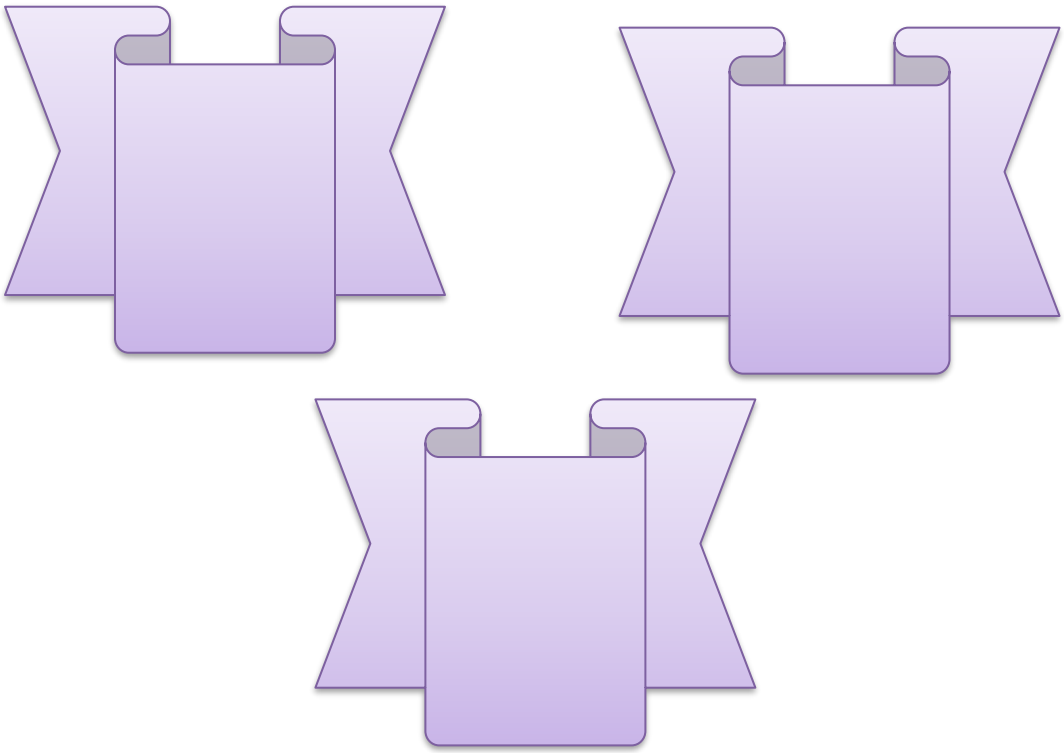
International Journal of Medical Arts

Volume 5, Issue 3, March 2023

https://ijma.journals.ekb.eg/



Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Surgery]

Original Article

Treatment of Venous Malformation by Direct Puncture Repair: Ethanol versus Polidocanol

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Article information

Received: 07-04-2023

Accepted: 06-05-2023

DOI: 10.21608/IJMA.2023.204753.1665.

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Citation: Alstohy AA, Sharaby A, Radwan T, Sayouh AS, Ewida A, khereba W. Treatment of Venous Malformation by Direct Puncture Repair: Ethanol versus Polidocanol. IJMA 2023 March; 5 [3]: 3106-3112. doi: 10.21608/IJMA.2023.204753.1665.

ABSTRACT

Background: Vascular malformations are birth defects that happen when different stages of angiogenesis shut down. 44 - 64% of all vascular malformations are venous malformations [VMs]. Sclerotherapy is the first treatment line for VMs. It acts by getting rid of the vascular endothelial cells in the lesion. One of the most common sclerosing agents for VMs is polidocanol, which is a popular counterpart for concentrated ethanol.

Aim of the work: This study aims to evaluate the efficacy of Ethanol in comparison to polidocanol foam sclerotherapy in the treatment of venous malformation.

Patients and Methods: This prospective interventional study included 20 patients with VM that operated at the department of surgery of Al-Azhar University Hospitals, New Damietta and International Medical Center, Cairo, Egypt from October 2018 to March 2021. Patients were divided into 2 groups. Group A [ethanol] and Group B [Polidocanol].

Results: The difference between the 2 groups regarding the demographics, postoperative change of symptoms, degree of satisfaction, and complications, was not significant indicating that polidocanol foam is nearly as effective as ethanol however, it was slightly more tolerated with fewer side effects compared to ethanol.

