Article

Sclerotherapy Impact in Modern Treatment Methods of Children With Extracranial Venous Malformations

Lev Voznitsyn [1, 2]*, Orest Topolnitskiy [1], Sergey Yakovlev [1], Artur Medzhidov [2]

[1] Department of Pediatric Maxillofacial Surgery, I.A.Evdokimov Moscow State University of Medicine and Dentistry (MSMSU), Moscow, Russia;
[2] Russian Association for Vascular Anomalies Research (RAVAR), Mahachkala, Republic of Dagestan, Russia;
* Correspondence: levmgmsu@mail.ru;
levmgmsu@mail.ru, https://orcid.org/0000-0001-9384-3944 (L.V.)
proftopol@mail.ru, https://orcid.org/0000-0002-3896-3756 (O.T.)
serg.yak@mail.ru, https://orcid.org/0000-0002-2501-8552 (S.Y.)
dr.medzhidov@gmail.com, https://orcid.org/0009-0002-4395-4894 (A.M.)

Citation: Voznitsyn L, Topolnitskiy O, Yakovlev S, Medzhidov A. Sclerotherapy impact in modern treatment methods of children with extracranial venous malformations. Otorhinolaryngology, Head and Neck Pathology (ORLHNP). 2023; 2 (2): 15-23.

https://doi.org/10.59315/ORLHNP.2023-2-2.15-23

Academic Editor: Valentin Popadyuk

Received: 13.05.2023
Revised: 15.05.2023
Accepted: 01.06.2023
Published: 30.07.2023

Publisher's Note: International Society for Clinical Physiology and Pathology (ISCPP) stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract:

Relevance. Venous malformation is an abnormal development of the collecting blood vessels based on the vascular wall formation disorder, which occurs during the peripheral vascular network differentiation. According to various sources, venous malformation prevalence ranges from 1 to 2 in 10 000 newborns. Head and neck VMs significantly reduce patients' quality of life, causing severe functional and aesthetic impairments. Sclerotherapy is an effective treatment method for children with venous malformations. In recent years, bleomycin has been the most commonly used sclerosant. It is a glycopeptide antibiotic synthesized by Streptomyces verticillus and belongs to cytostatic medications. It is successfully used for venous malformations sclerotherapy, also in children.

Purpose. The study aimed to improve the sclerotherapy method by combining the advantages of foam-form sclerotherapy and bleomycin.

Materials and methods. We provided experimental and clinical stages of the study. There were 48 samples of rats' external femoral veins morphologically examined in the experimental stage. We divided the rats into 2 groups depending on the administrated agent: the first group – 3% polidocanol (lauromacrogol 400), the second group – bleomycin-polidocanol mini-foam composition. The histological assessment identified the changes in the vein endothelium, necrosis of tissue structures, cell dystrophy characteristics. In the clinical stage we also divided patients into 2 groups following the same treatment protocols as in the experimental stage. The results assessment included presence or absence of clinical manifestations and magnetic resonance imaging malformation features.

Results. In the experimental stage the first group, in which the bleomycin-polidocanol mini-foam composition was used, demonstrated more pronounced irreversible changes in the venous vessel endothelium compared to the second group. In the clinical stage the second group where bleomycin-polidocanol mini-foam composition was used showed rather good and satisfied results than in the group where standard polidocanol technique was carried out.

Conclusions. The study revealed that the proposed method of venous malformation sclerotherapy using new bleomycin-polidocanol mini-foam composition is more effective than the polidocanol foam-form sclerotherapy. The new method is highly effective, minimally invasive, safe and can be considered an independent treatment method in children with head and neck venous malformations.

Keywords: venous malformation, sclerotherapy, bleomycin, polidocanol, vascular malformations, cytostatic agents, endothelium, rats, sclerosing solutions, quality of life.

1. Introduction

Venous malformation (VM) is an abnormal development of the collecting blood vessels based on the vascular wall formation disorder, which occurs during the peripheral vascular network differentiation. VMs are slow-flow vascular anomalies characterized with poor smooth muscle layer development. The VM endothelium is not prone to proliferation. However, clinical manifestations

