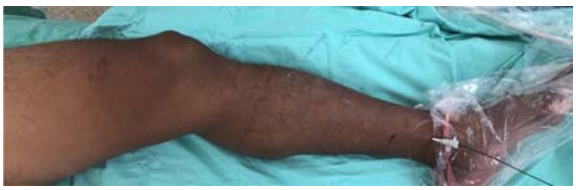

Figure 1. Puncture at the ankle level, with the 5 Fr x 5 cm sheath and hydrophillic guidewire in place.

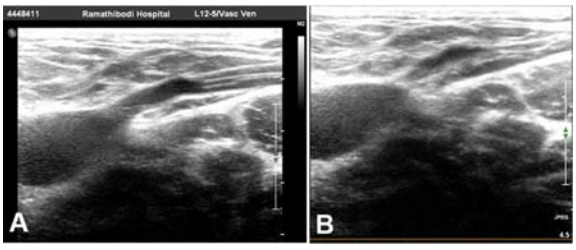

Figure 2. US image of the catheter 2 cm from the SFJ before tumescent injection (A), and after tumescent injection (B).

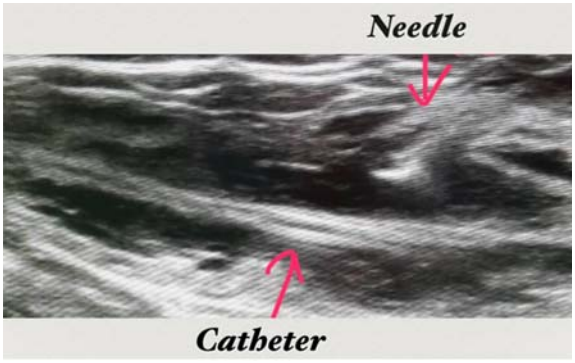

Figure 3. US image of tumescent injection with the injecting needle in the saphenous compartment and the catheter in the GSV.

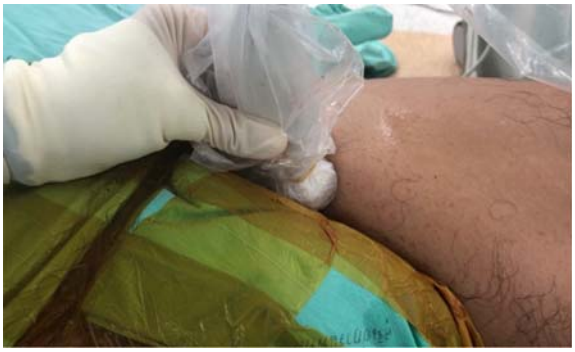

Figure 4. Ultrasound-guided compression at the SFJ.

Figure 5. Injection of the sclerosant.

Polidocanol (1% aethoxysklerol) was used as the sclerosant as it was available at the hospital[11]. Foam was produced by the modified Tessari method of one part sclerosant and four parts air[12]. Two 10 ml-syringes were connected by a three-way stopcock and foam was produced by rapid movements of the syringes twenty times[13]. After the foam was made it was injected via the catheter with the rate of withdrawing the catheter 1 cm/sec, in conjunction with ultrasound-guided compression at the SFJ (Figure 4 and 5).

At the end of the procedure, great saphenous vein was assessed for occlusion and the common femoral vein was assessed for any evidence of thrombosis by the ultrasound. Patients were advised to wear compression therapy up to 2 weeks after the procedure[14]. Then they were appointed for follow-ups at 2 weeks, 1 month, 3 months and 6 months after the procedure. Ultrasonography was performed by vascular fellows. The assessments were closure rate of the treated the GSV, VCSS (Table 1), evidence of DVT or symptomatic PE, any adverse events and satisfaction score on a scale of 1 to 5, with 1 being not satisfied and 5 being very satisfied[15].

Statistical analysis

Data were analyzed using STATA version 14th program. All categorical variables were evaluated using the Chi-square test. For continuous variables we compared using two-tailed student's t-test. The Kaplan-Meier curve was used to evaluate and compare the closure rate in tumescent group and non-tumescent group.