Conclusion: Polidocanol foam is an effective therapeutic option for VM. Although ethanol produces good outcomes with few major side effects, polidocanol has a low chance of damaging adjacent tissue. Polidocanol foam works almost as well as ethanol.

Keywords: Venous malformations; Sclerotherapy; Polidocanol; Ethanol.

INTRODUCTION

Vascular malformations are birth defects that happen when different stages of angiogenesis shutdowns. Typically, these are sporadic and may be localized or diffuse. Although they are present at birth, they may not manifest until puberty or maturity [1].

VMs were classified according to the flow characteristics into; slow-flow [capillary, lymphatic, and venous malformations], and fast-flow which includes arteriovenous mal-formation and arteriovenous fistulas [2].

As mentioned before there are many different types of vascular malformations, but VMs are the most frequent. According to the Hamburg classification, lesions are either truncular or extratruncular, with forty percent of occurrences appearing in the extremities, twenty percent in the trunk, and forty percent in the head and neck [3].

Muscle, skin, and mucosa are all examples of single-layer tissues that can exhibit focal vein masses. These focal vein masses are separated and drained into the neighboring veins via narrow pathways. By contrast, muscle, subcutaneous fat, and skin are all affected by diffuse VMs [4].

The primary diagnostic investigation modality is Magnetic Resonance Imaging [MRI]. The optimum sequence for evaluating the VM's size and blood flow is T2-weighted short tau inversion-recovery [STIR] imaging. Furthermore, MRI can be used to assess the degree of involvement of surrounding tissues. Doppler ultrasound and computed tomography [CT] can be helpful tools for VM diagnosis. CT is the investigation of choice for identifying the phleboliths the bone invasion. Combining MRI with Doppler ultrasound improves vascular architecture and venous flow characterization [5].

Sclerotherapy is the best treatment for VMs. It acts by getting rid of the vascular endothelial cells in the lesion. Sclerotherapy works well because VMs have a low flow rate, which means that sclerosing agents can be administered directly to the VM and maintain practically constant concentrations [6].

The most prevalent agents mentioned in the literature for the treatment of vascular malformations are sodium tetradecyl sulfate, bleomycin ethanol, and polidocanol [7]. One of the most common sclerosing agents for VMs is the concentrated ethanol. It acts by causing the protein to stick together in the vascular endothelial cells, which causes the cells to dry out and clot right away [8].

Concentrated ethanol has many common analogs, such as polidocanol. Like ethanol, this drug harms vascular endothelial cells, leading to fibrosis, thrombosis, and arterial collapse [9].

So, this study aims to compare between the Ethanol, and polidocanol foam sclerotherapy in the treatment of venous malformation.

PATIENTS AND METHODS

This prospective interventional study included 20 patients having VM that were operated at the department of surgery of Al-Azhar University Hospitals, New Damietta and International Medical Center, Cairo, Egypt from October 2018 to March 2021. Our research followed the Helsinki Declaration principles and ethical approval was obtained from the Damietta Faculty of Medicine, Al-Azhar University. We recruited the patient after taking informed consent according to the following criteria:

The inclusion criteria include Patients diagnosed with venous malformation of both genders and ages above one year.

The exclusion criteria include 1**]** Age below one year. 2] Patients had any other vascular malformations. 3] Indication for contrast material or Alcohol and polidocanol injection. 4] Unfit for general anesthesia. 5] Pregnancy. 6] Skin infection, inflammation, and ulcers. 7] Pulmonary embolism. 8] Acute Ischemia, and acute DVT.

Data collection

All patients in this study were subjected to medical history taking, fill clinical assessment of main presenting symptoms and lesion, clinical examinations, laboratory investigations, and radiological investigations. Vital signs were measured before the procedure in all patients. All patients received general anesthesia with continuous monitoring of oxygen saturation, pulse, electrocardiography, blood pressure, and carbon dioxide end tidal volume

Surgical procedure

Patients in group [A] underwent ethanol injection [fluoroscopy-guided, 1 ml/kg] through venous malformation direct puncture repair using a needle butterfly in shape [27 and 18 gauge for superficial, and deep lesions respectively] [Figure 1]. The contrast material and Ethanol were injected into the lesion until completely filled.

Patients in group [B] underwent polidocanol injection [fluoroscopy-guided] through venous malformation direct puncture repair using a needle butterfly in shape [27 and 18 gauge for superficial, and deep lesions respectively] [Figure 2]. The contrast material and Ethanol were injected into the lesion until completely filled. the Contrast material and polidocanol were injected into the lesion until completely filled. The concentration of polidocanol used in our study was 3% foam [made by Tessari's method] [Figure 3]. A dilution of 1 volume of sclerosant to 4 volumes of air was used to dilute the sclerosing solution. Within both categories the puncture site was handled with saline-soaked gauze and no compression, and the lesion's location and extent were determined using an earlier MRI scan.

