Journal of Cranio-Maxillo-Facial Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

MEST: Modified electrosclerotherapy to treat AVM (Extracranial Arterio-venous malformations). Better than BEST☆,☆☆

Giacomo Colletti [a,*,1], Linda Rozell-Shannon [b,1], Riccardo Nocini [c,1]

[a] Cranio-Maxillo-Facial Surgery, SMECHIMAI Department, University of Modena and Reggio Emilia, Modena, Italy
[b] The Vascular Birthmarks Foundation, Latham, NY, USA
[c] Department of Otorhinolaryngology, University of Verona, Verona, Italy

ARTICLE INFO

Keywords:
Arterio venous malformation
AVM
Bleomycin
Electro sclero therapy
Angioma
Hemangioma

ABSTRACT

Arteriovenous Malformations (AVM) can present themselves in an ample clinical spectrum. They worsen over time, creating local complications such as ulceration, destruction, infection, pain, and severe bleeding.

Small focal AVMs can effectively be cured by surgery and/or endovascular techniques, whereas larger ones are of difficult management.

Accordingly, S3 AVMs (according to SECg staging) are particularly troublesome. Here, endovascular treatment is only episodically curative while surgery leads to significant structural and functional damage.

Electrochemotherapy is an established means to manage selected neoplasms. Recently it was successfully used to treat sclerotherapy-resistant or extensive low-flow vascular malformations (electrosclerotherapy, EST).

EST was only anectodically tried with AVMs. A conventional EST is unlikely to effectively have an AVM responding.

We conceived the Modified EST (MEST) protocol and started a pilot study.

Modification of conventional EST was done by administering bleomycin locally, under ultrasound guidance, in the tissues around the nidus. After 8 min, electroporation was started and covered the entire involved area.

MEST was adopted in 10 patients with S3 AVMs of the cervicofacial region.

Most patients received 2 sessions of MEST.

The response was significant, and the patients all had a complete or near-complete reduction in the size of the AVM. Excellent aesthetic results were achieved. On follow-up imaging the AVMs were not detectable.

Side effects were minor and easily managed.

Results were stable.

The results of the present study suggest that MEST may be the treatment of choice in selected AVMs.

However, a longer follow-up is needed to further evaluate the risk of recurrence.

1. Introduction

Arteriovenous Malformations (AVM) are truly challenging diseases. Much is still unknown about them in terms of biology, pathophysiology, diagnostic framing, and treatment protocols (Colletti et al., 2014).

It is almost a given that AVMs tend to behave in a cancer-like manner (Liu et al., 2010).

Most AVMs will present a somatic mutation in genes like MAPK or RAS that, strikingly, are the same involved in some types of cancer (Dekeuleneer et al., 2020).

Although present at birth, they will most typically show signs and symptoms later in life, during puberty or pregnancy.

Their natural course is one of initial quiescence, followed by expansion and then associated with complications, local or systemic (Kohout et al., 1998).

Unwise treatments, like proximal embolization, ligatures, or partial surgery, create a proangiogenic environment that will produce more of the pathophysiologic unit characterizing AVM: Arterio-Venous Shunts. These will cause or worsen hypoxia in the affected tissues (the shunts will "steal" blood from the capillaries). The endpoint is almost

☆ The Authors have no financial disclosures or conflicts of interests to declare.☆☆ No Authors received no fundings.

* Corresponding author.
E-mail address: giacomo.colletti@gmail.com (G. Colletti).

[1] GC, RN and LRS equally contributed to this study.

https://doi.org/10.1016/j.jcms.2025.01.004
Received 21 May 2024; Received in revised form 26 November 2024; Accepted 10 January 2025

invariably a relapse of the disease that will be more aggressive and complicated than the "virgin" one (Liu et al., 2010).

Again, as in oncology, it would be advisable to approach the disease in a vigorous and hopefully curative manner in the first place. This is not always doable, or it is so at the price of dramatic aesthetic or functional impairments.

A rational approach should ideally be guided by staging the disease. Here, the SECg staging system comes in handy (Colletti et al., 2020). (Table 1)

While S1 and S2 AVMs are resectable with safety margins and can therefore be managed straightaway, S3 ones pose a therapeutic dilemma. Is it, in these patients, preferrable to proceed with a probable heavily disfiguring surgery, just wait and follow the patient, or adopt other approaches?

This is the focus of the present research.

Scholars have strived to find alternative methods. Great attention has been given to medical treatment. After finding the responsible genes, several targeted therapies have been introduced in the clinical practice. Specifically, Thalidomide and Trametinib have shown promising results (Queisser et al., 2021). However, they likely stabilize the disease while regression under those drugs seems to be anecdotal. Moreover, the therapeutic regimen is usually chronic, with patients taking the medication for a long time, or indefinitely.

Electroporation is a phenomenon occurring when the cell membrane is temporarily altered by the local application of an electrical pulse. This results in pores formation being created on the cell surface which allows the drugs present locally to enter the cell by passive diffusion (Mir, 2006). When electroporation is combined with an otherwise impermeant or poorly permeant anticancer drug, such as bleomycin, in the oncologic field the treatment is referred to as Electrochemotherapy (ECT) and results in a potent localized cytotoxic effect (Campana et al., 2021; Clover et al., 2020; Sersa et al., 2021). ECT is being increasingly used in the treatment of cutaneous malignancies in patients in whom previous standard of care options were unsuccessful and as a treatment for lesions recalcitrant to chemotherapy or radiotherapy (Clover et al., 2020).

Recently, Electroporation has been used in conjunction with bleomycin (Bleomycin-Electro-Sclero-Therapy, BEST) to treat low flow vascular anomalies with good results (McMorrow et al., 2017; Wohlgemuth et al., 2021).

