Comparison of Efficacy and Safety between Foam Sclerotherapy and Conventional Sclerotherapy: A Controlled Clinical Trial

Teerachai Ukritmanoroat MD*

** Department of Surgery, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *Conventional sclerotherapy of varicose vein is performed by injection of a sclerosing substance into the vein. The modern use of foam in sclerotherapy in which sclerosants can be transformed into fine-bubbled foam by special techniques is developed. Many studies report about the better efficacy of foam therapy than conventional liquid therapy.*
Objective: *To assess the efficacy of sclerosant Polidocanol in foam form compared to liquid form and to determine safety profile by monitoring the complications (Pain, inflammation and pigmentation).*
Material and Method: *Randomized controlled trial study, fifty patients with symptomatic varicose veins underwent duplex ultrasonography for measurement of the diameter of the varices. All patients underwent one session of sclerotherapy with both sclerosants (foam and liquid Polidocanol). Efficacy was assessed at 15, 30 and 90 days after the sclerotherapy by duplex ultrasound and the safety was evaluated at 15, 30, 90 days.*
Results: *The efficacy of sclerosis was reported in total occlusion of 46 sites (92.0%) in foam therapy and of 38 sites (76.0%) in Polidocanol liquid therapy after 90 days. The differences of occlusion for the two groups were statistically significant, foam therapy showed greater results than that of Polidocanol liquid therapy at 15 days, 30days and 90 days after therapy Pain and hyper pigmentation were significantly higher in foam group than that in liquid group at 15 days and 30 days.*
Conclusion: *Foam sclerotherapy has greater efficacy for treating varicose veins comparing to conventional liquid sclerotherapy. However Pain, inflammation, and hyperpigmentation appeared more often with foam Polidocanol therapy*

Keywords: *Foam sclerotherapy, Conventional sclerotherapy, Sclerosing agents, Polidocanol, Telangiectasia*

J Med Assoc Thai 2011; 94 (Suppl. 2): S35-S40
Full text. e-Journal: *http://www.mat.or.th/journal*

Sclerotherapy is the treatment with targeted elimination of varicose veins by injection of a sclerosing substance into the vein lumen. Sclerosing agents cause a chemical irritation of the venous intima that produces an inflammation of the endothelial lining of the vessel[1]. Subsequently, a secondary, wall-attached local thrombus is generated and, in the long term, the veins will be transformed into a fibrous cord, *i.e.*, sclerosis[2].

The modern use of foam in sclerotherapy directly owes to the work of Orbach. In 1944[3], he proposed introducing air before injection of the sclerosant, thus emptying the vessel of its blood content, a technique called "air-block". The techniques by which these foams are applied also vary widely, hampering the comparison of outcomes obtained by different groups.

Many studies report that the efficacy of foam therapy is better than conventional liquid therapy. Hamel-Desnos C et al[4] studied the efficacy of sclerosing foam (DSS) compared with sclerosing liquid in therapy of the GSV. They found that foam therapy was superior liquid therapy (with 84% elimination of reflux in the GSV treated with DSS foam versus 40% with liquid sclerosant).

The objective of this study is to assess the efficacy of the sclerosant Polidocanol in foam form comparing to liquid form at pre-established concentrations, and to determine the safety profile by measuring the frequency and degree of complications (pain, signs of inflammation, and pigmentation) in Thai patients.

Material and Method

The ethic committee of Rajavithi Hospital approved this randomized controlled trial study. Men and women with symptomatic varicose veins at the

Correspondence to:
Ukritmanoroat T, Department of Surgery, Rajavithi Hospital, College of Medicine, Rangsit University, 2 Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: 0-2354-8080 ext. 3149, Fax: 0-2354-8080
E-mail: teerachai05@hotmail.com

outpatient clinic, Department of Surgery, Rajvithi Hospital were selected in to the studies by:

Inclusion criteria

- Patients with primary reticular varices (more than 2 mm of diameter) or postoperative varices that did not involve the saphenofemoral junction.