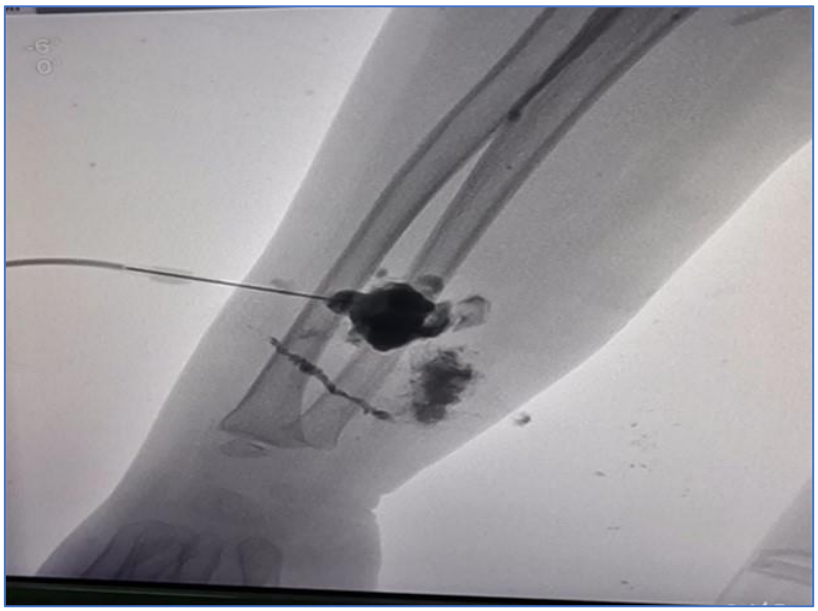

Figure 1: Direct puncture venography

Figure 2: Polidocanol sclerotherapy

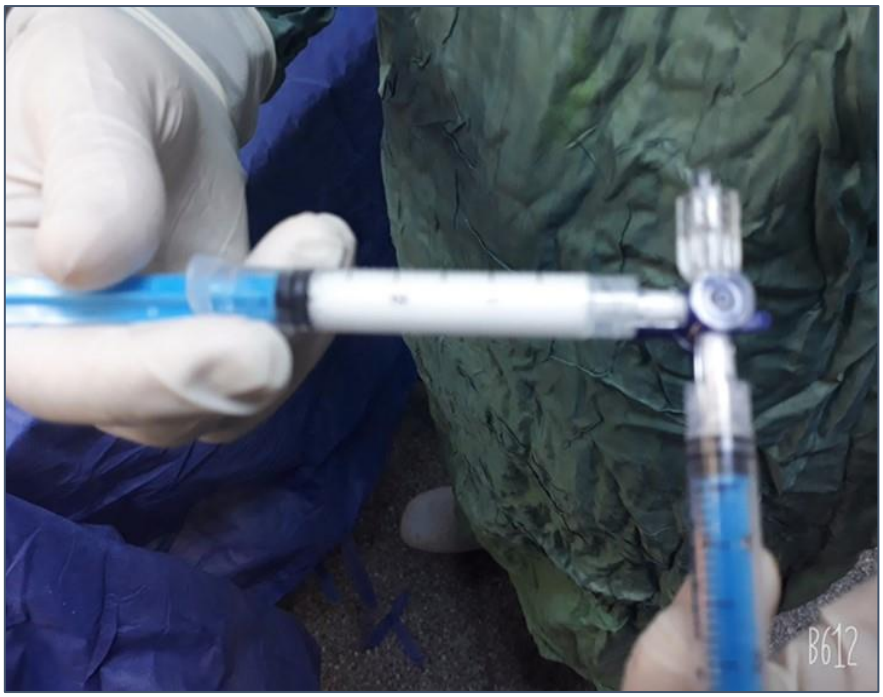

Figure 3: Foam production Tessari's method

After making sure that all of the patients were healthy, they were all sent home with oral NSAIDS, steroids that were tapered over ten days, and PPIs for a patient who had been given ethanol. Sclerotherapy was supposed to be done again on all of the patients every 3–4 months. All of the patients were checked on once a month for a year to see how their primary and secondary outcomes were going. Two months after the third sclerotherapy session, each patient had an MRI.