However, there is no experience with the use of EST in high flow vascular anomalies except for a single case report (Krt et al., 2022).

In another paper the Authors mentioned having treated 3 cases of AVMs, but that was not further explained or presented in the paper (Kostusiak et al., 2022).

EST, as is conventionally used, would be poorly effective with large AVMs which require high local doses of bleomycin.

We have conceived a modified technique of Electro-sclerotherapy (Modified-Electro-Sclero-Therapy, MEST) for larger and complex Extracranial AVMS (the results of which are presented in this paper.

2. Materials and methods

This work was conceived as a pilot study. It can be considered the evolution of simple bleomycin injection in the management of AVM which was previously conducted and published by the Authors (Colletti et al., 2024).

Starting July 2022, 10 patients affected by Head and Neck AVMs have been treated by means of MEST (Modified-Electro-Sclero-Therapy). There were 8 Female and 2 Male Patients. On average, patients were 26.9 years old (range 15–56, see Tables 2 and 3).

Inclusion criteria were:

- AVM staged as S3 according to the SECg staging system regardless of E, C or g
- Volume of the AVM larger than 125cm3 (for example: 5cm × 5cm × 5cm or bigger)
- No contraindications to the use of bleomycin and/or electroporation

Exclusion criteria were.

- AVM staged other than S3 (S1, S2, S4)
- AVM smaller than 125cm3 (these were managed with the bleomycin sandwich protocol according to Colletti et al. (2024))

Seven out of 10 patients had had several previous treatments including embolization, ethanol sclerotherapy, and surgery.

All patients received 1 to 3 sessions of MEST.

3. Technique

As a first step the AVM is mapped with duplex ultrasound. The afferent, efferent vessels and the true nidal areas are identified (Colletti et al., 2022).

Under ultrasound guidance Bleomycin 1000 IU/ml is injected

Table 1
The SECg staging system for arterio venous malformations (Colletti et al., 2020).

S - Surgical	E – Endovascular	C - Clinical	g - growth
S1 One Tissue Involved No Aesthetic or Functional Impairment after Treatment	**E1** Arterio-Venous	**C0** Light to no Symptoms	**g-** AVM stable in the previous 6 months
S2 Two or More Tissues Involved No Aesthetic or Functional Impairment Anticipated after Treatment	**S2** Arteriolo-Venous	**C1** Local Symptoms but no Complications	**g+** AVM worsened in the previous 6 months
S3 Severe Aesthetic or Functional Impairment Anticipated with Treatment	**E3** Arteriolo-Venular	**C2** Local Complications (Hemorrhage, Ulceration, Infection, Pain)	
S4 AVM not Curable Anymore Vital Structures Involved		**C3** Systemic Complications (High Output Hearth Failure)	

Table 2
Patients' cohort.

Patient	Age	Sex	Site	Previous Treatments
S.S.	20	F	Chin	Two Embolizations
A.M.	27	F	Left Hemiface	Sixty-Seven Embolizations; 2 Surgeries
E.E.	25	F	Left Mandible and Soft Tissues	Twenty-Three Embolizations
N.H.	28	M	Left Hemiface	Nine Embolizations, 3 Surgeries, 4 Ethanol Sclerotherapy
F.S.	34	M	Left Forehead and Orbit	None
A.B.	56	F	Left Cheek	None
E.Z.	15	F	Right Mandible and Soft Tissues	Eight Ethanol Sclerotherapies
S.S.	17	F	Right Hemiface	Eleven embolizations, 7 Ethanol Sclerotherapy, 3 Surgeries
A.D.C.	21	F	Right Mandible and Soft Tissues	Two Embolizations, 4 Ethanol Sclerotherapy
L.T.	26	F	Left Zygomatic Soft Tissues	None

Table 3
Details of treatment, response and complications.

Patient	Number of Sessions	Response (%)	Complications
S.S.	2	100	Pigmentation, Retraction, Pain
A.M.	2	80	Retraction, Necrosis, Pain
E.E.	1	95	Pigmentation, Retraction, Pain
N.H.	2	100	Pigmentation, Retraction, Necrosis, Pain
F.S.	3	70	Pigmentation
A.B.	3	100	Pigmentation
E.Z.	2	100	Pigmentation
S.S.	2	90	Pigmentation, Retraction, Pain
A.D.C.	1	100	Retraction, Nerve Injury[a]
L.T.	1	100	None

[a] marginal mandibular branch of the facial nerve.

around the nidus. Not inside the diseased nidal vessels, but around them. The whole pre-mapped area is injected. Electroporation is delayed 7–8 min to allow local diffusion of Bleomycin. Electroporation is administered with Cliniporator. The Cliniporator device (IGEA, Carpi, Mo, Italy) is an electric field generator used to deliver 8 electric pulses of high intensity electric field (1000 V/cm) and short duration (100 μs) to 6 steel AISI needle electrodes inserted into the tissue by means of a handful isolated plastic support. This apparatus formed by the plastic support and the needles is called "finger electrode" as it is a wearable on the finger. In this way a short intense electric field is produced in the volume covered by the needle electrodes, thus giving rise to cell membranes electroporation.

The entire area involved by the AVM is then managed by serial electroporation. This is done meticulously, and no void is left. Caution is taken not to overlap the area of application of the needles.

Significant bleeding after removing the handpiece is expected and managed with peroxide hydrogen-soaked sponges.

In the first 2 patients a total dose of 5000 IU of Bleomycin was injected but the results were only partial. The dose per session was then increased and adjusted to the volume of the AVM to treat.

After the treatment, nurses were told to not remove any patch, EKG ones included, and the patients were asked not to scratch themselves for 7 days.

The study was granted the local IRB approval.

No funding was received at any moment of the trial.

All patients signed a written informed consent before undergoing the procedure.