of the disease are associated with local hemodynamic disturbances resulting from the inclusion of the malformed vascular bed into the circulation. Hemodynamic disturbances are characterized by local venous stasis with intravascular chronic coagulopathy development resulting in calcinates and phleboliths formation. The incidence of VM according to various data sources ranges from 1-2 cases per 10,000 newborns [1, 2] up to 1-4% of the population [3]. According to the U.S. consolidated data, venous malformations occur in 48% among all types of vascular malformations [4]. According to the literature, VMs are localized in the head and neck area with the frequency from 14.7% [5] up to 74% [6]. The venous malformations incidence among all vascular malformations in children is 21.5% [7]. The main pathogenetic mechanism of the disease is TEK gene mutation, locus 9p21.2 (short arm of the ninth chromosome). The TEK gene encodes the TIE2 protein, which is the intracellular domain of the tyrosine kinase receptor in endothelial cells; this protein functions as an angiopoietin I receptor. The TEK gene signaling pathway is the main factor in the formation of intercellular connections between the endothelium and the smooth muscle layer in venous vessels development. The TEK gene mutations are the major causes of an abnormal venous formation [8]. Clinical manifestations of head and neck venous malformations vary from the limited oral mucosa phlebectasis to the extensive diffuse angiomatosis spreading to several anatomical areas. Head and neck VMs, in addition to functional disorders, cause the aesthetic defects, thus, significantly hampering patient's social adaptation. The majority of authors recognize a surgical method to treat VM [9, 10, 11]. The authors note the angiomatous tissues radical excision difficulty due to the high risk of intra- and postoperative bleeding. Also, an excision of significantly sized malformation can be compromised due to the high aesthetic requirements of maxillofacial surgery [12, 13]. In addition, the frequency of VM's recurrences is high [14].

According to mentioned above the treatment tactic of patients with VM of head and neck should be pathogenetically reasonable and based on principles of:

1. Efficiency;
2. Minimal invasivness;
3. Safety.

The sclerotherapy method is fully corresponded to these criteria. Sclerosing therapy or sclerotherapy is an alteration on the venous malformation endothelium using a chemical substance to destroy its intima, followed by venous wall adhesion and, as a consequence, removal of pathological veins from the blood flow.

Sclerotherapy advantages are:

1) Selective effect on decompensated collective blood vessels (in case of endovascular agent injection);

2) Minimally invasive procedure;

3) Malformations management in complicated localization;

4) The procedure can be carried out without anesthetic assistance in elderly patients;

5) Absence of postoperative defects and scars.

Foam-form sclerosing therapy has been widely spread in clinical practice since 1993. It is based on the irregular bubbles dispersion with increased sclerosing agent concentration on the surface injection into the vessel lumen, and, as a result, has maximal sclerosing effect.

The described form has a number of advantages:

1) "Empty vein" effect by evenly displaced blood from the venous malformation lumen;

2) Sclerosing solution and the VM endothelium contact prolongation by keeping the agent in the vessel lumen until the bubbles decay, whereas the native agent form rapidly dissolves in the blood, losing its initial effectiveness;

3) Administrated agent's amount reduction;

4) Persistent pronounced vasospasm after the sclerosing solution foam-form injection into the vessel's lumen contributes to the development of sclerophlebitis, which is a predictor of VM persistent remission.

Considering foam-form sclerotherapy advantages, not all sclerosing agents are suitable for foam formation. Only detergents are suitable for this purpose due to its lyophilic center that reduces surface tension. However, recently, other pharmacological agent groups have become widespread. A large data amount about using bleomycin in the treatment of children with venous malformations is recorded in the foreign and domestic literature. Bleomycin is a glycopeptide antibiotic synthesized by Streptomyces verticillus and belongs to cytostatic medications. This agent is being successfully used for venous and lymphatic malformations sclerotherapy, also in children.

In order to improve the sclerotherapy method for venous malformations of the head and neck, we combined the advantages of foam-form sclerotherapy and the effectiveness of the bleomycin.

2. Materials and Methods

The presented mini foam composition is prepared of 3 components which are polidocanol (Aethoxysklerol 3%, Kreussler Pharma, Germany), bleomycin and an atmospheric air. 3% Aethox-

ysklerol and the same amount of bleomycin solution are mixed in a three-component syringe according to the Tessari method (Tessari L. 2000) with an atmospheric air in the second syringe. The optimal ratio of bleomycin-polidocanol-air is 1:1:4. The detergent component molecule of the foam composition (polidocanol) is a dipole with a lyophilic center and hydrophilic and hydrophobic sites at the opposite ends. Due to this feature, some of these molecules are fixed by the hydrophobic part to the membrane of endotheliocytes, causing denaturation of proteins and destroying the vascular endothelium with an extended exposure of the basal membrane. The second component of the mini foam composition (bleomycin) enhances the damaging effect on the malformation endothelium, complementing the total sclerosing effect and reducing the risk of disease recurrence by local angiogenesis suppression.