The primary endpoint was the clinical, and radiological improvement after three ethanol or polidocanol injection sessions. The secondary endpoint was the occurrence of ethanol, and polidocanol sclerotherapy-related adverse event. Patient satisfaction was graded on a 1 - 4 scale. patients were asked to indicate whether they were very satisfied, satisfied, unsatisfied, or dissatisfied.

Statistical analysis

Statistical analysis was done by MedCalc software version 20. We tested the normality of our data by Shapiro–Wilk test. Continuous parametric data were expressed as mean ± SD. We compared the parametric data by the independent t-test. However, we compared the categorical data by chi-square test and described it in the form of numbers and percentages [N [%].

RESULTS

Our study included 20 patients, 10 patients in each group. Table [1] shows the demographic data. The mean age of the patients in group A was 12.7 ± 12.1 years, and 11.7±7.7 years in group B, with no significant difference between the 2 groups [P value = 0.1]. In our study, the percentages of females [65%] were more than males [35%].

In terms of venous malformation locations, the lower limb is considered the most common site in our study with no significant difference between the 2 groups. As regards to the size of VM before treatment, 55% of the studied patients had a size of >10 cm^2, and 45% had a size of < 10 cm^2, with no significant difference between the 2 groups [p-value = 0.56]. The mean number of sclerotherapy sessions was 7.6±6.7 times in group A, and 7±4.1 times in group B, with no significant difference between the 2 groups [P value = 0.4] [table 2].

As regards postoperative symptoms, it was decreased in 7 patients [70%] in group A, and in 6 patients [60%] in group B, it also completely disappeared in 20% of the patients in each group [P value = 0.4]. We didn't report any case of relapsing symptoms in our study, however, only 3 patients [1 in group A and 2 in group B] still have the same symptoms as before the intervention.

In terms of radiological findings post-intervention, the size of VM was decreased in 60 % of the patients in group A and in 40% of the patients in group B, it also completely disappeared in 40 % of the patients in group A and in 60% of the patients in group B, with no significant difference between the 2 groups [P value = 0.2]. The 2 groups were compared as regards their satisfaction after treatment, and we found that 70% of group A were satisfied, and 80% of group B were satisfied, with no significant difference between them [P value = 0.7].

As regards the complications, table 2 shows our reported complications which include; pain, swelling [figure 3], hematoma, and ulcers, with no significant difference between the 2 groups.

Table [1]: Demographics and clinical characteristics of the patients

Variables	Group A [n=10]	Group B [n=10]	P-value
Age [years] [mean and SD]	12.7±12.1	11.7±7.5	0.148 [a]
Range	1.5-36	3-24	
Sex [M: F]	4: 6	3: 7	0.639 [b]
Location, n [%]			
Lower limb	6 [60%]	4 [50%]	
Upper limb	3 [30%]	4 [30%]	0.645 [b]
Head and neck	1 [10%]	2 [20%]	
VM's size before treatment, n [%]			
>10 cm ^{2}	6 [60%]	5 [50%]	0.528 [b]
<10 cm ^{2}	4 [40%]	5 [50%]	

[a]: independent t test. [b]: Chi square test

Table [2]: Operative and postoperative outcomes

Variables	Group A [n=10]	Group B [n=10]	P-value
Number of sessions [mean ± SD]	7.6 ± 6.3	7 ± 4.1	0.463 [a]
Changes in symptoms, n [%]			
Unchanged	1 [5%]	2 [20%]	0.845 [b]
Decreased	7 [70%]	6 [60%]	
Symptom-free	2 [20%]	2 [20%]	
Relapsed	0	0	
Changes in size according to radiological findings, n [%]			
Unchanged	0 [0%]	0 [0%]	0.245 [b]
Decreased	6 [60%]	4 [40%]	
Disappeared	2 [40%]	6 [60%]	
Relapsed	0	0	
Degree of satisfaction, n [%]			
Very satisfied	2 [20%]	2 [20%]	0.75 [b]
Satisfied	5 [50%]	6 [60%]	
Neither	1 [10%]	2 [20%]	
Dissatisfied	2 [20%]	0	
Complications, n [%]			
Pain	4 [40%]	0	0.163 [b]
Swelling	3 [30%]	2 [20%]	
Hematoma	2 [20%]	2 [20%]	
Stiffness	1 [10%]	0	
Neurologic complaint	1 [10%]	0	
Ulcers	2 [20%]	0	

[a]: independent t test. **[b]:** Chi square test.