Specifically, every patient was instructed on the experimental nature of the treatment. Other alternatives such as radical surgery or ethanol sclerotherapy were explained and offered.

There were a few ethical issues that were dealt with.

First, the existence of the above-mentioned gold-standard approaches and what to expect from MEST. We decided to proceed with MEST because the effectiveness of bleomycin, especially as part of a sandwich protocol, was already investigated by the Authors in another study and proved a reliable alternative to more invasive treatments for small S3 AVM (Colletti et al., 2024). The addition of electroporation was deemed as having solid scientific bases as it is already adopted in the management of low-flow vascular malformations.

The second aspect that was considered is the long-term safety profile of bleomycin. We leaned on the literature concerning the use of bleomycin in low-flow malformations once again. All the available data seems to demonstrate that bleomycin is well tolerated if the total dose does not exceed 100000 IU lifelong and if the dose per session is limited to 1 mg/kg and 15000IU (Horbach et al., 2016; Horbach et al., 2016). Specifically, the most feared complication, pulmonary fibrosis, was never reported.

Similarly, there is no data on long-term safety of repeated electroporation in AVM but there is preliminary literature with low flow malformations (Schmidt et al., 2024).

All these aspects were discussed with the patients and females were also instructed to prevent any pregnancy for 12 months after the last treatment.

All patients agreed to the use of their pictures for scientific purposes (publications, presentations, divulgation) in a signed written consent.

4. Follow-up

Each patient was reevaluated 7 days after the procedure and then monthly. Clinical appraisal as well as color-doppler US were used. If, at 3 months follow-up, there was still signs of active AVM, a new session of MEST was carried out. When there was no evidence of residual disease, no further sessions of MEST were done.

Six months and 1 year after the last MEST all patients underwent a CT scan or MRI to objectivate the result.

Results were judged based on residual disease in terms of volume and vessel density.

Patients' satisfaction was assessed based on a questionnaire. Patients were asked: 1) How tolerable was the procedure; 2) how satisfied are you of the result; 3) how do you compare the result to other previous treatments; 4) would you choose to undergo the same treatment again.

Also, aesthetics and functional results were addressed independently by the 3 Authors.

Electroporation and Bleomycin are not approved for use in Vascular Anomalies although significant literature is already available.

5. Results

5.1. Response to treatment

All patients responded to treatment (Figs. 1–10). Six patients had a 100% clearance of the AVM, meaning no clinical or radiological disease was detectable. Two patients had a nearly complete disappearance of the AVM with 90 and 95% of response rate. Two patients showed a 70 and 80% disease reduction respectively.

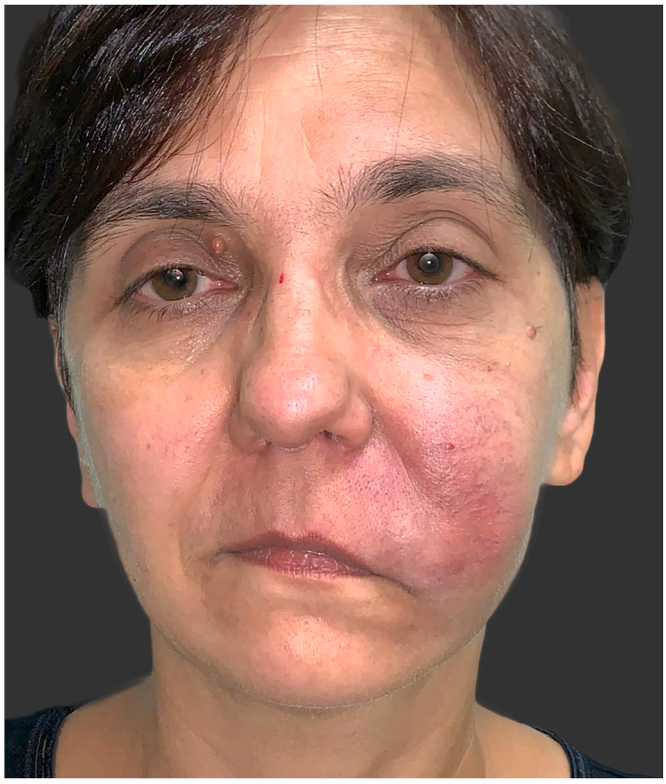

Fig. 1. Patient 1. S3 AVM of the left cheek. Clinical appearance.

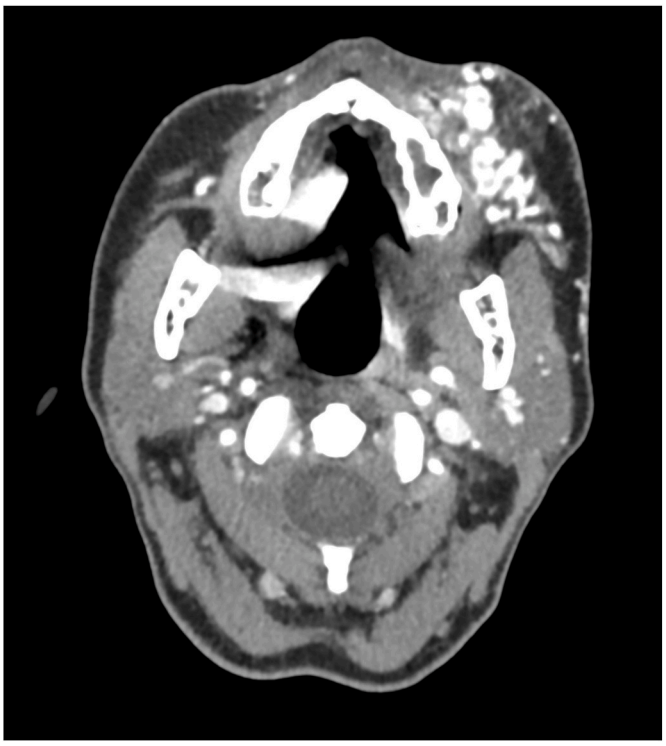

Fig. 2. Patient 1: Contrast Enhanced CT. Axial Scan. Typical aspects of an AVM are evident with a plethora of increased-size vessels running in the left cheek.