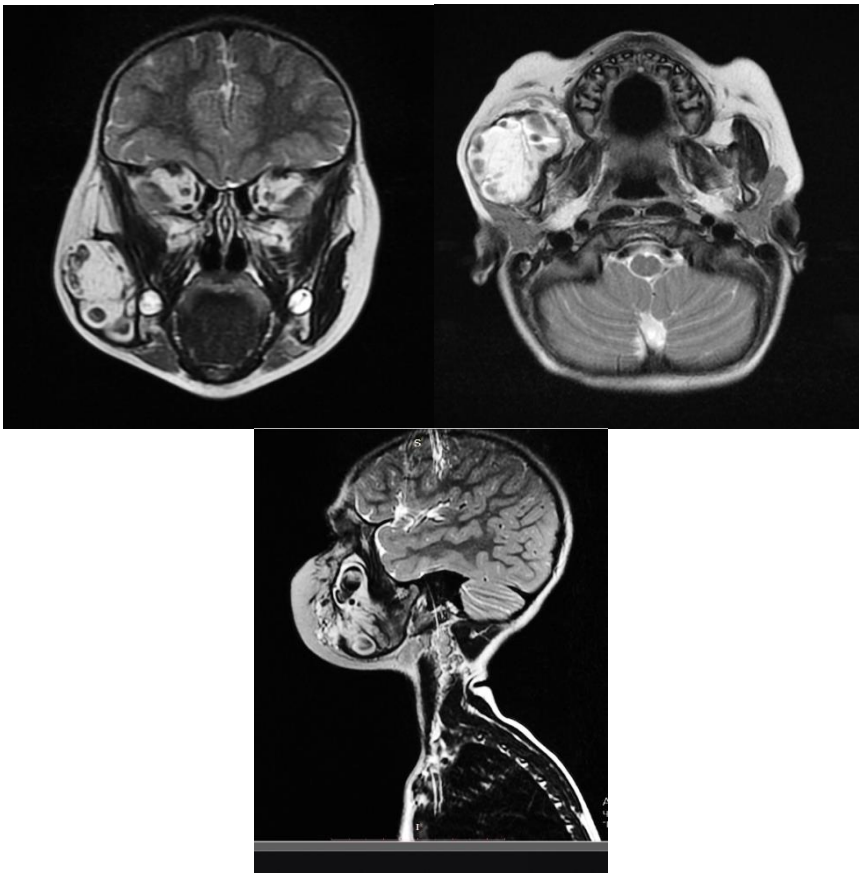

Figure 1. Magnetic resonance imaging of a patient with extensive venous malformation of the right parotid, buccal regions and right pterygopalatine fossa

The study was approved by the Ethics Committees of A.I. Evdokimov Moscow State Medical University of Dentistry and Medicine (MSMSU). In the period from 2016 to 2021 in A.I.Evdokimov MSMSU Clinical center of Maxillofacial and Plastic surgery we treated 62 patients 0 - 18 years of age diagnosed with venous malformation of head and neck. The diagnosis was based according to general examination data: interview, anamnesis, physical examination, functional tests (filling and compression symptoms, Valsalva maneuver) and additional methods of examination. All patients underwent Doppler color flow mapping ultrasound. Doppler color flow mapping should be the primary link in the diagnostic of this pathology, since it has several advantages: it is noninvasive, does not require special patient preparation and anesthesia. Also, ECHO-graphy combined with color flow Doppler is a rather informative technique in VM diagnostic: it allows not only revealing the vascular component of the malformation, but also determining the blood flow type and angioarchitectonics of the malformation. Ultrasonography also detected the presence of cavities sharply increasing in volume when performing compression tests. Thrombi, including those with signs of organization, and phleboliths were detected echographically.

Magnetic resonance imaging (MRI) is the most informative method to diagnose the venous malformations (Fig.1). This technique is highly informative to determine the malformation's size, localization and configuration. It also allows determining the volume of venous hyperemia in the affected area. No bolus contrast enhancement is required; the malformation is clearly visualized on T2-weighted image. At low blood flow rates, it is possible to detect signs of sedimentation. The

necessity of providing head and neck soft tissue MRI in venous malformations of all sizes and vocalizations is due to the probability of intra- and extracranial lesion foci, which may not manifest clinically. However, this highly informative technique has its disadvantages: the study is time-consuming and can be only performed under general anesthesia in young children.

Multi slice computer tomography (MSCT) angiography was additionally performed in 5 patients with extensive VMs. This method was not highly informative in VM diagnostic, a moderate accumulation of contrast agent in the venous cavities was detected 5 minutes after the injection. The method is also characterized by high radiation exposure and the need for intravenous injection of a contrast agent. In young children this study can be performed only under anesthesia support (Fig.2).