DISCUSSION

VMs are the most frequent low-flow symptomatic vascular malformations. VMs are treated for cosmetic flaws, malfunction, and pain [10]. Absolute ethanol is a therapeutic substance that is utilized frequently and successfully. Absolute ethanol, with its properties of dehydration and denudation, when injected into the affected vessel, causes rapid deterioration and fall off the vascular endothelial cells [11].

Polidocanol is a less intense sclerotherapy agent with a local anesthetic effect. When injected into a blood vessel, polidocanol

destroys the endothelium lining the blood vessel. The damaged endothelium triggers a cascade of events in which platelets gather at the spot, bind to the venous wall, and finally form a dense network of platelets, cellular debris, and fibrin, closing the vein [12].

Patients' mean age upon treatment onset was 12.7 years in group A and 11.7 years in group B. VMs were located in the lower limb [60%, 50%], in the upper limb [30%, 30%], and in the head and neck [10%, 20%]. There were no significant statistical differences between the study groups. Pain, swelling, and cosmetic disfigurement were the most common symptoms experienced before treatment in the current study.

According to a systematic review conducted by **Sun *et al.*** [11] 83.99% of patients reported improvement following treatment of VMs with 100% ethanol. There was a reported 70% - 95% response rate while using pure ethanol, and 44% - 90% while using polidocanol, which is in line with our findings.

In the current study, three patients from group A and five patients from group B had a size decrease of less than 50%, while a decrease of more than 50% was seen in six patients in group A and four patients in group B. Two patients' malformations didn't change, 14 patients' malformations were partially thrombosed, and 6 patients' malformations were completely thrombosed.

In a study by **Berenger *et al.*** [13] 40 patients were given high doses of ethanol and 30 of them [75%] got much better or were completely cured. The other 10 [25%] got a little better or didn't respond to treatment. Acute blistering was reported by 50% of people, hemoglobinuria by 28%, deep ulceration by 13%, and nerve injury by 7.5%. Two patients had temporary facial paralysis, and one had permanent paralysis of one vocal cord.

The effects of high-volume ethanol sclerotherapy on 87 individuals were monitored by **Lee *et al.*** [14] [305 sessions in total; mean 3.5]. A total of 23 patients [32.4%] had great outcomes, whereas 37 [52.1%] had good outcomes, and 11 [15.5%] had bad outcomes. Patients with injury-related edema and pain were given analgesics intravenously or directly into the muscle. Additional adverse events included respiratory distress in two individuals [4.6%], tongue hypoesthesia in 1 patient, and temporary facial nerve paralysis in one patient [4.6%].

Liu *et al.* [15] monitored 23 patients who were treated with low dosages of ethanol for an average of 20 months after treatment. The majority of individuals experienced complete symptom resolution. A total of 9 patients had excellent clinical outcomes, whereas 14 patients had good outcomes. Patients with mild to moderate pain and swelling responded effectively to conservative care and felt better in a few of days. There were no reports of skin necrosis or nerve injury.

In this study, sclerotherapy reduced analgesic use with an excellent response to pain following treatment which is in agreement with previous studies. It has been suggested by **Nakahata *et al.*** [16] that cosmetic issues are the most challenging to resolve and that adequate informed permission is essential prior to start VM treatment.

In a study done by **van der Linden *et al.*** [17], 53% of patients were satisfied while, another study done by **Nakamura *et al.*** [18] reported a satisfaction rate of 80%.

In our study, pain, swelling, hematoma, stiffness, and neurologic complaints at the injection site were common right after treatment, as was to be expected. Most of these problems were short-term and got better on their own over the next few days to weeks.

The impact of polidocanol monotherapy on cervicofacial VMs and LMs was investigated in two retrospective studies including a total of 39 patients [19, 20]. Both a liquid and a foam version of polidocanol were employed. In most cases, only a few sessions were required. There was a completely positive response. One patient with a labial VM experienced superficial necrosis of the vermillion, which was treated and cured by the second intention.

Conclusion: To treat VM, sclerotherapy can be used in conjunction with a number of different sclerosing agents. Although ethanol produces favorable outcomes with few major adverse effects, polidocanol poses much less of a threat to the body's soft tissues. Foam made from polidocanol is almost as effective as foam made from ethanol. Sclerotherapy of venous malformations can be performed in any area of

the body because it is well tolerated and does not cause discomfort upon injection.

Conflict of Interest and Financial Disclosure: None.

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International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780