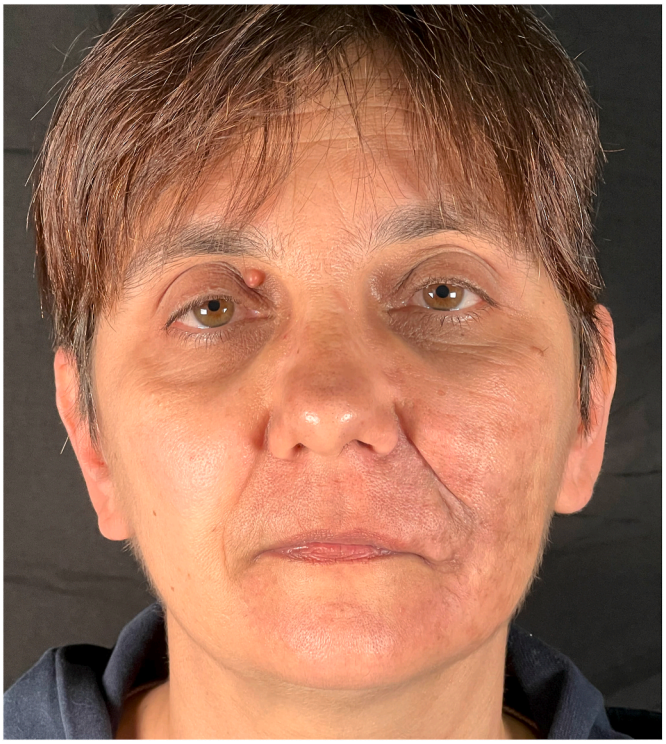

Fig. 3. Patient 1. Clinical picture of the patient after 2 MEST

Aesthetic and functional results are presented in Table 4.

Overall, the aesthetic outcomes were very good, with most cases showing excellent results with normal size and shape in the previously affected areas.

Results stayed stable at the follow up consultations.

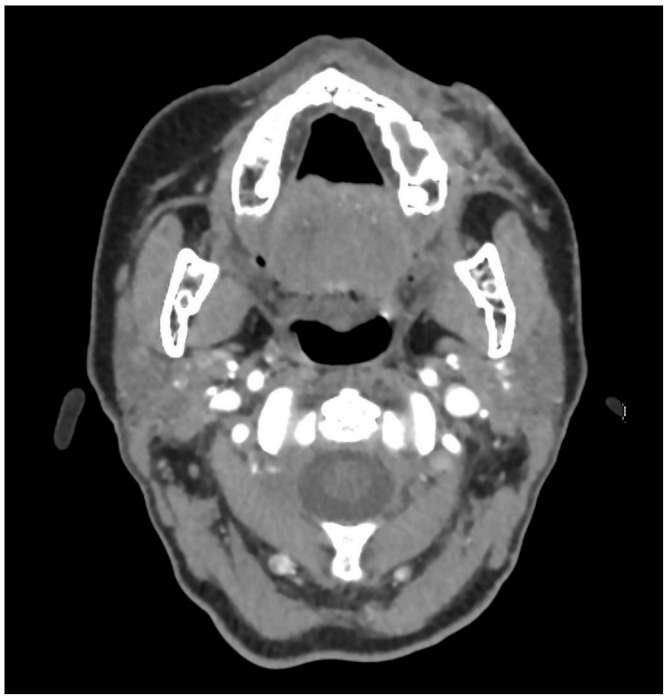

Fig. 4. Patient 1. Post treatment Contrast Enhanced CT. No residues of diseased vessels.

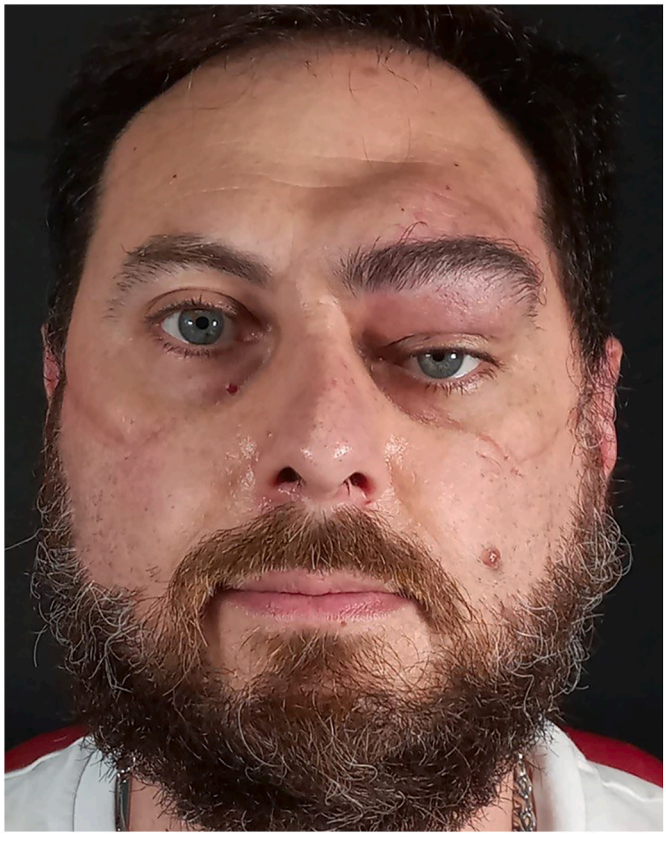

Fig. 5. Patient 2. S3 AVM of the left Frontal-Orbital area.