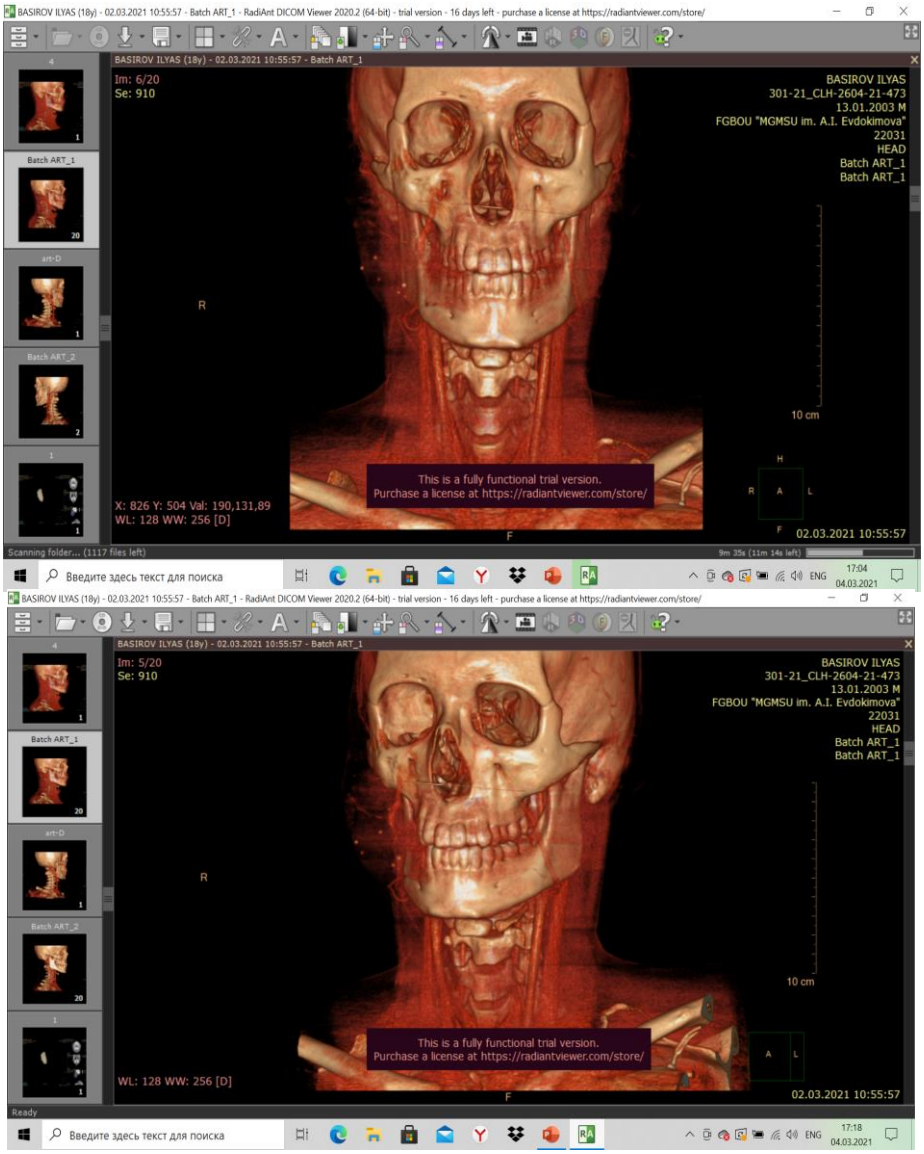

Figure 2. MSCT angiography of a 17-year-old patient with extensive venous malformation of the right side of the face. 3D reconstruction

All patients underwent sclerosing therapy: 41 patients were treated using the standard "foam-form" technique with 3% polidocanol solution and 21 patients - using the new bleomycin-polidocanol mini foam composition. The method was carried out as follows (FIg.3): under inhalation anesthesia, we performed puncture of one of the venous malformation cavities with an injection needle (two needles for extensive malformations) under ultrasound navigation; after the aspiration test, the foam was injected through one needle. The volume of injected sclerosant was calculated according to the formula: Vo = x A x B x C, where: Vo - malformation volume, cm; A - height, cm; B - width, cm, C-thickness, cm. In most cases, foam leaking through the second needle is determined, which is one of the signs of intravascular needle placement. The needle position does not change

throughout the procedure, the foam spreads in full volume through all the VM cavities, which is confirmed by intraoperative ultrasound monitoring. After the necessary volume of the drug is injected, the needles are removed and manual compression is performed for 5 minutes. The technique did not differ in the studied groups.