Exclusion criteria

- Patients with truncal varices with junctional (terminal valve) and extra-junctional incompetence.
- Postoperative varices that involved the saphenofemoral junction.
- Post-thrombotic varices with occluded deep veins.
- Chronic ischemia of the lower limbs.
- Severe arterial hypertension (blood pressure greater than 180/95 mmHg).
- Patients being treated with anticoagulants and anti-inflammatories and/or diuretics to avoid affecting the appearance of possible secondary effects.

Fifty patients with symptomatic varicose veins were included in the study after informed consent was obtained, underwent duplex ultrasonography for measurement of the mean diameter of the varices. The length of the vein to be treated was determined using a simple tape measure and skin pigmentation was recorded.

All patients underwent one session of sclerotherapy in which both sclerosants (foam and liquid Polidocanol) were given. Patients received the sclerotherapy in both regions by the same doctor, whether in different limbs or the same limb at different regions. The assignment of the first region to be treated to liquid or foam was performed according to a list of random numbers from 0 to 50.

The intervention in the study group consisted of injecting 2 mL of foam into only one varicose vein. Foam was obtained from 0.5 mL of liquid Polidocanol mixed with air at a ratio of 1: 4, using the Tessari method which uses a three-way stopcock to mix the sclerosant. Two mL of foam therefore contained 0.5 mL of Polidocanol. After the sclerosant was injected, the sclerosed vein was compressed for 48 h with stockings at a pressure of 25-35 mmHg. After the sclerosant injection, any pain, dizziness, blurred vision, or other complication that could be related to the injection were recorded. The intervention in the control group consisted of a 0.5 mL liquid Polidocanol injection in only one varicose vein in the corresponding region. An antegrade injection technique was used with the same kind of material (a 2 mL syringe and a 25 g, 5/8 needle) and the same postoperative care as the study group.

Efficacy was assessed according to whether sclerosis of the vein was complete as shown by duplex ultrasound performed by an observer unaware of the treatment group assigned to each area of the limb. The length of the sclerosed vein, measured in cm with a tape, was also assessed. Appearance of the following side effects was recorded: pain in the treated region graded on an ordinal scale (absent, mild, moderate, or severe), requirement for analgesic treatment and type of analgesic given, inflammation in the treated region and degree of severity of inflammation (mild, moderate), appearance of skin pigmentation in the sclerosis region, formation of bulla, cutaneous necrosis and other effects. Efficacy was assessed at 15, 30 and 90 days after the sclerotherapy and safety was evaluated at 15, 30 and 90 days. Results were assessed by research team other than the doctor who had performed the treatment.

Statistical analysis

The Chi-square test or Fishers' exact test was used to compare the proportions between the two interventions groups unpaired t-test was need to compare between the two means. In all cases a p-value < 0.05 was considered significant.

Results

One hundreds sclerotherapy were perfomed, 84 reticular varices and 16 postoperative varices were treated by foam sclerotherapy and conventional liquid sclerotherapy, as shown in Table 1.

Efficacy of Sclerosis

The efficacy of sclerosis is as following: 92.0% of total occlusion was found in foam therapy and 76.0%

Table 1. Baseline characteristics

Characteristics		n = 50 case
Gender		
	Male n (%)	5 (10.0)
	Female n (%)	45 (90.0)
Age (years)	Mean $\pm$ SD	45.5 $\pm$ 11.3
	min-max	19-66
Number of sclerotherapy n = 100 sites		
	reticular varices n (%)	84 (84.0)
	postoperative varices	16 (16.0)

in Polidocanol liquid therapy after treatment for 90 days. The differences of occlusion in two groups were statistically significant, the foam therapy showed greater results than those from Polidocanol liquid therapy at 15, 30 and 90 days after therapy.

The length of the sclerosed vein after 15, 30 and 90 days treatment was also significantly greater in foam therapy group than in liquid therapy group ($p < 0.001$), as shown in Table 2.

Complication and Adverse Reaction of Treatment

No immediate complication occurred in both foam therapy and Polidocanol liquid therapy groups. At 15 and 30 days after therapy, significantly more pain at the area of injection was found in the foam group than in the liquid group ($p < 0.001$). At 90 days after therapy, no statistically significant pain in both groups of therapy was found ($p = 0.080$) as shown in Table 3.

