Original Article

Use of foam form of 3% Ethoxysclerol in the venous malformations treatment of the maxillofacial region

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ABSTRACT

This article describes the experience of treating 60 patients with venous malformations of the maxillofacial region with a foam form of ethoxysclerol. The possibilities of application were studied and the expediency of using this method of treatment was justified. Based on the data of the clinical examination and the results of the ultrasound examination, the volume of the injected sclerosant in the foam form, the tactics, and the method of optimal surgical treatment were determined. Clinical observations, confirmed by ultrasound data, showed the significant difference in criteria of assessment only for involved zone amount ($p<.05$), and the effectiveness of sclerosing treatment method with 3% ethoxysclerol for the venous malformations of the maxillofacial region: for small, average, and huge focus of malformation, the significant decrease in size was observed after 14 and 30 days ($p< .001$). Thus, the 3% ethoxysclerol can be recommended for use in maxillofacial surgery for the treatment of all venous malformations.

Keywords: Ethoxysclerol, Sclerosis, Sclerosant, Vascular malformation, Ultrasonography, Maxillofacial region

Introduction

Diagnosis and treatment of vascular malformations (VASM) of the maxillofacial region (MFR) is still an urgent problem. According to many authors, the detection rate of VASM localized in the MFR reaches 60-80%, while patients with venous malformations (VM) account for about 40% of the total number of patients with VASM localized in the head and neck region [1, 2].

Ultrasound examination (US), being non-invasive, safe, easily accessible, and without contraindications, the method is currently one of the standard methods for the diagnosis of vascular pathology [3]. US allows visualizing the presence of volume formations, including VM, in the soft tissues of the MFR. Portable ultrasound devices take a special place among modern ultrasound diagnostic devices. They allow performing a diagnostic procedure directly in the operating room.

Here are the following indications for the US of the soft tissue in patients with suspected malformation:

- VASM verification.
- determination of the structure of the malformation (venous or arteriovenous).
- determination of the depth of the malformation location.
- navigation in the treatment of VM by sclerosing with the foam form of ethoxysclerol.
- specifying the size of the VM when planning a surgical operation.
- assessment of the condition of the surrounding soft tissues. US can be used to improve the safety and effectiveness of sclerosis of VM surface [4].

Despite great achievements in modern maxillofacial surgery, the treatment of VM of MFR cannot be considered completely

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resolved yet, since none of the methods of treating VM is universal, and therefore the problem remains relevant. Considering the anatomical features of MFR, the proximity of large vessels, sensory and motor nerves, vital organs (ENT, visual organs, brain), this area is one of the most difficult for vascular, maxillofacial, and plastic surgeons [5].

The most common methods of treatment of VM of MFR include surgical removal and sclerosis with 70% ethanol. Recently, such treatment methods as laser obliteration and microwave therapy have become widespread.

Such a wide range of methods of treatment of VM of MFR is due to the peculiarity of their clinical manifestations, localization, and size.

Surgical treatment is advisable to use if VM can be removed entirely within healthy tissues without significant cosmetic damage and functional impairment, in cases when the use of other methods of treatment is not so effective [6].

The use of 70% ethanol for sclerosing VM is based on its properties of causing cell death by causing cell membrane lysis, protein denaturation followed by vascular occlusion. Injection of 70% ethanol is accompanied by severe pain, the possibility of coagulation necrosis of the surrounding organs and tissues with the development of persistent paresis of the branches of the trigeminal and facial nerves. Also, when sclerosing medium and large malformations, 70% ethanol causes a toxic effect on the entire body [7].

The choice of an optimal treatment method of VM of MFR is especially important when they are localized in aesthetically significant areas. An optimal treatment method is determined only on an individual basis, considering clinical manifestations, localization, size, depth, and the number of anatomical areas affected by VM.

Materials and Methods

We analyzed the archival records of the Department of Maxillofacial and Plastic Surgery of the Moscow State University of Medicine and Dentistry for the period from 1997 to 2016. This analysis showed that out of 742 patients who were on inpatient treatment with various forms of VASM of the face, neck, organs, and tissues of the oral cavity, 450 (60.6%) were diagnosed with VM. According to the statistics of the polyclinic division of the Department of Maxillofacial and Plastic Surgery of the Moscow State Medical University for the period from 2010 to 2017, out of 276 patients with VASM of MFR, 188 (68.1%) were diagnosed with VM. All these numbers indicate that the largest number of patients with vascular pathology who were treated in inpatient and outpatient settings are patients with VM. These factors make the development and implementation of modern, effective, and minimally invasive treatment methods urgent.