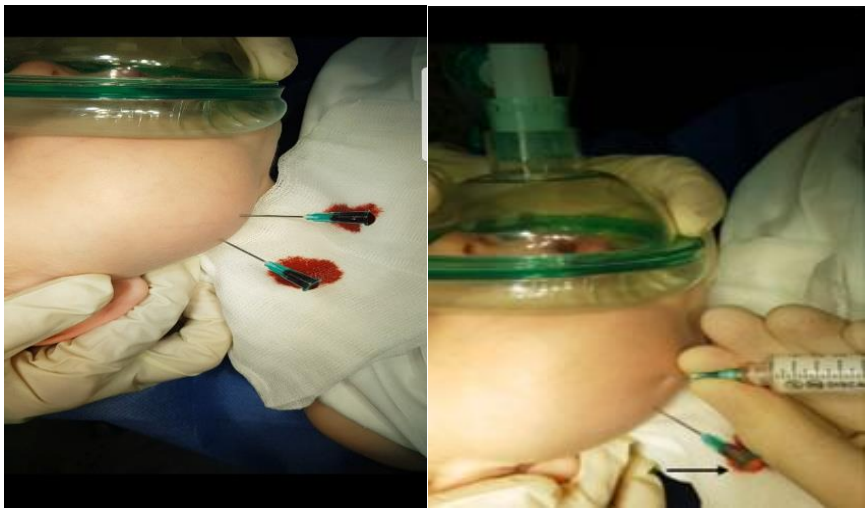

Figure 3. The process of performing VM sclerotherapy with the new bleomycin-polidocanol mini-foam composition. The arrow indicates the foam leaking through the second needle.

The number of procedures varied from 1 to 6. The time interval between the sclerotherapy procedures ranged from 30 days to 4 months, depending on the severity of the lesion, stage of treatment and social factors. An ultrasound was performed 30 days after the surgery in order to decide on the next stage of treatment. In the case of pathological vascularization absence according to the ultrasound findings, the patient underwent a control MRI scan. We performed MSCT in 12 patients on the third day after surgery. Numerous air bubbles evenly filling the entire volume of the malformation were visualized (Fig. 4). It should be noted that during paravasal injection of the foam form of the drug, air bubbles are concentrated strictly in the place of needle puncture. Thus, this method can be used as a postoperative control in the treatment of VM.

For morphological assesment of the proposed VM sclerotherapy efficiency, an experimental study was performed. Wistar laboratory rats of both genders with an average body weight of 180-220 g were used in the experiment. All experiments were performed according to the "Statute on legal and ethical principles of medical and biological research" (VAK Bulletin of the Ministry of Education of Russia. 2002. №3. P. 77-75); "Rules for work with experimental animals" (Appendix to the Order of the Ministry of Health of the USSR, August 12, 1977, N 755) and the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes", March 18, 1986. In order to assess morphological changes in the studied site we injected sclerosing agents into the intact tissues of laboratory rats: external vein of right and left hind limbs.

A total of 12 rats were involved in the experiment and divided into 2 groups depending on the injected agents: group 1 - 3% polydocanol (lauromacrogoal 400), group 2 - new bleomycin-polydocanol mini-foam composition.

The animals were weighed and the amount of administered drugs was calculated. Medetomidine 0.05 ml/100 g was administered intramuscularly in order to provide anesthesia and zoletil 100 5 mg/100 g intramuscularly was also administrated 10 minutes later. The lower extremities were fixed and a tourniquet was applied. 0.2 ml of sclerosing agents were slowly injected into the external femoral vein through an insulin needle. The needle was removed, hemostasis was performed by finger compression. For morphological study, animals were removed from the experiment by intramuscular injection of zoletil 100 10 mg/100 g on the 7th day after the drug administration. Histological evaluation included revealing changes in the endothelial layer of the venous vessel, necrosis of tissue structures and cell dystrophy.

