Management of low flow venous malformations using sclerotherapy: A randomized controlled trial

Original Article

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ABSTRACT

Background: Vascular malformations are structural irregularities of the blood vessels, which occur during vasculogenesis, angiogenesis, and lymphangiogenesis. Venous malformations (VMs) are common vascular malformations that may be located in any region of the body, with a preference for head and neck. Low-flow vascular malformations (LFVM) include venous, capillary, and lymphatic forms and are present at birth.

Aim: The work aimed to compare the success rate of different sclerosing agents (ethanol, cyanoacrylate, and polidocanol foam) used in the treatment of LFVM.

Patients and Methods: This computer based randomized prospective comparative study was conducted on 60 patients suffering from LFVM, admitted to the vascular surgery department in Mansura University Hospitals (MUH) from September 2019 to September 2021.

Results: A total of 60 patients were treated by sclerotherapy using ethanol (n=20 patients), polidocanol (n=20 patients), and cyanoacrylate (n=20 patients). A total of 182 sclerotherapy sessions were performed (range, 1-4 sessions for each lesion) with mean of two sessions for every lesion. Follow-up of lesions was done after injection for incidence of cure, complications, and need for surgery. There was a statistically significant difference between the three studied groups as regard follows-up of lesions after injection, where ethanol group cases had more complete cure (55%) followed by cyanoacrylate group (50%) and there was a statistically significant difference considering complications after sclerotherapy where the majority of Polidocanol group cases had no complication (70%). In cyanoacrylate group, 40% of cases need surgery to excise a remnant solid mass.

Conclusion: Sclerotherapy is effective for the treatment of LFVM. Polidocanol is a safer sclerosing agent compared with ethanol and Cyanoacrylate. Ethanol was associated with a better cure rate than polidocanol and Cyanoacrylate. Cyanoacrylate was associated with a sufficient cure rate but complicated by hard mass so better to be used before surgical excision.

Key Words: Cyanoacrylate, low-flow vascular malformations (LFVM), polidocanol, sclerotherapy.

Received: 29 March 2024, **Accepted:** 23 April 2024, **Published:** 4 October 2024

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ISSN: 1110-1121, October 2024, Vol. 43, No. 4: 1226-1232, © The Egyptian Journal of Surgery

INTRODUCTION

Vascular anomalies are structural irregularities of the blood vessels, which occur during vasculogenesis, angiogenesis, and lymphangiogenesis. CVMs are always present at birth, but the clinical signs may be subtle in neonates, infants, and young children[1]. Historically, the classification of vascular anomalies has been inconsistent leading to inaccurate diagnosis and inappropriate treatment. In 1982, Mulliken and Glowacki introduced a biological classification for head and neck vascular anomalies according to clinical presentation, behavior, and histology. There were two main categories, hemangiomas and vascular malformations, which were revised later to vascular tumors and vascular malformations. Vascular malformations are further split into high- and low-flow types[2].

Low-flow vascular malformations (LFVM) include venous, capillary, and lymphatic forms and are present at birth, never involutes, remain throughout life, and tend to grow. Current treatments include laser, surgery, and sclerosing agents[3].

Irregular growth of vascular anomalies into the surrounding soft tissue makes complete surgical excision difficult and may lead to incomplete excision/recurrence, local nerve damage, and severe blood loss during surgery. This has prompted interest in other treatment options, especially sclerotherapy[4].

Sclerotherapy is the preferred treatment for venous malformation (VM) in the majority of patients, performed under fluoroscopy under general anesthesia. Different sclerosants have been used for VM including polidocanol,

DOI: 10.21608/EJSUR.2024.280281.1039

ethanol, sodium tetradecyl sulfate, and cyanoacrylate[5]. Ethanol has been associated with the lowest incidence of lesion re-expansion and therefore is suggested as the most effective and first choice for sclerosing agent. However, ethanol has also been cited as being associated with more painful injections and having a higher complication rate[6].

Cyanoacrylate intralesional injections have been shown to significantly reduce the size and blood loss during excision of VMs and unresolved hemangiomas. Their application is low-cost, results in successful devascularization with few side effects, and can be applied right before surgery. After sclerotherapy, small vascular lesions totally eliminated and the lesions' technical removal became simpler[4]. In 1936, polidocanol was first made and sold as a topical and local anesthetic. Since the 1960s, it has been utilized as a sclerosing agent because of its propensity to sclerose blood vessels with little danger of causing harm to the surrounding tissue. Anesthesia is not required because polidocanol has anesthetic properties that prevent pain during intravenous or perivascular injections. Polidocanol foam is easier to use for sclerotherapy if it is prepared beforehand. This approach was first reported by Cabrera and Yamaki[7].