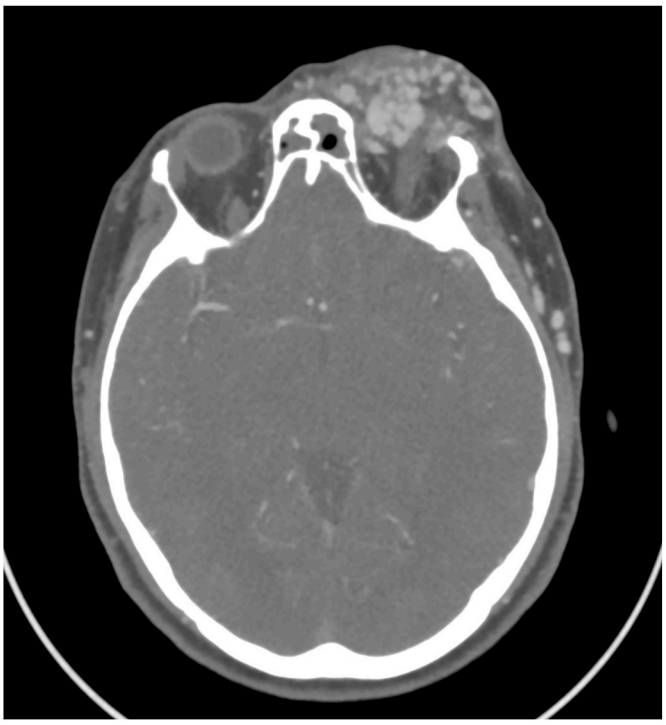

Fig. 6. Patient 2: Contrast Enhanced CT. Axial Scan. A vast tangle of enlarged vessels are involving the frontal and orbital region.

Fig. 7. Patient 2. Post treatment appearance. The AVM disappeared. The eye is still displaced caudally but binocular vision is preserved. Patient refused further morphological corrections.

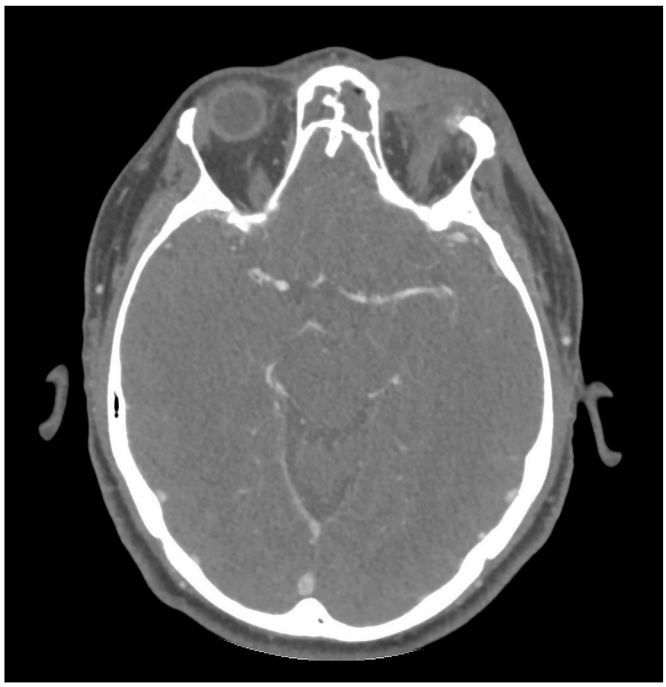

Fig. 8. Patient 2. Post treatment Contrast Enhanced CT. No residual disease.

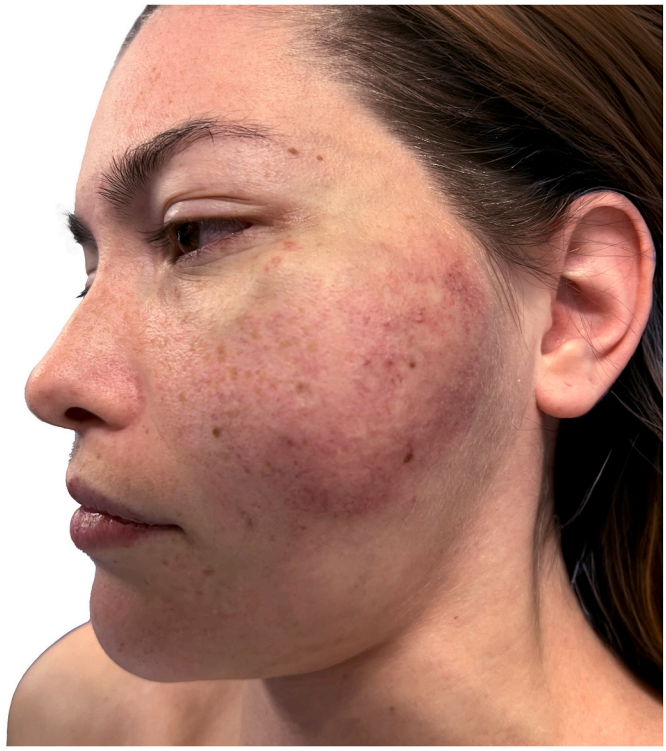

Fig. 9. Patient 3. S3 AVM of the left zygomatic area. Pre treatment.

5.2. Complications

Immediately after treatment there always was severe swelling. It disappeared spontaneously in 2–3 weeks.