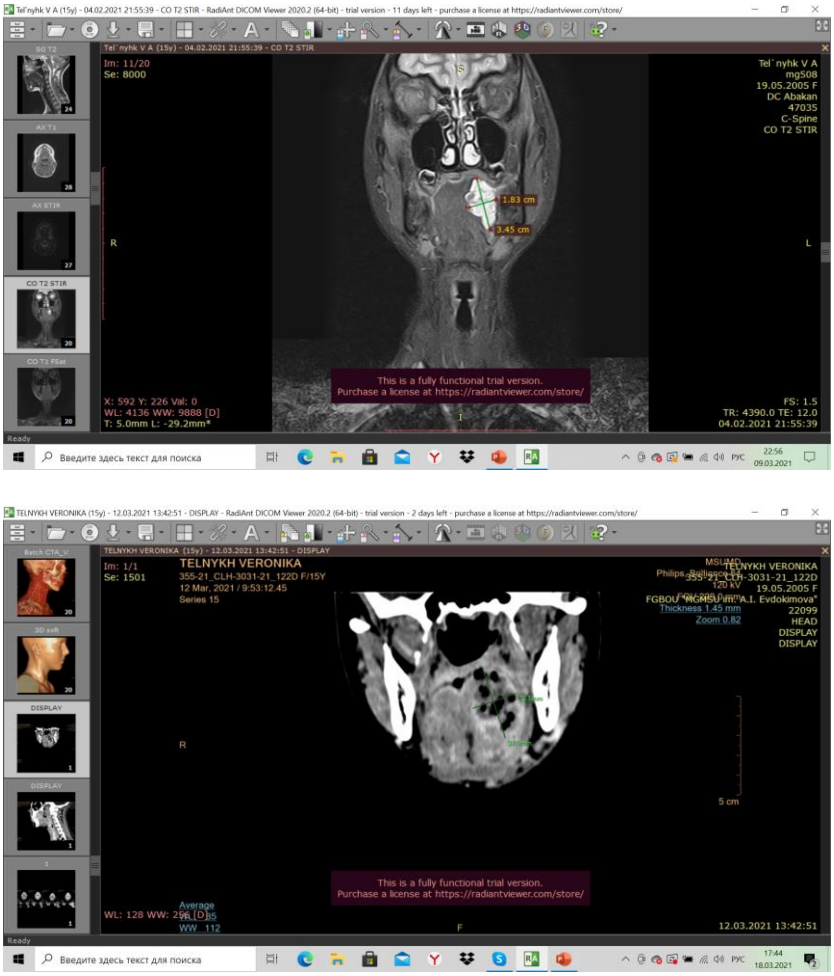

Figure 4. MRI scan of a 13-year-old patient with venous malformation of the tongue. MSCT of the same patient on the 2nd day after sclerosing therapy. Even distribution of gas bubbles over the entire volume of the malformation is visualized.

3. Results

3.1. Results of the clinical stage of the study.

The results were assessed as follows: absence of clinical manifestations and MRI features of malformation - good, clinical manifistation and malformation volume decrease according to MRI data - satisfactory, clinical manifestation persistence, absence of MRI dynamics - unsatisfactory. Good result was achieved in 33 patients (80%), satisfactory - in 6 patients (15%). In 2 patients (5%) we considered the result to be unsatisfactory. The results in the second group of 21 patients who underwent sclerosing therapy with bleomycin-polidocanol mini-foam composition were assessed in the similar way. The results were distributed as follows: good result was achieved in 19 patients (90.5%) and satisfactory result- in 2 patients (9.5%). We did not obtain unsatisfactory result in the group where bleomycin-polidocanol mini-foam composition was used. The results of the treatment of children are summarized in Table 1.

Bleomycin-polidocanol mini-foam composition in addition to its significant advantages such as minimal invasivness, selective effect on the pathological venous pool, absence of surgical trauma of the adjacent anatomical structures, has also the following advantages:

1.The combined effect of two sclerosing agents on the vascular endothelium significantly increases the sclerotherapy efficiancy;

2.Relapse probability decrease due to angiogenesis inhibition in the injection site of the composition;

3.This technique has been shown to be highly effective in large venous malformations (3 or more anatomical areas of the head and neck);

4.Surgeries that are necessary to achieve permanent irreversible sclerophlebitis of pathological venous vessels number decrease;

5.The total rehabilitation time of the child is significantly reduced (Fig.5).

Table 1. Sclerotherapy results

The agent	Average amount of sclerotherapy procedures	Obtained results			Total amount of patients
		Good	Satisfactory	Unsatisfactory	
Polidocanol foam-form	2.68	33(80%)	6(15%)	2(5%)	41
Bleomycin-polidocanol mini foam composition	1.46	19(90.5%)	2(9.5%)	0	21