The work aimed to compare the success rate of different sclerosing agents (ethanol, cyanoacrylate, and polidocanol foam) used to treat LFVM.

PATIENTS AND METHODS:

This computer-based randomized prospective comparative study was conducted on 60 patients admitted to the Vascular Surgery Department in Mansura University Hospitals (MUH) from September 2019 to September 2021 suffering from LFVM.

Inclusion criteria: All patients with LFVM and Diagnosis were confirmed by detailed duplex examination and MRI examination.

Exclusion criteria: Patient refusal to grant consent or to be randomized and known hypersensitivity to used agents.

Methods

The included patients were subjected to: detailed history taking, Careful clinical examination, Investigations, and intervention.

Procedure

The 60 patients who had a definitive diagnosis of LFVM were randomly assigned to treatment by either ethanol, polidocanol foam, or cyanoacrylate. Ethanol sclerotherapy was performed under general or regional anesthesia with fluoroscopic guidance. Percutaneous direct puncture of VM was done using 23 G butterfly needle, and confirmation of placement by blood coming back. Non-ionic contrast was injected under fluoroscopy (Figs 1, 2). The volume of ethanol required was estimated from the amount of contrast injected into the lesion before its 'spillage' into adjacent normal veins and not exceeds 0.5 ml/kg per treatment session with maximum amount less than or equal to 50 ml per session. Ethanol was injected into the VM under fluoroscopy, while observing the washout of the previously injected contrast, this process was repeated in multiple sessions until obliteration of the VM (judged by clinical response and fluoroscopy). Polidocanol foam (3%) was generated by mixing the sclerosing liquid with air in a ratio of 1 : 4. The Volume of the dosage was calculated with fluoroscopy. The maximum dose did not exceeded 2 mg/kg. Polidocanol injections were performed under fluoroscopy guidance using the same procedure as ethanol. The available trade name (aethoxysklerol 3% – kreussler pharma) was used. Cyanoacrylate was injected by direct puncture of VM using a 23 G butterfly needle. Cyanoacrylate used in the dose of 1 ml/2 cm^2 surface area at the interval of 4 days. Injections were given by palpating and compressing the lesion and guided by duplex U/S, and after injection, pressure was applied for 5 min to ensure occlusion of the malformation. Injections were given according to size, one injection for lesion less than 2 cm^2, two injections for 3-5 cm^2 lesion, four injections for 6-10 cm^2 lesion, and six injections for greater than 10 cm^2 size lesion. All these injections were given at the interval of at least 4 days and the size of the lesion was assessed. The available trade name (histoacryl – B. Braun) was used. All patients were followed-up within 6 months of treatment by clinical examination and detailed duplex U/S examination and all complications were recorded and evaluation of outcome (success and partial response).

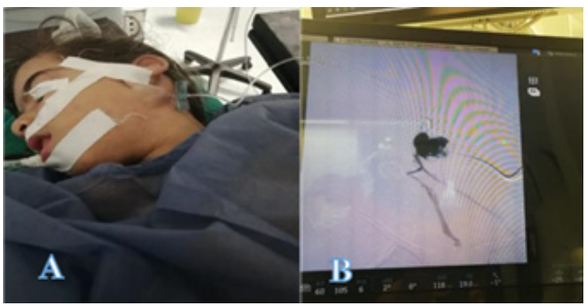

Fig. 1: Percutaneous direct puncture of VM was done using 23G butterfly needle, and confirmation of placement by blood coming back. (a). Nonionic contrast was injected under fluoroscopy (b).

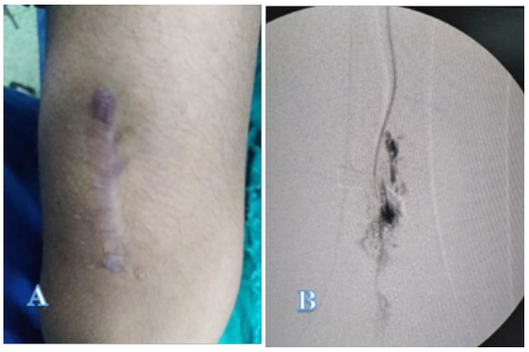

Fig. 2: Recurrent venous malformation in the right thigh after previous surgery (a), direct venography was done before sclerotherapy (b).