Results

Technical success of the procedure was 100% in this study and the characteristics of the data collected were evenly distributed between the two groups.

The amount of sclerosant used in each group was not statistically different. Pre-operative VCSS in the tumescent group was statistically higher than that in the non -tumescent group.

The satisfaction scores between the two groups were high with the average of 4 out of 5 and they were statistically indifferent (Table 2).

Both groups were not statistically significantly different in terms of closure rates by the Kaplan-Meier curve ($p = 0.891$). The closure rates at 90 days were 93.75% in the tumescent group and 100% in the non-tumescent group. At 150 days, the closure rates were 81.2% in the tumescent group and 78.1% in the non-tumescent group (Figure 7, Table 2).

On the ultrasound assessment immediately after the sclerosant injection, we achieved total occlusion along the length of the GSV treated and that the sclerosant was distributed well (Figure 6). We experienced successful occlusion of all the GSVs treated at 2 weeks and 1 month in each group.

DVT or symptomatic PE was 0%. Adverse events were ecchymosis in two patients and cord like tenderness which represented superficial thrombophlebitis in one. Ecchymosis occurred in the tumescent group and superficial thrombophlebitis in the non-tumescent group. Mean satisfaction score at last follow-up was 4 out of 5. Reduction in the VCSS at the end of follow-up period compared to pre-operatively was not statistically different between the two groups.

The closure rates seemed to be statistically,

Table 1. Venous clinical severity score

	None: 0	Mild: 1	Moderate: 2	Severe: 3
Pain or other discomfort (i.e., aching, heaviness, fatigue, soreness, burning); presumes venous origin	None	Occasional pain or other discomfort (i.e., not restricting regular daily activity)	Daily pain or other discomfort (i.e., interfering with but not preventing regular daily activities)	Daily pain or discomfort (i.e., limits most regular daily activities)
Varicose veins "Varicose" veins must be ≥3 mm in diameter to quality in the standing position	None	Few: scattered (i.e., isolated branch varicosities or cluster); also includes corona phlebectatica (ankle flare)	Confined to calf or thigh	Involves calf and thigh
Venous edema Presumes venous origin	None	Limited to foot and ankle area	Extends above ankle but below knee	Extends to knee and above
Skin pigmentation Presumes venous origin; does not include focal pigmentation over varicose veins or pigmentation due to other chronic disease (ie, vasculitis purpura)	None or focal	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Inflammation More than just recent pigmentation (i.e., erythema, cellulitis, venous eczema, dermatitis)	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
Induration Presumes venous origin of secondary skin and subcutaneous changes (i.e., chronic edema with fibrosis, hypodermitis); includes white atrophy and lipodermatosclerosis	None	Limited to perimalleolar area	Diffuse over lower third of calf	Wider distribution above lower third of calf
No. of active ulcers	0	1	2	≥3
Active ulcer duration (longest active)	NA	<3 mo	>3 mo but <1 y	Not healed for >1 y
Active ulcer size (largest active)	NA	Diameter <2 cm	Diameter 2 to 6 cm	Diameter >6 cm
Use of compression therapy	None: 0 Not used	Occasional: 1 Intermittent use of stocking	Frequent: 2 Wears stockings most days	Always: 3 Full compliance: stockings

significantly higher in women and smaller diameter veins. There were no relationships between closure rate and vein diameter, CEAP classification, amount of sclerosant used or ultrasound findings. The preoperative VCSS of the tumescent group was statistically higher than the non-tumescent group and a decrease in postoperative VCSS was demonstrated in this group (Figure 8).

Upon follow-up with the non-occluded GSVs, the CEAP classification was improved in 1 patient who received tumescent injection. C3 became asymptomatic C2. In the other 2 non-occluded GSV, pain was improved. The patients whose GSVs were not occluded in the non tumescent group, the CEAP classification remained the same upon follow-up. One patient had an improvement in pain.