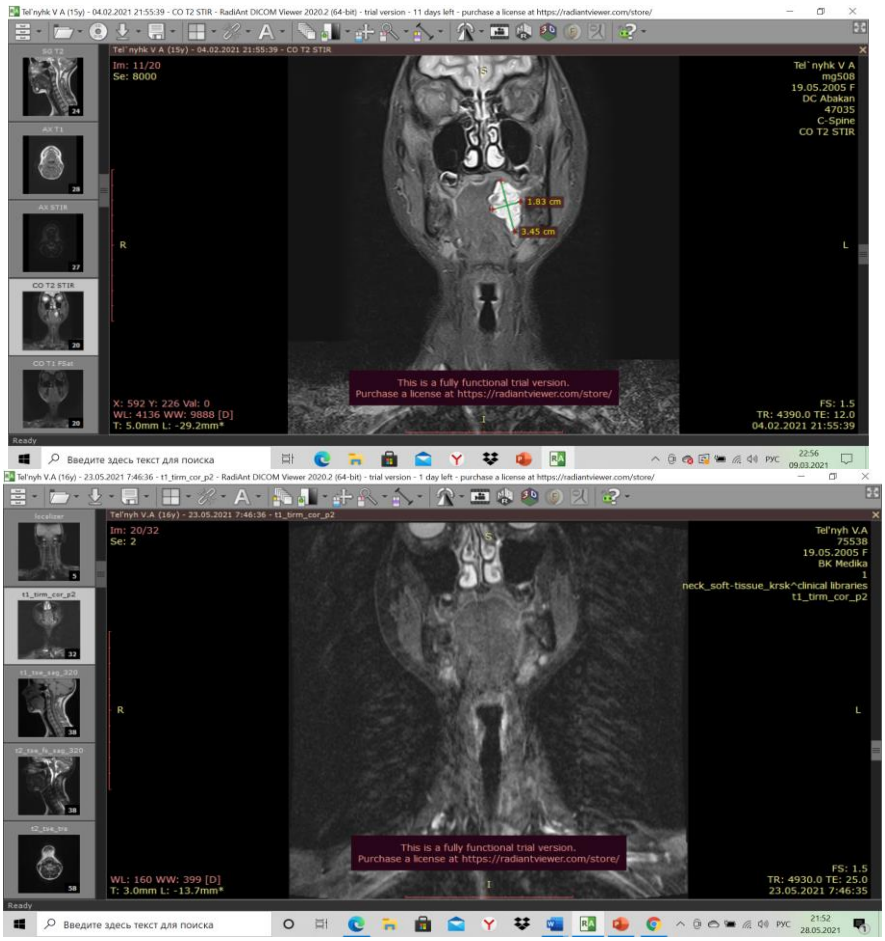

Figure 5. MRI of a 13-year-old female patient with venous malformation of the tongue. Before treatment (left) and after one session of sclerotherapy with the new bleomycin-polidocanol mini-foam composition (right - complete absence of pathological vascularization).

3.2. Results of the experimental stage of the study

Morphological study of 24 specimens divided into 2 groups depending on the injected drugs was performed: Group I - 3% polidocanol (lauromacrogol 400), Group II - bleomycin-polidocanol mini-foam composition. 12 specimens of external vein of Group I revealed different degrees of plasma impregnation and one case of vessel wall unwinding; the endothelium is preserved in 11

samples. In four specimens a collapsed lumen with "adhered" endothelium was detected. In 8 other samples the lumen was narrowed. In three samples a mixed clot was detected in the vein lumen.

12 specimens of external vein of Group II revealed different degrees of plasma impregnation and vessel wall unwinding; in 3 samples there was a collapsed lumen with "adhered" endothelium, and in the remaining 9 samples there was no endothelium and the vessel's lumen was dilated. There was a mixed clot in venous lumen in one specimen;

Comparative data by groups are presented in Table 2.

Table 2. Compatarive data of the groups

Changes characteristics in the vein	Specimens amount	
	Bleomycin-polidocanol foam composition	Polidocanol (lauromacrogol 400)
Complete absence of endothelium	18	2
Partial absence of endothelium	6	8
Totally preserved endothelium	0	6
"adhered" endothelium	6	8
Vein thrombosis	2	6