The diagnosis of VM of MFR, especially those located superficially, is based on the typical clinical manifestations and anamnesis of the disease [8] and does not present great difficulties. The clinical method of the examination remains the main method of diagnosing VM [9, 10]. Often examination, palpation, and the presence of a positive symptom of "filling" are enough to make a correct diagnosis. Difficulties may occur in the diagnosis of deep-seated VM due to the absence of external clinical manifestations. The etiology of this disease can be different. According to the analysis of the archival records of the Department of Maxillofacial and Plastic Surgery of the Moscow State Medical University, for the period from 1997 to 2016, most commonly VM was diagnosed from birth (54.4%), 20.9% of patients associate the occurrence of VM with sustained injuries, 23.1% cannot associate the occurrence of VM with any causes **(Figure 1)**.

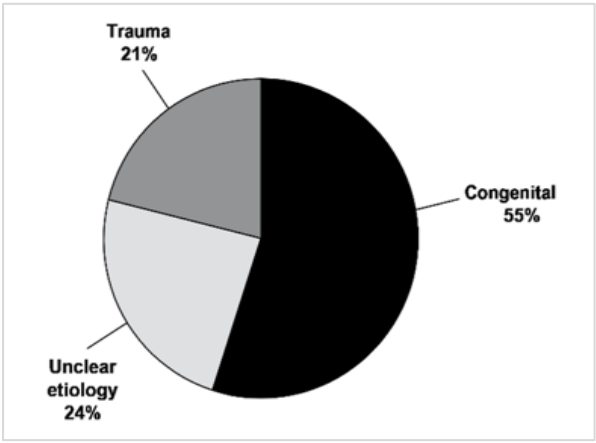

Figure 1. Statistics of VM etiology.

From 2015 to 2018, the Department of Maxillofacial and Plastic Surgery of I.M.Sechenov First Moscow State Medical University examined and treated 60 patients aged 18 to 80 years **(Figure 2)**, including 21 (35%) men and 39 (65%) women. In 44 patients, VM occupied one anatomical area, in 16 patients - 2 areas or more.

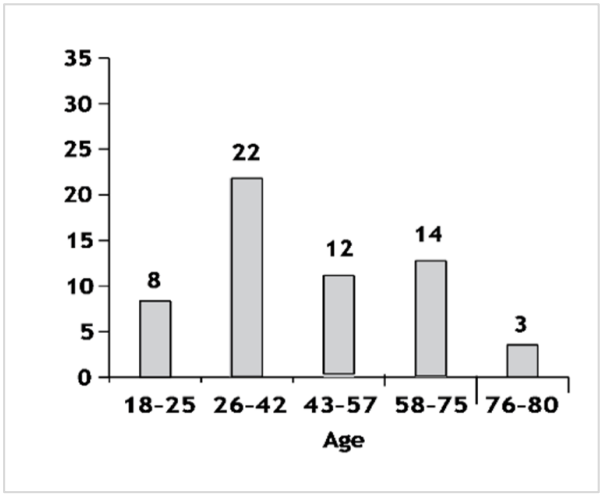

Figure 2. Distribution of the examined patients by age.

Predominant localization of VM was upper lip and cheek area in 42 (70%) patients **(Figure 3)**.

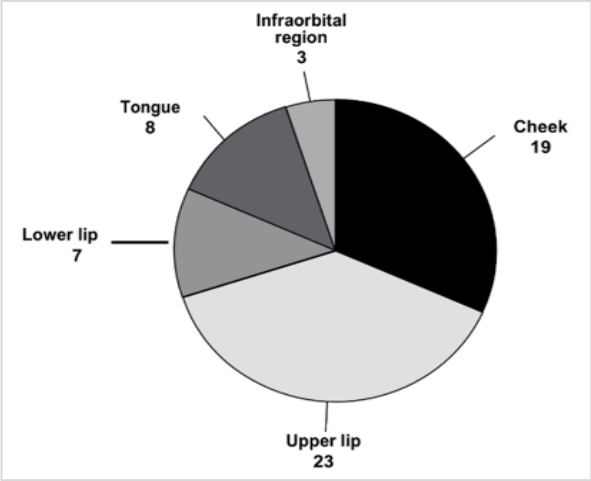

Figure 3. Preferential localization of venous malformations.