Some of the complications weren't really complications. We have observed pigmentation in the treated skin in all but 3 patients. Pigmentation is a known side effect of bleomycin and is therefore almost expected in MEST where bleomycin is injected locally while in the same

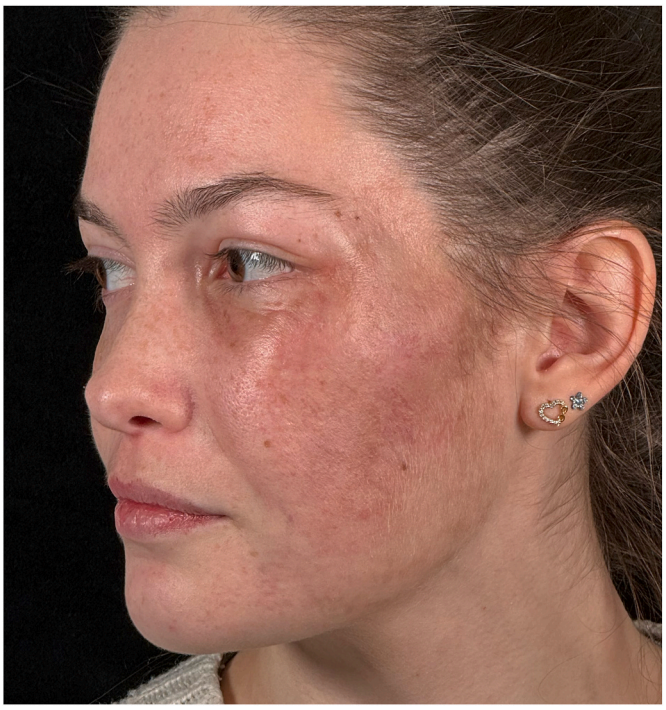

Fig. 10. Patient 3: Clinical appearance after 1 session of MEST.

area the trauma from the needle insertion occurs. Similarly, 7 out of 10 patients showed a form of light indentation which corresponds to the area of insertion of the electroporator's needles.

Four patients experienced severe pain. This, of note, had an atypical presentation. It wasn't present immediately after the procedure. It appeared 7–10 days after, and it was intermittent. On the visual analogue scale, patients reported to episodically reach a value of 9. It responded to common painkillers and receded after 2–3 weeks.

Interestingly, all patients that had severe pain had received previous embolizations.

5.3. Patient satisfaction

All patients were extremely satisfied with the procedure.

Patients declared that the procedure was tolerable but burdensome. They complained especially about the severe swelling that took place after the procedure and that lasted up to 15 days.

All patients were totally satisfied by the outcomes.

Patients that had previous treatments before declared that MEST was significantly more effective than embolization.

All patients stated that they would have preferred MEST instead of other procedures as their first choice.

6. Discussion

Treatment of Head and Neck AVMs is still very challenging (Rosenberg et al., 2018).

Often a therapeutic regimen is planned based on the center's philosophy, preferences, and experience (Jia et al., 2023).

In our view, based on the experience on more than 300 cases of head and neck AVMs, treatment should be based on a deep knowledge of the pathophysiology of the disease and decided only after the AVM has been staged.

Staging, in particular, is utterly useful to route the patient to the best approach.

Based on the SECg staging, S1 or S2 AVMs can be effectively resected with a very high chance of cure with surgery. This needs to be radical, and intraoperative US guidance is highly commendable (Colletti et al., 2022).

Table 4
Aesthetic and functional outcomes.

Patient	Pre-Treatment Issues	Aesthetic Outcome	Functional Result
S.S.	- Lower Lip Bulkiness - Periodic Bleeding	Excellent - Normal Lower Lip Shape and Volume	- Normal Lower Lip Function - No Further Bleedings
A.M.	- Left Hemiface Bulkiness - Frequent Severe Bleeds	Moderate - Significant (80%) Reduction in Size - Visible Retraction of the Upper Lip and Lower Lid	- Significant Reduction in number and entity of bleedings
E.E.	- Left Lower Third of Face - Swelling - Gingival Bleedings - Pain	Very Good - Smaller in Volume as compared to Contralateral	- No Further Gingival Bleeds - No Pain
N.H.	- Left Third of Face Bulkiness - Nose Bleeds	Very Good - Normal Volume and Shape - Minor Retraction in Naso-Labial Area	- No Further Bleeds
F.S.	- Upper Eyelid Bulkiness - Eye Dystopia - Redness - Disturbing Pulsations	Very Good - No Residual Bulk - Reduced Eye Dystopia	- No Residual Pulsations
A.B.	- Left Middle Third of the Face Bulkiness - Redness	Excellent - Normal Volume and Shape - No Redness	- No Pre-Treatment Disturbances
E.Z.	- Right Middle and Lower Third Bulkiness - Visible Venous Varices	Excellent - Normal Volume - No Residual Varices	- No Pre-Treatment Disturbances
S.S.	- Right Hemiface Bony Hypertrophy and Soft Tissues Excess - Redness - Pulsating Tinnitus	Moderate - Reduction in Size - Reduced Redness - Persistent Minor Lower Eyelid Edema	- Tinnitus Only Occasionally Perceived
A.D.C.	- Right Lower Third Bulkiness - Redness - Pain	Very Good - Normal Volume and Shape - No Redness - Marginal Madibular Nerve Weakness	No Pain
L.T.	Left Zygomatic Bulkiness Redness	Excellent - Normal Volume - No Redness	No Pre-Treatment Disturbances

S3 AVM on the other hand, involve critical anatomical areas. Surgically removing those is doable, but disfigurement or severe functional sequalae are the rule rather than the exception (Richter and Suen, 2010).

In these patients a more conservative approach may be preferrable.

Embolization doesn't seem to be a mutually agreed upon choice. Although very effective in filling up the AVM - thus vastly reducing symptoms in the short-term, the proangiogenic effect it produces almost always results in a relapse (Buell et al., 2014). That is often worse and much less manageable than the original disease.

The same holds true for partial surgery, which leaves behind part of the AVM that will respond with significant expansion. Local complications will eventually take place.