Ethical considerations: official permission was obtained from the ethical committee of the Vascular Surgery Department of Mansoura University. Approval from the ethical committee in the faculty of medicine (Institutional Research Board IRB). Informed written and oral consent was obtained from all participants after being informed about the aims and process of the study as well as applicable objectives. And, patients had the right to withdraw from the study at any point of time during the study without objection.

Data management and statistical analysis

Data entry, processing, and statistical analysis were carried out using SPSS (IBM, New York, USA) version 20 (Statistical Package for the Social Sciences). Tests of significance (Kruskal–Wallis, Wilcoxon's, χ^2, logistic regression analysis, and Spearman's correlation) were used. Data were presented and suitable analysis was done according to the type of data (parametric and nonparametric) obtained for each variable. *P values* less than 0.05 was considered to be statistically significant. The following tests were used: descriptive statistics (Mean, Standard deviation (±SD), range, Median, inter-quartile range (IQR), Frequency, and percentage), Analytical statistics (Kruskal–Wallis test, one-way ANOVA, Tukey test and Mann–Whitney U test) and *P value*: level of significance. CONSORT flow chart for study design is shown in (Fig. 3).

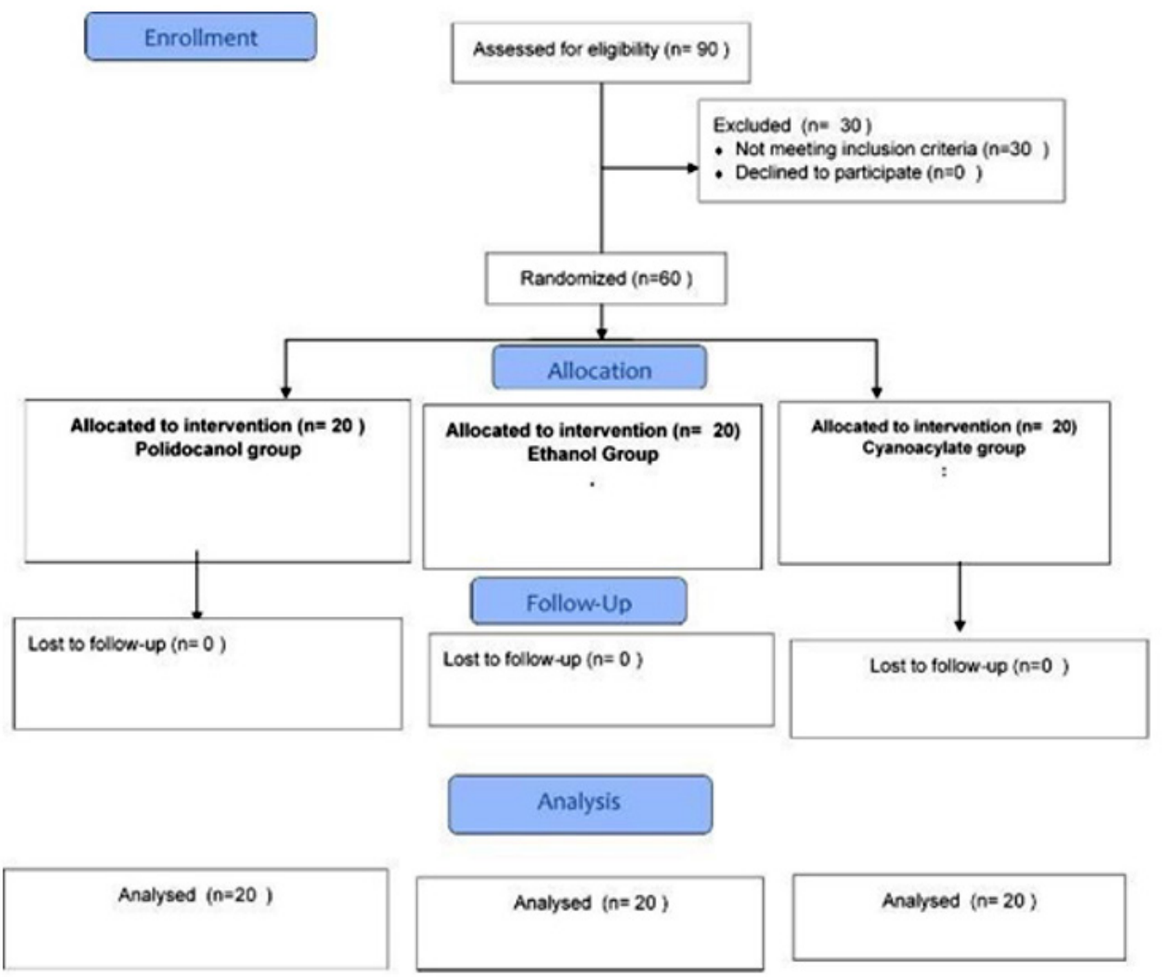

Fig. 3: CONSORT flow chart showing study design.

RESULTS:

A total of 60 patients were treated by sclerotherapy using ethanol (n=20 patients), polidocanol (n=20 patients), and cyanoacrylate (n=20 patients). There was no statistically significant difference found as regard sex (*P=0.449*) as shown in (Table 1).

There were different presentations according to skin characteristics, some lesions presented by reddish, bluish or no skin affection. Studied lesions were found in different sites of a body and the majority of studied lesions (49%) affected the extremities (Table 2).

No statistically significant difference was found between the three studied groups regard median size measured by duplex ultrasound (*P=0.085* and 1.0, respectively) (Table 3).

There was no statistically significant difference found regard Number of sessions needed for every patient treatment (*P=0.086*) (Table 4).