Regarding the degree of pain, foam therapy group had analgesics uses more often than liquid therapy group at 15 days after therapy. Acetaminophens were used in 20% of foam therapy group and 6% of liquid therapy group and diclofenac were used in 12% of foam group and 4% of liquid therapy group, as shown in Table 4.

Local inflammation was found higher in foam group than that in liquid group at 15 days and 30 days but not statistically significant. The inflammation had disappeared in both groups at 90 days post therapy, as shown in Table 5.

Percentage of hyperpigmentation in foam therapy group was significantly higher than that in liquid therapy group at 15 days and 30 days after therapy. The percentage of hyper pigmentation was

Table 2. Assessment of efficacy according to degree of occlusion and Length of treated vein

Control	Efficacy	Liquid n = 50 sites	Foam n = 50 sites	p-value
Day 15	Total sclerosis n (%)	32 (64.0)	43 (86.0)	< 0.001*
	Partial sclerosis n (%)	18 (36.0)	7 (14.0)	< 0.001*
	Length (cm) mean $\pm$ SD	5.90 $\pm$ 1.69	7.22 $\pm$1.47	< 0.001*
Day 30	Total sclerosis n (%)	38 (76.0)	45 (90.0)	< 0.001*
	Partial sclerosis n (%)	12 (24.0)	5 (10.0)	< 0.001*
	Length (cm) mean $\pm$ SD	6.10 $\pm$ 1.45	7.66 $\pm$ 1.52	< 0.001*
Day 90	Total sclerosis n (%)	38 (76.0)	46 (92.0)	< 0.002*
	Partial sclerosis n (%)	12 (24.0)	4 (8.0)	< 0.002*
	Length (cm) mean $\pm$ SD	6.14 $\pm$ 1.39	7.70 $\pm$ 1.51	< 0.001*

* Significant at $p < 0.05$

Table 3. Presentation of Pain (n = 50)

Control	Parameter	Liquid n (%)	Foam n (%)	p-value
Day 15	Absent	35 (70.0)	16 (32.0)	< 0.001*
	Mild	10 (20.0)	13 (36.0)	
	Moderate	3 (6.0)	10 (20.0)	
	Severe	2 (4.0)	6 (12.0)	
Day 30	Absent	42 (84.0)	28 (56.0)	< 0.001*
	Mild	6 (12.0)	16 (32.0)	
	Moderate	2 (4.0)	4 (8.0)	
	Severe	0	2 (4.0)	
Day 90	Absent	49 (98.0)	46 (92.0)	0.080
	Mild	1 (2.0)	4 (8.0)	
	Moderate	0	0	
	Severe	0	0	

* Significant at $p < 0.05$

highest at 30 days after therapy in both groups and decreased at 90 days after therapy (Table 6).

Discussion

The study shows that the efficacy of selerotherapy by foam injection is higher than that of the conventional Polidocanol liquid injection. However, local complications after injection therapy such as pain at the area of injection, inflammation and skin hyper pigmentation were found more frequent in foam group than conventional therapy group. The results of experiment are similar to the other authors reported previously[5-9]. The characteristics of foam sclerosants can explain the greater efficacy and irritant effect. Foam sclerosants are compact solutions which replace blood volume rather than dissolving in blood. The better adherent effect of foam to walls of the veins allows greater contact with the endothelium, contributing to great efficacy at lower concentration and lower quantity of sclerosant.

Regarding the safety of the treatment, Henriet[10] analyzed the passage of air to the circulation system under several conditions of extracorporeal circulation or during echocardiograms using air to confirm the safety of the procedure. These results are consistent with several later clinical studies using foam produced by various techniques[11,12] proving that small doses of air injected intravenously do not produce major systemic changes and are well tolerated by patients. The presentation of major complications *i.e.* deep vein thrombosis or lung thromboembolism is unusual with this technique and is probably related to the dose used and the sclerosis region. Complications are found considerably more often with truncal saphenous

Table 4. Analgesic drugs used

Control	Parameter	Liquid n = 50	Foam n = 50
Day 15	acetaminophen n (%)	3 (6.0)	10 (20.0)
	diclofenac n (%)	2 (4.0)	6 (12.0)
Day 30	acetaminophen n (%)	2 (4.0)	4 (8.0)
	diclofenac n (%)	0	2 (4.0)
Day 90	acetaminophen n (%)	0	0
	diclofenac n (%)	0	0