Ethanol sclerotherapy for AVMs has the potential to cure (Lee et al., 2013). However, this is a technique where the therapeutic index is utterly narrow and severe complications can happen, fatality included (YANG et al., 2021). Moreover, several sessions are needed to obtain the

desired effectiveness.

In the pursuit of a better management for S3 AVMs other approaches have been tried.

Medications have been introduced in the clinical practice for non-otherwise treatable AVMs. Thalidomide and Trametinib (Dekeuleneer et al., 2020; Edwards et al., 2020) have proved effective in terms of relief from symptom such as pain and ulceration.

In our view, given the potentially significant side effects of such drugs and the need for long or life-long treatments, this regime is better suited for S4 AVMs (Colletti et al., 2015).

Jin et al. published a pilot study where small AVMs were well managed with a course of interstitial injections of bleomycin (Jin et al., 2018).

We adopt the same strategy in similar cases (Colletti et al., 2024).

However, bleomycin alone is insufficient to destroy larger AVMs as per our previous experience.

Electrochemotherapy was introduced in the clinical practice to treat neoplasms in patients where a conventional surgical removal is contraindicated or not advisable.

This is now a well-established option in such instances.

More recently, electrosclerotherapy was introduced to manage low-flow vascular malformations. Here it has proven effective, and in our practice, we use it in large venous and lymphatic malformations where sclerotherapy only led to partial results or surgery is not indicated.

Electrosclerotherapy for AVMs was previously reported in a single patient by Krt et al., in 2022 (Krt et al., 2022). The Authors used it to treat a small-sized AVM of the lip. They administered the bleomycin intraarterially after reducing the flow with a balloon catheter. Necrosis and infection affected the area, and the patient had to be managed with repeated debridements and necrosectomies. We judge the result as a good one, although in the clinical photograph a small AVM remnant seems to be there. However, this may just be our impression.

Kostusiak et al. published a case series of 30 patients treated with EST. Of these, 3 were AVMs. It is impossible to extract data from this paper because, aside from mentioning those cases, no further detail is described nor presented. This is unfortunate, since all other data in the paper is very detailed.

The here-described technique is philosophically and technically different from the previously mentioned ones.

The cohort is based on patients with large S3 AVMs. The choice of MEST was based on considerations described in a previous paper (Colletti et al., 2020). We chose to not administer bleomycin intra-arterially because the angioarchitecture of the AVMs was too vast and complex to fill one with sufficient indwelling time. Based on our experience, intralesional extravascular administration of bleomycin is already effective and sufficient to treat small AVMs (Colletti et al., paper under review), so we decided to opt again for interstitial administrations. However, bleomycin cannot be given in doses exceeding 15000 IU per session and should not reach a life-long total dose greater than 250000 IU.

So, bleomycin in that dose, alone, wouldn't be sufficient for extensive AVMs or it would require too high doses as per our previous experience.

MEST is different from BEST.

In MEST there is a pre-treatment duplex-US mapping of the AVM architecture. The nidus is identified, and the injection is only done around the vessels and not into it (this is a fundamental difference with usual BEST). The dose of bleomycin is always the maximum allowed per session (i.e. 15000 IU) while in BEST, it is determined by oncologists using the algorithms used in oncology. The whole area is covered entirely, and no void is left in-between the different electrode insertions. On the contrary, one of the principles described by the Authors for BEST is that no dense electroporation is needed in Vascular Malformations (Muir et al., 2023). The opposite is true, and the sites of electroporation are distant up to 3 cm (Schmidt et al., 2024).In this sense, MEST is more similar to Electro-Chemo-Therapy.

The technical variations are enough to consider MEST a proper significant modification of the usual BEST technique.

Electroporation works (among other effects) by increasing cell membrane permeability. It increases the effectiveness by roughly 400 times (up to 700 times in vitro)(Orlowski et al., n.d.).

With MEST the already observable effectiveness of bleomycin is amplified and thus a larger volume can be treated.

It is worth noting that the alternatives to treat this cohort of patients would have been either only partially successfully or severely affecting esthetics and function.

This study has a few weaknesses.

The sample is rather small in absolute terms. However, considering the scarcity of the numbers in the literature, this case series allows for some inference.

More importantly, the follow up is not so long as it is advisable for definitive judgement. A 5-years follow up is desirable when dealing with AVMs since relapses are possible up to that time and beyond it. However, most AVMs relapses will happen in 12–18 months according to the literature and as a result, again, the data presented here seems to be significant.

7. Conclusions

In selected cases of vast S3 AVMs of the head and neck, Modified Electro Sclero Therapy (MEST) showed promising results in this pilot study. It may be considered preferrable to other less radical or more invasive approaches in similar instances. However, larger samples and longer follow-up are needed.

References

Buell, T.J., Ding, D., Starke, R.M., Crowley, R.W., Liu, K.C., 2014. Embolization-induced angiogenesis in cerebral arteriovenous malformations. J. Clin. Neurosci. 21 (11), 1866–1871. https://doi.org/10.1016/j.jocn.2014.04.010.

Campana, L.G., Peric, B., Mascherini, M., Spina, R., Kunte, C., Kis, E., Rozsa, P., Quaglino, P., Jones, R.P., Clover, A.J.P., Curatolo, P., Giorgione, R., Cemazar, M., de Terlizzi, F., Bosnjak, M., Sersa, G., 2021. Combination of pembrolizumab with electrochemotherapy in cutaneous metastases from melanoma: a comparative retrospective study from the inspect and slovenian cancer registry. Cancers 13 (17). https://doi.org/10.3390/cancers13174289.