The size and shape of VM of MFR were diverse; most of the small, medium-sized, and relatively regular rounded shape **(Table 1)**.

Table 1. Distribution of patients depending on the size of venous malformations in the maxillofacial region.

Size	Diameter, cm	Number of patients
Small	Less than 2	18
Medium-sized	Less than 6	34
Large	More than 6	8
Total		

Our proposed method of treatment of patients with VM of MFR consisted of sclerosing it with 3% ethoxysclerol in the foam form, which had been made in an operating room according to the method of L. Tessari (2000) [11]. This technique is also used in the clinical practice of phlebologists.

Ethoxysclerol is a detergent that damages the cytoplasmic membrane of target endothelial cells lining the inner wall of blood vessels. As a result, platelets are collected at the site of injury and attached to the venous wall. Then the vessel is clogged with a dense network of platelets, cellular debris, and fibrin. At a later stage, the obliterated vein is replaced by fibrous-adipose tissue.

The technique consists of combining two disposable plastic syringes with the capacity of 5 ml, connected through a three-way tap at an angle of 90°, which is used for infusion. One syringe was filled with 1 ml of 3% ethoxysclerol, and the other with 4 ml of air (in a sterile operating room setting). After that, the pistons of the syringes were moved alternately and rapidly (back and forth), mixing the contents from one syringe to another (mixing air with sclerosant) until 5 ml of a white foam emulsion was formed. Generally accepted criteria for preparing foam for injection into VM cavity is 20-25-fold mixing of it from one syringe to another syringe.

Sclerosant in the micro-foam form changes its physical properties, improving distribution in the venous vessels, reducing the rate of drainage from vessel lumen, increasing the exposure time of surfactant to endothelial cells of the vascular wall [12].

During the preoperative period, all patients underwent US to determine the prevalence and size of VM. In addition to that, we paid attention to large vessels located near the VM, especially arteries, since ingress of a sclerosant into the arterial system is an absolute contraindication and can lead to extensive soft tissue necrosis.

Patients underwent an ultrasound on IU-22 devices ("Philips", Netherlands) using a high-frequency linear sensor of 5-17 MHz and a high-frequency linear intraoral sensor of 7-15 MHz. In addition to that, the US was performed with the help of a portable ultrasound device S2 ("SonoScape", China) using a linear sensor of 1-15 MHz in V-modes and Doppler modes.

The clinical criteria for a complete filling of VM with foam was a transition from a bluish color to a pale pink color and its compaction.

The evaluation of treatment results was carried out during routine follow-up examinations with mandatory ultrasound and photographing of patients on the 7, 14 days, and in 1 month after treatment.

In the future, control examinations were performed once every 6 months or at the patient's request.

Statistics

We determined the mean, median, standard deviation, minimal and maximal parameters. After testing of normality of distribution in all groups and inside of them in dynamics, we proved or declined null hypothesis 1 ('There is no difference between different size VMs for main characteristics'), null hypothesis 2 ('There is no difference between different size VMs in the US-square'), null hypothesis 3 ('There is no difference for different size VMs in the US-square inside the groups in dynamics'). The null hypothesizes were approved for p-value > .05 and declined for p-value < .05.

For analysis of VM of the maxillofacial region, we assessed different forms with their characteristics in points and compared them with the Kruskal-Wallis test due to the lack of distribution normality and inside the groups in dynamics, the hypothesis was proved or declined with the T-Wilcox test. For statistical analysis, the program RStudio (R version 3.6.3 (2020-02-29) was used.

Results and Discussion

We marked the main features of VM besides size: localization, number of the involved anatomic areas, the deepness of process, closeness of facial nerve, and possibility of complications after treatment.

For analysis of different forms of VM of maxillofacial surgery we coded these characteristics with points:

Localization: 1 point - infraorbital area; 2- tongue; 3- lower lip; 4- upper lip; 5- cheek.

The number of anatomic areas: 1 point- only one zone; 2 – 2 and more zones.

Deepness of process: 1 point- superficial; 2- deep.

Closeness with facial nerve: 1 point- far; 2- closely.

Complications (minor as light hyperaemia, short-term pain): 0 point- absence; 1 point- presence.