Follow-up of lesions after injection for detection of cure rate (Table 5) showed statistically a significant difference between the three studied groups (*P<0.001*), as ethanol group cases had more complete cure rate. There was a statistical difference between the three groups regarding partial response to sclerotherapy where 55% of the polidocanol group had remnants after treatment versus 30% among the ethanol group and no remnants were observed in the cyanoacrylate group (*P=0.005*). Regarding post-treatment solid mass, we found a statistical difference between the studied groups, where 50% of the cyanoacrylate group was presented by solid mass after treatment but no solid masses were observed in ethanol and polidocanol groups (*P<0.001*).

Regarding postsclerotherapy complications and need for surgery we found statistically significant differences among the studied groups (*P<0.001*), where the majority of Polidocanol group cases had no complications (70%). In cyanoacrylate group, 40% of cases need surgery to excise a remnant solid mass (Table 6).

Kaplan mire survival analysis showed that, there was statistically significant association between a number of sessions and the outcome of the study (log rank test =0.96, *P value* =0.021). Totally occluded lesions by duplex U/S examination with minimal skin improvement had a greater number of sessions followed by lesions with partial response while least number was observed in lesions with remnant Solid mass followed by lesions associated with complete cure by duplex examination and maximum patient satisfaction. (Table 7, Fig. 4).

Table 1: Demographic characteristics of the studied groups

	Polidocanol group *n*=20	Ethanol group *n*=20	Cyanoacrylate group *n*=20	Test of significance
Age/years median (min–max)	5 (2–17)	9 (4–20)	25 (19–34)	KW=41.90 *P*=0.001*
Sex				
Male	12 (60)	8 (40)	10 (50)	χ^2=1.6 *P*=0.449
Female	8 (40)	12 (60)	10 (50)	

KW, Kruskal–Wallis test; χ2, Chi-Square test.
*statistically significant.

Table 2: Site, and skin characters among studied groups

	Polidocanol group *n*=20 (%)	Ethanol group *n*=20 (%)	Cyanoacrylate group *n*=20 (%)	Test of significance
Site				
Face and check	4 (20)	1 (5)	1 (5)	
Upper limb	7 (35)	10 (50)	8 (40)	MC=6.16
Lower limb	8 (40)	6 (30)	10 (50)	*P*=0.406
Back	1 (5)	3 (15)	1 (50)	
Skin characters				
Not affected	5 (25)	11 (55)	15 (75)	
Reddish	8 (40)	0	0	MC=32.27

Bluish	7 (35)	6 (30)	0	$P<0.001^*$
Scar of previous Operation (recurrent)	0	3 (15)	5 (25)	

MC, Monte Carlo test.
*statistically significant.

Table 3: Size and flow among studied groups

	Polidocanol group	Ethanol group	Cyanoacylate group	Test of significance
Median size measured by duplex U/s in cm (min–max)	5 (2–8)	7 (2–12)	5 (2–6)	KW=4.92 P=0.085

KW, Kruskal–Wallis test.
*statistically significant.