Discussion

There was a recent study by N. Devereaux et al[16] attempting to reduce the size of the vein diameter for the treatment of sclerotherapy. In the present study, they could not use adrenaline in the combined tumescent solution. In our study, we were allowed to use the adrenaline in our solution and expected the effect of the adrenaline to take into account in reducing the vein diameter. Therefore, a better contact of the sclerosant to the vein wall.

Nonetheless, tumescent injection did not demonstrate any improvement in the closure rate in the treatment of the great saphenous vein reflux with ultrasound-guided catheter-directed foam sclerotherapy. The closure rates between the two groups were not statistically significant. However, the closure rates in the tumescent group was lower than the non-tumescent group. This was also shown in previous study by N. Devereaux et al[16]. From our study, tumescent injection showed a decrease the percentage of closure rate compared to the non-tumescent group. And that the effect of the foam sclerosant might not depend on the external compression of the vein diameter at all.

Vein diameter trended to be higher in the non-occluded great saphenous veins, which obviously was the main disadvantage in its treatment with sclerotherapy. That the sclerosant would not come in good contact with the vein

Table 2. Data characteristic

Variable	Non tumescent (n = 18)	Tumescent (n = 20)	*p*-value
Age (yr), mean (±SD)	58.28 (±10.80)	59.85 (±14.01)	0.703
Gender			0.564
Male	7 (38.89)	6 (30)	
Female	11 (61.11)	14 (70)	
CEAP			0.565
C2	5 (27.78)	3 (15)	
C3	8 (44.44)	9 (45)	
C4	4 (22.22)	6 (30)	
C5	1 (5.56)	0	
C6	0	2 (10)	
Sclerosant (ml), mean (±SD)	8.11 (±1.32)	8.75 (±1.77)	0.220
US findings			0.255
GSV reflux	12 (66.67)	7 (35)	
GSV reflux + SFJ incompetence	4 (22.22)	9 (45)	
GSV reflux + perforator incompetence	1 (5.56)	3 (15)	
GSV reflux + deep venous reflux	1 (5.56)	1 (5)	
Diameter_1 (mm), mean (±SD)	4.78 (±1.87)	4.98 (±1.09)	0.695
Diameter_2 (mm), median (IQR)	3.45 (2.45 to 4)	3.65 (2.85 to 4)	0.631
GSV occlusion within 2 weeks			-
No	-	-	
Yes	18 (100)	20 (100)	
GSV occlusion within 1 month			0.488
No	-	2 (10)	
Yes	18 (100)	18 (90)	
GSV occlusion within 3 month			0.999
No	3 (23.08)	1 (6.67)	
Yes	10 (76.92)	14 (93.33)	
GSV occlusion within 6 month			-
No	-	-	
Yes	6 (100)	6 (100)	
DVT			-
No	-	-	
Yes	18 (100)	20 (100)	
VCSS pre op, mean (±SD)	4.06 (±1.30)	5.45 (±2.16)	0.020
VCSS 2 weeks, mean (±SD)	3.78 (±1.31)	4.45 (±2.06)	0.244
VCSS 1 month, mean (±SD)	3.31 (±1.30)	3.5 (±1.76)	0.725
VCSS 3 month, mean (±SD)	3.08 (±1.66)	2.94 (±2.41)	0.863
VCSS 6 month	-	-	-
Satisfaction score at the end of follow-up, median (IQR)	4 (4 to 5)	4 (3.5 to 4.5)	0.264

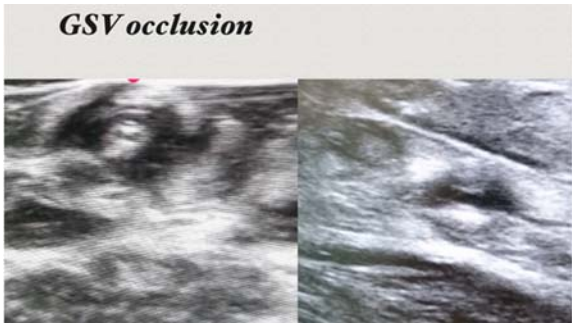

Figure 6. Immediate GSV occlusion after sclerosant injection.