The analysis results are in **Table 2**.

Table 2. Characteristics of different malformation groups

Characteristic	Size: Small (n=17) M±m, Me, Min-Max	Size: Average (n=34) M±m, Me, Min-Max	Size: Huge (n=8) M±m, Me, Min-Max	H, p
Localization	3.72±1.45, 4, 1-5	3.85±1.3, 4, 1-5	3.6±1.3, 4, 1-5	$H = 0.1838$ .9122, $p > .05$.
Zone amount	1±0.32, 1, 1-1	1.24±0.39,1, 1-2	2±0.37,2, 2-2	H=16.5709 **.00025**, $p < .05$.
Deepness	1.1±0.3, 1, 1-2	1.35±0.45, 1, 1-2	1.25±0.45, 1, 1-2	H=2.0386 .36085, p > .05.
Facial nerve closeness	1.33±0.48, 1, 1-2	1.35±0.49, 1, 1-2	1.5±0.53, 1.5, 1-2	H=0.4976 .77974, p > .05
Complications	0.17±0.34, 0, 0-1	0.12±0.34, 0, 0-1	0, 0, 0	H=0.4542 .79684, p > .05.

In the treatment of 52 (86.7%) of our patients, one session of sclerosis with the foam form of 3% ethoxysclerol was sufficient to achieve a positive result. At the same time, 8 (13.3%) patients needed several surgical interventions, which was associated with the large size of the VM. Of these 3 (5%) patients were treated with 3% ethoxysclerol foam as the preparation for surgical excision, and 5 (8.3%) patients were treated with laser obliteration to reduce the size of VM and risk of bleeding.

In 6 (10%) patients the sclerosis was performed in the hospital setting under general anesthesia, in 54 (90%) - under local anesthesia Sol. Articaini 1:200 000 to 2 ml.

After receiving a positive aspiration test, 3% ethoxysclerol was injected into the foam form under continuous ultrasound control until the foam filled the VM cavities.

Based on the ultrasound data, it is possible to calculate the volume of the VM and the volume of injected sclerosant in the foam form.

The volume of VM was calculated by the formula:

$$V=L\times W\times H\times 0,5, \quad (1)$$

where V is the volume, L is the length, W is the width, H is the anteroposterior size, 0.5 is the constant coefficient.

For example V=5×7×2×0,5=35 ml.

The optimal amount of 3% ethoxysclerol in the foam form was selected depending on localization, size, and depth of the lesion, as well as determination of the volume of the VM, which corresponded to the approximate volume of the VM. Based on the results of the ultrasound, a decrease in the formation by 25-35% was noted on the 7th day after controlled sclerosis with a 3% solution of ethoxysclerol in the foam form. The zone of reduced echogenicity was visualized around malformation, in the projection of which multiple hyperechogenic inclusions were determined due to the accumulation of air bubbles, that indicated the presence of a sclerosant in the lumen of the vein. There were signs of edema in surrounding soft tissues. Clinically, it was difficult to determine the change in the size of the VM due to collateral edema and infiltration of the soft tissues surrounding the VM. The skin surface may be slightly hyperemic, bruising may occur. Also, soft tissues above the surface of the VM may be slightly compacted and painful during palpation.

The dynamics of VM after treatment according to the US results are introduced in **Table 3**.

Table 3. US dynamics of different malformation groups after treatment

Days	Size: Small (n=17) M±m, Me, Min-Max	Size: Average (n=34) M±m, Me, Min-Max	Size: Huge (n=8) M±m, Me, Min-Max	H, p
7 days	35.4±1.77, 35, 32-38	30.03±3.33, 29, 25-37	25.12±2.18, 25, 22-28	H=32.7288 **.00001, p<.05**
14 days	57.7±3.7, 57.5, 51-63	54.1±3.7, 55, 48-58	50.3±1.5, 50.5, 48-52	H=21.9725 **.00002, p < .05**
30 days	75±1.8, 75, 72-78	73.2±1.7, 72, 70-76	70.6±1.7, 70.5, 68-73	H= 20.7737 **.00003, p < .05**

7/30 days	0, 4.363e-07, **p<.001**	0, 1.214e-12, **p<.001**	0, .0009069, **p<.001**	Wilx-test, p

The analysis of the main characteristics of different sized VM of the maxillofacial region has shown a logical significant difference in the number of involved zones ($p<.05$).