Table 4: Number of treatment sessions for each lesion

	Polidocanol group n=20 (%)	Ethanol group n=20 (%)	Cyanoacrylate group n=20 (%)	Test of significance
Number of treatment sessions				
One	5 (25)	8 (40)	10 (50)	MC=11.06
Two	8 (40)	3 (15)	5 (25)	P=0.086
Three	5 (25)	6 (30)	0	
Four	2 (10)	3 (15)	5 (25)	

MC, Monte Carlo test.
*statistically significant.

Table 5: Follow-up results among studied groups

	Polidocanol group n=20 (%)	Ethanol group n=20 (%)	Cyanoacrylate group n=20 (%)	Test of significance	
Follow-up					
Totally occluded by duplex but still skin Affection	4 (20)	3 (15)	0	P=0.122	
Solid mass	0	0	10 (50)	$P<0.001^*$	MC=36.81 $P<0.001^*$
Remnant (partial response)	11 (55)	6 (30)	0	$P=0.005^*$	
Complete cure by duplex u/s and maximum patient Satisfaction	5 (25)	11 (55)	10 (50)	P= 0.12	

MC, Monte Carlo test.
*statistically significant.

Table 6: Incidence of complications and need for surgery among studied groups

	Polidocanol group n=20 (%)	Ethanol group n=20 (%)	Cyanoacylate group n=20 (%)	Test of significance
Complications:				
Hard mass	3 (15)	0	10 (50)	
Sever postinjection edema	3 (15)	0	0	MC=34.82 $P<0.001^*$
Increase heart rate during injection	0	8 (40)	0	
Surgical intervention for mass post sclerotherapy	0	0	8 (40)	MC=18.46 $P<0.001^*$

MC, Monte Carlo test.
*statistically significant.

Table 7: Kaplan–Mire survival analysis among studied groups regarding number of sessions and follow-up results

			95% Confidence Interval			
	Estimate	Std. Error	Lower Bound	Upper Bound	Log rank test	*P* value
Total occluded by duplex u/s but still skin affection	3.286	0.184	2.924	3.647		
Solid mass	1.500	0.167	1.173	1.827		
Remnant (partial response).	2.412	0.228	1.965	2.858	9.69	0.021
Complete cure by duplex and maximum patient satisfaction	1.885	0.244	1.407	2.363		
Overall	2.133	0.144	1.852	2.415		

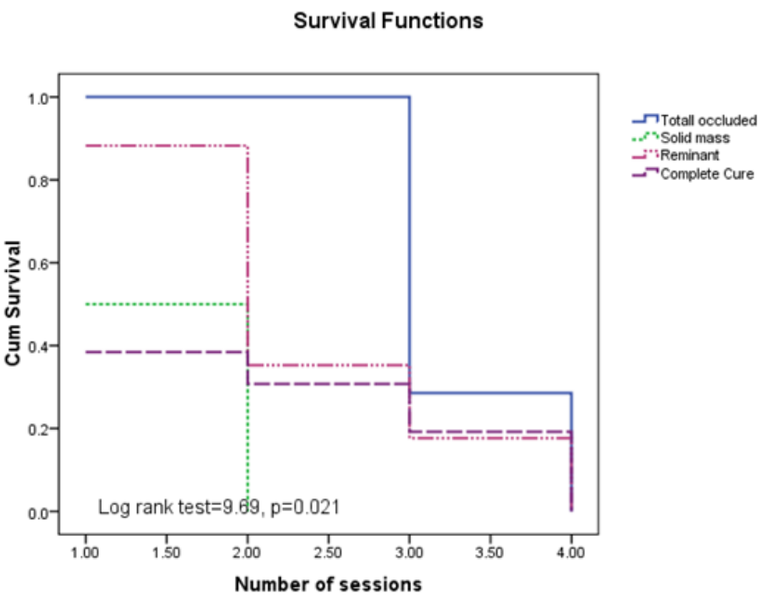

Fig. 4: Kaplan mire curve for survival analysis.

DISCUSSION

The current study showed a statistically significant difference between the three studied groups as regard follow-up of lesion after injection (*P<0.001*), where ethanol group cases had more complete cure (55%) followed by the cyanoacrylate group (50%).

In agreement with current study, Do and colleagues study reported that ethanol sclerotherapy was effective in 27 (68%) of 40 patients (cure: 16 patients; partial remission: 11 patients)[8].