Table 3. Closure rates timeline

Time (day)	Non-tumescent n (%)	Tumescent n (%)
15	18 (100)	20 (100)
30	14 (100)	20 (100)
45	13 (100)	19 (100)
60	12 (100)	19 (100)
75	12 (100)	16 (100)
90	12 (100)	14 (93.75)
105	4 (81.82)	5 (78.13)
120	3 (81.82)	5 (78.13)
135	3 (81.82)	2 (78.13)
150	1 (81.82)	2 (78.13)

wall if the diameter of the vein was larger and therefore the result was less effective. In our attempt to elude this with perivenous tumescent injection to aid with reduction in the vein diameter, the results were uneventful.

The results might have been affected by bias in the operators that we had three second-year vascular fellows operating on the procedure and the skills in each operator might be different in performing the perivenous tumescent injection. The GSV might not have been properly compressed

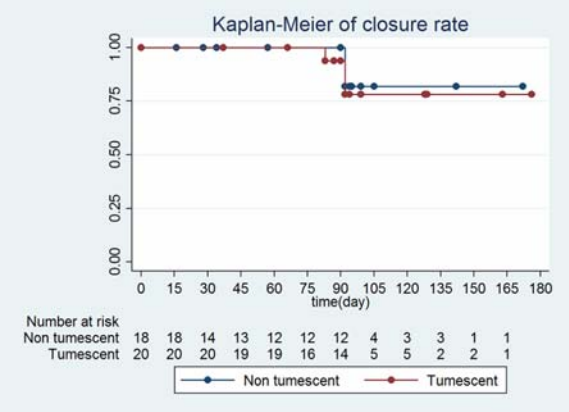

Figure 7. Kaplan-Meier curve for closure rates.

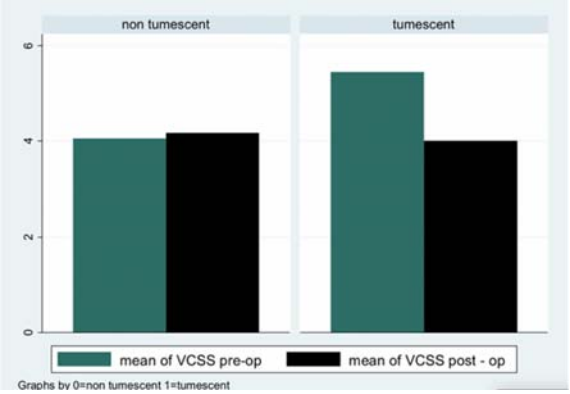

Figure 8. Preoprative VCSS vs. postoperative VCSS.

Table 4. Comparison of data characteristics between the occluded and non occluded GSV

Variable	Non tumescent (n = 32)	Tumescent (n = 6)	*p*-value
Age (year), mean (±SD)	59.41 (±12.16)	57.5 (±15.04)	0.735
Gender			0.012
Male	8 (25)	5 (83.33)	
Female	24 (75)	1 (16.67)	
CEAP			0.419
C2	8 (25)	0	
C3	14 (43.75)	3 (50)	
C4	8 (25)	2 (33.33)	
C5	1 (3.13)	0	
C6	1 (3.13)	1 (16.67)	
Sclerosant (ml), mean (±SD)	8.37 (±1.52)	8.83 (±2.04)	0.524
Ultrasound findings			0.537
GSV reflux	16 (50)	3 (50)	
GSV reflux + SFJ incompetence	11 (34.38)	2 (33.33)	
GSV reflux + perforator incompetence	4 (12.50)	0	
GSV reflux + deep venous reflux	1 (3.13)	1 (16.67)	
Diameter_1 (mm), mean (±SD)	4.78 (±1.47)	5.43 (±1.55)	0.329
Diameter_2 (mm), median (IQR)	3.3 (2.5 to 4)	4 (4 to 5)	0.019
Treatment			0.999
Non-tumescent	15 (46.88)	3 (50)	
Tumescent	17 (53.13)	3 (50)	
DVT			-
No	32 (100)	6 (100)	
Yes	0	0	
VCSS pre op, mean (±SD)	4.56 (±1.61)	6 (±3.03)	0.304
VCSS 2 wks, mean(±SD)	4.06 (±1.76)	4.5 (±1.87)	0.582
VCSS 1 Mo, mean(±SD)	3.47 (±1.59)	3.17 (±1.47)	0.672
VCSS 3 Mo, mean(±SD)	2.77 (±2.07)	4.5 (±1.73)	0.124
VCSS 6 Mo	-	-	-
Satisfaction score at the end of follow-up, median (IQR)	4 (4 to 5)	4.5 (4 to 5)	0.168