Table 5. Presentation of Inflammation

Control	Parameter	Liquid n (%)	Foam n (%)	p-value
Day 15	Absent	45 (90.0)	38 (76.0)	0.082
	Inflammation	5 (10.0)	12 (24.0)	
Day 30	Absent	48 (96.0)	43 (86.0)	0.232
	Inflammation	2 (4.0)	7 (14.0)	
Day 90	Absent	50 (100.0)	50 (100.0)	-
	Inflammation	0	0	

Table 6. Presentation of Pigment

Control	Parameter	Liquid n (%)	Foam n (%)	p-value
Day 15	Absent	45 (90.0)	35 (70.0)	0.002*
	Mild hyper pigmentation	4 (8.0)	10 (20.0)	
	Moderate hyper pigmentation	1 (2.0)	5 (10.0)	
Day 30	Absent	42 (84.0)	30 (60.0)	0.002*
	Mild hyper pigmentation	6 (12.0)	12 (24.0)	
	Moderate hyper pigmentation	2 (4.0)	8 (16.0)	
Day 90	Absent	45 (90.0)	39 (78.0)	0.051
	Mild hyper pigmentation	4 (8.0)	8 (16.0)	
	Moderate hyper pigmentation	1 (2.0)	3 (6.0)	

* Significant at $p < 0.05$

sclerosis, incompetent perforator veins and when large doses of foam are used.

No immediate severe complication after therapy was found in this study. Pain, inflammation, and hyper pigmentation appeared more often with foam Polidocanol therapy, but the presence of inflammation in both groups are not statistically significant and both of them disappeared after 90 days of therapy. From the practical point of view, foam Polidocanol therapy seems to be a safe procedure by using cheap, readily available and easy-to-use products in daily practice. Foam sclerotherapy should be considered the treatment of first choice in symptomatic patients with varicose veins in Thai patients.

Conclusion

The study demonstrates that foam Polidocanol therapy has greater efficacy for venous sclerosis comparing to conventional liquid Polidocanol therapy in the treatment of reticular varices not involving the saphenofemoral junction and postoperative recurrent varices. These results, however, must be confirmed by larger experience in other institutions, and long term follow-up should be included.

Potential conflict of interest

None.

References

1. Bergan JJ. Varicose vein treatment by surgery and sclerotherapy. In: Rutherford RB, editor. Vascular surgery. 5th ed. Philadelphia: WB Saunders; 2000: 2007-15.
2. Weiss RA, Goldman MP. Advances in sclerotherapy. Dermatol Clin 1995; 13: 431-45.
3. Orbach EJ. Sclerotherapy of varicose veins: utilization of intravenous air block. Am J Surg 1944; 66: 362-6.
4. Hamel-Desnos C, Desnos P, Wollmann JC, Ouvry P, Mako S, Allaert FA. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. Dermatol Surg 2003; 29: 1170-5.
5. Cabrera J, Cabrera J Jr, Garcia-Olmedo A. Treatment of varicose long saphenous veins with sclerosant in microfoam form: longterm outcomes. Phleblogy 2000; 15: 19-23.
6. Cabrera J, Cabrera J Jr, Garcia-Olmedo MA. Sclerosants in microfoam. A new approach in angiology. Int Angiol 2001; 20: 322-9.
7. Kakkos SK, Bountouroglou DG, Azzam M, Kalodiki E, Daskalopoulos M, Geroulakos G. Effectiveness and safety of ultrasound-guided foam sclerotherapy for recurrent varicose veins: immediate results. J Endovasc Ther 2006; 13: 357-64.
8. Alos J, Carreno P, Lopez JA, Estadella B, Serra-Prat M, Marinel-Lo J. Efficacy and safety of sclerotherapy using polidocanol foam: a controlled clinical trial. Eur J Vasc Endovasc Surg 2006; 31: 101-7.
9. Henriet JP. Un an de pratique quotidienne de lasclerotherapie (veines reticulaires et telangiectasies) parmousse de polidocanol: faisabilite, resultats,complications. Phlebologie 1997; 50: 355-60.
10. Cavezzi A, Frullini A, Ricci S, Tessari L. Treatment of varicose veins by foam sclerotherapy: two clinical series. Phlebology 2002; 17: 13-18.
11. Mingo JG. Tratamiento de la insuficiencia venosa cronica con esclerosantes en espuma: metodo F.M.S (Foam Medical System). Anales de Cirugia Cardiaca y Vascular 2001; 7: 300-24.
12. Varcoe P. Complications of duplex guided sclerotherapy. Int Angiol 2001: 20 (Suppl 1): 25.