In contrast to our results, Qiu and colleagues reported that ethanol had (27.1%) cure rate, which is lower than polidocanol (41.6%), and the patients treated with ethanolamine oleate received the highest cure rate of up to 59.2%, according to the objective measurement of volume by different means[9].

The current study showed statistically significant differences as regard the incidence of complications and need for surgery among studied groups (*P<0.001*), where the majority of Polidocanol group cases had no complication (70%) followed by the Ethanol group (60%) and 40% of Cyanoacrylate group need surgery as large number of Cyanoacrylate cases complicated by solid mass.

Agarwal and colleagues found that in the cyanoacrylate group, the complication rate was 12%. One patient developed facial nerve paresis but improved after the excision of the lesion. In another case, the patient with a lesion affecting left arm experienced skin necrosis over the lesion, which was due to superficial injection of cyanoacrylate in the dermis. The necrotic skin was excised and the wound was closed primarily. One patient developed hyperpigmentation[4].

Qiu and colleagues found that the patients treated with ethanol had the highest (15.5%) incidence of skin damage. Other common minor complications after ethanol treatment involved nerve damage (4.8%), muscle fibrosis (1.5%), and transient hemoglobinuria (0.95%). Most cases of nerve damage were reversible. Among the patients treated with polidocanol, 15 (9.2%) cases showed skin damage, 8 cases showed transient hemoglobinuria, and two (1.2%) cases showed numbness of limbs[9]. Among the available sclerosing agents, ethanol seems to be the most powerful according to cure rates. It worked through inducing thrombosis by denaturing blood proteins, denuding the vascular wall of endothelial cells, precipitating their protoplasm, and segmentally fracturing the vascular wall to the level of the internal elastic lamina[10].

CONCLUSION

Sclerotherapy is effective for the treatment of LFVM. In our randomized trial, we found that polidocanol is a safer sclerosing agent compared with ethanol and Cyanoacrylate. The utilization of polidocanol for the treatment of AVMs can lead to good efficacy. However, ethanol was associated with better cure rate than polidocanol and Cyanoacrylate. Cyanoacrylate was associated with a sufficient cure rate but complicated by hard mass that may need surgical excision.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Limaye N, Vikkula M. Molecular and genetic aspects of hemangiomas and vascular malformations. Hemangiomas and vascular malformations: An atlas of diagnosis and treatment 2015; ■:21–38.

2. Gorman J, Zbarsky SJ, Courtemanche RJ, Arneja JS, Heran MK, Courtemanche DJ. Image guided sclerotherapy for the treatment of venous malformations. CVIR endovascular 2018 Dec; 1:1–6.

3. Balasundaram I, Al-Hadad I, Rehman K, McCafferty I, Monaghan A. The use of foam sclerotherapy to treat low-flow vascular malformations of the head and neck. J Surg Case Rep 2014; 2014:rju095.

4. Agarwal P, Sharma A, Sharma D. Results of intralesional injection of n-butyl cyanoacrylate (NBCA) and fibrin glue in hemangioma and low flow vascular malformations. Indian Jf Vasc Endovasc Surg 2018; 5:160–4.

5. Ahmad S. Efficacy of percutaneous sclerotherapy in low flow venous malformations-a single center series. Neurointervention. 2019; 14:5360.

6. Prasetyono TO, Kreshanti P. Efficacy of intra-lesional alcohol injection as alternative and/or complementary treatment of vascular malformations: a systematic review. J plast reconstr aesthetic surg 2010; 63:1071–9.

7. Weitz-Tuoretmaa A, Keski-Nisula L, Rautio R, Laranne J. Quality of life after endovascular sclerotherapy of low-flow venous malformations: the efficacy of polidocanol compared with ethanol. Acta Radiologica 2018; 59:946–52.

8. Do YS, Yakes WF, Shin SW, Lee BB, Kim DI, Liu WC, et al. Ethanol embolization of arteriovenous malformations: interim results. Radiol. 2005; 235:674–82.

9. Qiu Y, Chen H, Lin X, Hu X, Jin Y, Ma G. Outcomes and complications of sclerotherapy for venous malformations. Vasc endovasc surg 2013; 47:454–61.

10. Fan G, Wang H, Ding J, Xu C, Liu Y, Wang C, Li Z. Application of absolute alcohol in the treatment of traumatic intracranial hemorrhage via interventional embolization of middle meningeal artery. Front Neurol 2020; 11:8.