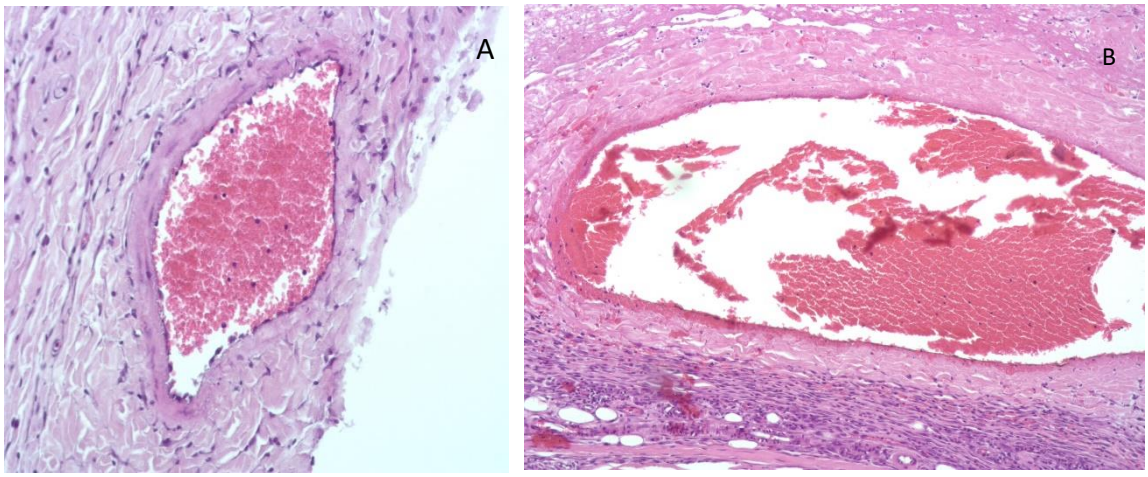

Figure.6. Comparison of external femoral vein specimens after polidocanol 3% (A) and new bleomycin-polidocanol mini-foam composition (B). Hematoxylin and eosin staining, magnification 200x. A – Partially preserved endothelium. B – Complete absence of endothelium

4 Conclusions

Clinical and experimental studies revealed that the proposed method of treatment of children with head and neck venous malformations using the new bleomycin-polidocanol mini-foam composition showed greater efficacy than "foam-form" sclerosing therapy using polidocanol. This method is highly effective, minimally invasive, safe and can be considered as a first-line method in the treatment of children with this pathology.

Author Contributions: Research concept and design - L.V. and O.Z., collecting and processing material - L.V, S.Y and A.M., writing and editing the text - L.V and A.M.

All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

References

1. Dan VN, Sapelkin SV, Goloviuk AL, Timina IE, Losik IA. Transcutaneous laser coagulation in treatment of venous forms of angiodysplasias. Angiol Sosud Khir. 2009; 15(4):62-7. (In Russian)
2. Dan VN, Sapelkin SV, Sharobaro VI, Timina IE, Tsygankov VN, Karmazanovskii GG, Subbotin VV, Vafina GR. Angiodisplazii Golovy I Shei – Sovremennye Printsipy Lecheniya S Ispol''zovaniem Elementov Plasticheskoi Khirurgii. Angiologiya i sosudistaya khirurgiya. 2013; 19(4):136-142. (In Russian)
3. Kenkel J. Vascular anomalies and lymphedema. Select Read Plast Surg. 2010; 126(2):55-69.
4. Rutherford RB. Congenital vascular malformations: diagnostic evaluation. Semin Vasc Surg. 1993; 6:225-232.
5. De Lorimier AA. Sclerotherapy for venous malformations. J Pediatr Surg. 1995; 30(2):188-194.

6. Lowe L. Vascular malformations: Classification and terminology the radiologist need to know. Elsevier, Seminars un Roentgenology. 2012; 7(2):106-117.
7. De Greef C, Flandroy P, Mathurin P et al. Low flow venous malformations in children. Phlebologie. 1992; 45(4):477-481.
8. Blind AM, Vabres P, Carmignac V, Duffourd Y, Mahé A. Malformations veineuse liées à des mutations du gene TEK: illustration d'un continuum Clinique et génétique à partir d'un cas de syndrome de Bean. Annales de Dermatologie et de Vénérélogie. 2017; 144(12):S243-4
9. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: A classification based on endothelial characteristics. Plast. Reconst. Surg. 1982; 69(3):412-420
10. Wassef M, Enjolras O. Superficial vascular malformations: classification and histopathology. Ann Pathol. 1999; 19:253-64.
11. Feied CF, Jackson JJ, Bren TS et al. Allergic reactions to polidocanol for vein sclerosis. Two case reports. J. Dermatol. Surg. Oncol. 1994; 20:466-468.
12. Gomolyako IV. Morphological characteristics of capillary malformations of head and neck. Gomolyako IV, Galich SP, Gindich OA, Ogorodnik YAP Patologiya. 2014; (1). (In Russian).
13. Enjorlas O, Picard A, Soupre V. Congenital haemangiomas and other rare infantile vascular tumours. Ann. Chir. Plast. 2006: 51:339-346.
14. Hennedige A. Sturge-Weber syndrome and dermatomal facial port– wine stains: incidence, association with glaucoma, and pulsed tunable dye laser treatment effectiveness. Plast. Reconstr. Surg. 2008; 121(4):1173-1180.
15. Christoph U. Herborn, Mathias Goyen, Thomas C. Lauenstein, Jörg F. Debatin, Stefan G. Ruehm, Knut Kröger. Comprehensive time-resolved MRI of peripheral vascular malformations . Amer. J. Roentgenol. 2003; 181(3):729-735.
16. Ohnuma T, Holland JF, Masuda H. et al. Microbiological assay of bleomycin: inactivation, tissue distribution, and clearance. Cancer (Philad.) 1974; 33:1230–1238.