Ultrasound examination showed a decrease in the formation by 50-55% on the 14th day after sclerosis. Practically multiple hyperechoic inclusions (air bubbles) were not visualized. With Doppler color mapping, the zone of pathological vascularization was not determined. Clinically, the reduction in the size of the venous malformation up to 40% of its original parameters was determined. Palpation was slightly painful and of a dense consistency.

Also, ultrasound signs of edema of soft tissues surrounding the VM were not visualized on the 30 days after the sclerosis session. In Dopplerography zones of pathological vascularization were not determined. A decrease in venous malformation up to 70-75% of the original size was noticed. Clinically, the size of the VM decreased up to 70%.

In the case of incomplete disappearance of VM, there was a need for repeated sclerosis, as well as the use of other methods of treatment, such as surgical excision or laser obliteration. A session of repeated sclerosis with the foam form of 3% ethoxysclerol was performed no earlier than 4-5 weeks after the previous procedure. This is since only after 4-5 weeks after sclerosis, it is possible to assess the effectiveness of treatment, reduce the volume of the VM, and identify remaining venous cavities that have not undergone fibrous transformation both clinically and according to ultrasound data.

With the introduction of high-tech Nd-diode lasers in the treatment of VM of MFR, it became possible to choose laser modes that selectively act on vessels without severe damage to the outer layers of skin.

This method is based on the principle of selective absorption of laser energy of a certain length by all components of biological tissue, which leads to their destruction without harming surrounding tissues. Laser energy, which releases heat inside the vessel, leads to the vaporization of blood and plasma corpuscles, which is accompanied by a thermal burn of the endothelium.

The effectiveness of treatment with the use of diode lasers was proven for surface located VM. However, there are cases of VM in which the use of this method remains less effective, for example, if VM occupies multiple anatomical areas or if it is extensive or diffuse.

Like other methods, laser obliteration has several advantages and disadvantages. Advantages include the use of the method in aesthetically significant areas of the face and neck due to minor trauma, tissue asepsis during dissection, and hemostatic effect [13]. In addition to that, the usage of this method in outpatient settings can be named as a great advantage [14]. During the postoperative period pain syndrome, as well as collateral edema of the soft tissues surrounding VM, is less pronounced [15].

The method of endovenous laser obliteration (EVLO) of VM of MFR, which has been used since 2000, is also of great interest [16]. This technique consists of the intravascular thermal effect of laser radiation on the vascular wall. The purpose of EVLO is to damage the venous cavity from the pathological blood flow by its fibrous transformation.

With local exposure to microwave radiation, it is possible to destroy deep-located large-sized VM of MFR that occupy several anatomical areas in almost 100% of cases. However, it is difficult to obtain even heating on an affected area with nearby organs and tissues. Due to that, there is a risk of tissue inflammation with subsequent suppuration [17]. Unfortunately, this method is not widely used due to technical difficulties.

The proposed method of treating the VM using 3% ethoxysclerol in the foam form makes it possible to effectively treat small, medium-sized, and even huge VM of various anatomical localization. This method is easy to use and can be used by maxillofacial surgeons in outpatient practice after appropriate training. Ultrasound data allows to accurately calculate the volume of the VM, which makes it possible to determine the amount of the foam form of sclerosant injected into the VM cavity.

Ultrasound control during surgery allows controlling the amount of injected foam form of 3% ethoxysclerol until the entire volume of the VM is filled.

Evaluation of early and long-term results of treatment of VM by sclerosing with the foam form of 3% ethoxysclerol showed the absence of complications in the form of soft tissue necrosis with a correctly determined amount of sclerosant administered using ultrasound control.

Conclusion

Clinical observations confirmed by ultrasound data showed that the technique of controlled sclerosis with 3% ethoxysclerol in the foam form is effective in the treatment of venous malformations of the maxillofacial region. The advantages of this method of treatment are minimally invasive, easy manipulation, and the absence of a pronounced pain syndrome during the intervention. The advantages of this method of treatment are minimally invasive, easy manipulation, and the absence of a pronounced pain syndrome during the intervention. Correctly determining volume and concentration of the injected 3% ethoxysclerol in the foam form, the long exposure time of the drug with the effect on the vascular wall of the venous cavity, causing its fibrous transformation, allows getting a positive treatment result in patients with small and medium-sized venous malformations during one intervention.

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