การศึกษาผลการใช้ foam sclerotherapy ในการรักษาภาวะหลอดเลือดดำขอดที่ขาเปรียบเทียบกับวิธีดั้งเดิม (injection sclerotherapy)

ธีระชัย อุกฤษฏ์มโนรถ

***ภูมิหลัง**: การรักษาภาวะหลอดเลือดดำขอดที่ขาโดยวิธี sclerotherapy ใช้การฉีดสาร sclerosing agent เข้าไปในหลอดเลือดดำ ทำให้เกิด chemical irritation ต่อผนังชั้น intima ของหลอดเลือดและทำให้หลอดเลือดตีบตัน (sclerosis) มักได้ผลดีในหลอดเลือดขอดขนาดกลาง และขนาดเล็กมีผู้ศึกษาใช้วิธี foam sclerotherapy โดยผสมฟองอากาศเข้าไปในน้ำยา sclerosing agent ทำให้เกิด microfoam นำมาใช้ฉีดรักษาหลอดเลือดดำขอดที่ขา ซึ่งได้ผลดีกว่าการรักษาแบบดั้งเดิม*

***วัตถุประสงค์**: เพื่อศึกษาเปรียบเทียบประสิทธิภาพ และผลข้างเคียงของการใช้ foam sclerotherapy กับวิธีการใช้ liquid sclerotherapy*

***วัสดุและวิธีการ**: เป็นการศึกษาแบบ prospective randomized controlled trial ในผู้ป่วยที่มีหลอดเลือดดำขอดที่ขาขนาดมากกว่า 2 มม. มีอาการและไม่มีภาวะ sapheno femoral junction reflux ทั้งชายและหญิงที่มารักษาที่กลุ่มงานศัลยศาสตร์ โรงพยาบาลราชวิถี จำนวน 50 คน โดยทุกรายได้ รับการสุ่มเพื่อรักษาโดยวิธีการใช้ foam sclerotherapy และ liquid sclerotherapy ควบคู่กันในขาเดียวกันหรือคนละข้าง และตรวจเปรียบเทียบผลการรักษาก่อนและหลังโดย duplex ultrasonography รวมทั้งศึกษาผลแทรกซ้อนด้านความปวด การอักเสบ และสีผิวที่เข้มขึ้น โดยเก็บข้อมูลหลังฉีด 15 วัน 30 วัน และ 90 วัน*

***ผลการศึกษา**: ประสิทธิภาพการรักษา และทำให้หลอดเลือดตีบตัน (sclerosis) พบ 92% ในกลุ่ม foam sclerotherapy เทียบกับ 76%ในกลุ่ม liquid sclerotherapy หลังฉีด 90 วันโดยแตกต่างกันอย่างมีนัยสำคัญทางสถิติทั้งในช่วง 15 วัน 30 วัน และ 90 วัน (foam sclerotherapy vs. liquid sclerotherapy: 86% vs. 64% at 15 days $p < 0.001$, 90% vs. 76% at 30 days $p < 0.001$, 92% vs. 76% at 90 days $p < 0.002$) อาการข้างเคียงพบว่าอาการปวดและสีผิวเข้มขึ้นพบในกลุ่ม foam sclerotherapy มากกว่าอย่างมีนัยสำคัญที่ระยะ15 วันและ 30 วัน แต่ระยะ 90 วันไม่แตกต่างกันทางสถิติ*

***สรุป**: การรักษาภาวะหลอดเลือดดำขอดที่ขาโดยวิธีการใช้ foam sclerotherapy มีประสิทธิภาพสูงกว่าวิธี liquid sclerotherapy แต่มีผลข้างเคียงในด้านอาการปวดและสีผิวเข้มขึ้นมากกว่ากลุ่ม liquid sclerotherapy*