each time the procedure was performed. As there was not a standardized volume of the tumescent solution to be used in each procedure and also the patient's habitus would affect the volume of the tumescent solution to be used each time. The volume used was varied. A larger volume of foam sclerosant used in the procedure might be considered as we limited the amount not to exceed 10 ml in each session. We used the catheter technique to deliver the sclerosant, some amount of it was in the catheter and was not delivered to the lumen of the GSV, and not all of the actual amount that was recorded went into the vein. Hence, produced less concentration than expected it would have.

There are emerging studies on maintaining the compressive effect weeks post procedurally in order to prevent reflux, with the use hyarulonan gel; they achieved total occlusion at 2 weeks and were able to maintain the reduction in the vein diameter[17]. This could probably be another factor that if the vein was still compressed for longer time, the closure rate might be improved as supposedly the vein would be emptied of blood and that they would eventually become fibrotic before the compressive effect wore off. And with tumescent solution could not achieve this long period of compressive effect.

Our follow-up time was too short. It would be of more value on the closure rates in the long-term basis, for example a 12-month period. This was the main limitation of our study. And that our short-term results did not elucidate any differences in outcomes between the two studied groups.

The decrease in VCSS in the tumescent group was explained by the higher pre-operative VCSS than in the non-tumescent group.

Ecchymosis was the adverse effect of tumescent injection. Cord-like tenderness was a result of thrombophlebitis from sclerosant injection but we found this side effect only in the non-tumescent group. Perhaps, that tumescent injection could have a protective effect of irritation that would contribute to superficial thrombophlebitis because we did not come across this adverse event in the tumescent group, yet again if not administered properly, ecchymosis could occur in its use.

At Ramathibodi Hospital, the total cost of sclerotherapy was 12,200 baht compared to the total cost of RFA of 34,800 baht, which was 22,600 baht more expensive than sclerotherapy. Although, the closure rate of sclerotherapy is inferior to standard endovenous treatments such as RFA/EVLA, the cost was much less.

Conclusion

Perivenous tumescent enhanced ultrasound-guided foam sclerotherapy solution did not demonstrate improvement in closure rate compared to conventional catheter-directed foam sclerotherapy. But it could be performed as an outpatient setting with no major adverse events and with satisfaction.

What is already known on this topic?

The foam sclerotherapy is able to be an alternative therapeutic option for chronic venous disease caused by reflux of great saphenous vein.

The cost of foam sclerotherapy is much cheaper than the other standard endovenous thermal ablation technique.

However the effectiveness in occlusion of great saphenous vein is lower when using foam sclerotherapy.

What this study adds?

This study shown that the perivenous tumescent injection did not improve the outcome of foam sclerotherapy in treatment of great saphenous vein reflux but may add value in terms of satisfaction of the patient due to decrease postprocedural pain from superficial thrombophlebitis

Acknowledgements

Ms. Nipapan Choonu for assistance in the present study.

Potential conflicts of interest

The authors declare no conflict of interest.

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