Clover, A.J.P., de Terlizzi, F., Bertino, G., Curatolo, P., Odili, J., Campana, L.G., Kunte, C., Muir, T., Brizio, M., Sersa, G., Pritchard Jones, R., Moir, G., Orlando, A., Banerjee, S.M., Kis, E., McCaul, J.A., Grischke, E.M., Matteucci, P., Mowatt, D., et al., 2020. Electrochemotherapy in the treatment of cutaneous malignancy: outcomes and subgroup analysis from the cumulative results from the pan-European International Network for Sharing Practice in Electrochemotherapy database for 2482 lesions in 987 patients (2008–2019). European Journal of Cancer 138, 30–40. https://doi.org/10.1016/j.ejca.2020.06.020.

Colletti, G., Biglioli, F., Ierardi, A.M., Dessy, M., Tombris, S., Mattassi, R., Stillo, F., Dionisio, A., Rozell-Shannon, L., Carrafiello, G., Waner, M., 2020. SECg staging system: a new approach to the management of arteriovenous malformations of the head and neck. J. Craniofac. Surg. 31 (4), E420–E424. https://doi.org/10.1097/SCS.0000000000006446.

Colletti, G., Dalmonte, P., Moneghini, L., Ferrari, D., Allevi, F., 2015. Adjuvant role of anti-angiogenic drugs in the management of head and neck arteriovenous malformations. Med. Hypotheses 85 (3), 298–302. https://doi.org/10.1016/j.mehy.2015.05.016.

Colletti, G., Nocini, R., Rozell-Shannon, L., Chiarini, L., Anesi, A., Dessy, M., 2022. Intraoperative ultrasound-guided resection for extracranial arteriovenous malformations of the head and neck. Journal of Vascular Anomalies 3 (4), e056. https://doi.org/10.1097/jova.0000000000000056.

Colletti, G., Trotolo, A., Sanna, G., Negrello, S., Anesi, A., Chiarini, L., Rozell-Shannon, L., Nocini, R., 2024. Surgical treatment of small-sized S3 arterio-venous malformations with neo-adjuvant and adjuvant bleomycin. J. Cranio-Maxillofacial Surg. https://doi.org/10.1016/j.jcms.2024.08.003.

Colletti, G., Valassina, D., Bertossi, D., Melchiorre, F., Vercellio, G., Brusati, R., 2014. Contemporary management of vascular malformations. J. Oral Maxillofac. Surg. 72 (3). https://doi.org/10.1016/j.joms.2013.08.008.

Dekeuleneer, V., Seront, E., Van Damme, A., Boon, L.M., Vikkula, M., 2020. Theranostic advances in vascular malformations. J. Invest. Dermatol. 140 (4), 756–763. https://doi.org/10.1016/j.jid.2019.10.001.

Edwards, E.A., Phelps, A.S., Cooke, D., Frieden, I.J., Zapala, M.A., Fullerton, H.J., Shimano, K.A., 2020. Monitoring arteriovenous malformation response to genotype-targeted therapy. Pediatrics 146 (3). https://doi.org/10.1542/PEDS.2019-3206.

Horbach, S.E.R., Lokhorst, M.M., Saeed, P., De Goüyon Matignon De Pontouraude, C.M.F., Rothová, A., Van Der Horst, C.M.A.M., 2016a. Sclerotherapy for low-flow vascular malformations of the head and neck: a systematic review of sclerosing

agents. J. Plast. Reconstr. Aesthetic Surg. 69 (3), 295–304. https://doi.org/10.1016/j.bjps.2015.10.045. Churchill Livingstone.

Horbach, S.E.R., Rigter, I.M., Smitt, J.H.S., Reekers, J.A., Spuls, P.I., Van Der Horst, C.M. A.M., 2016b. Intralesional bleomycin injections for vascular malformations: a systematic review and meta-analysis. Plast. Reconstr. Surg. 137 (1), 244–256. https://doi.org/10.1097/PRS.0000000000001924. Lippincott Williams and Wilkins.

Jia, H., Chen, Y., Yang, X., Lee, Y., Zou, Y., Zhou, J., Jin, Y., Hua, C., Lin, X., 2023. Treatment of challenging extracranial arteriovenous malformations: a single-center experience and literature review. Ann. Plast. Surg. 90 (5), S177–S182. https://doi.org/10.1097/SAP.0000000000003375.

Jin, Y., Zou, Y., Hua, C., Chen, H., Yang, X., Ma, G., Chang, L., Qiu, Y., Lyu, D., Wang, T., Chang, S.J., Qiao, C., Luo, C., Tremp, M., Lin, X., 2018. Treatment of early-stage extracranial arteriovenous malformations with intralesional interstitial bleomycin injection: a pilot study. Radiology 287 (1), 194–204. https://doi.org/10.1148/radiol.2017162076.

Kohout, M.P., Hansen, M., Pribaz, J.J., Mulliken, J.B., 1998. Arteriovenous malformations of the head and neck: natural history and management. Plast. Reconstr. Surg. 102 (3), 643–654. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=9727427&retmode=ref&cmd=prlinks.

Kostusiak, M., Murugan, S., Muir, T., 2022. Bleomycin electrosclerotherapy treatment in the management of vascular malformations. Dermatol. Surg. 48 (1), 67–71. https://doi.org/10.1097/DSS.0000000000003220.

Krt, A., Cemazar, M., Lovric, D., Sersa, G., Jamsek, C., Groselj, A., 2022. Combining superselective catheterization and electrochemotherapy: a new technological approach to the treatment of high-flow head and neck vascular malformations. Front. Oncol. 12. https://doi.org/10.3389/fonc.2022.1025270.

Lee, B.B., Baumgartner, I., Berlien, H.P., Bianchini, G., Burrows, P., Do, Y.S., Ivancev, K., Kool, L.S., Laredo, J., Loose, D.A., Lopez Gutierrez, J.C., Mattassi, R., Parsi, K., Rimon, U., Rosenblatt, M., Shortell, C., Simkin, R., Stillo, F., Villavicencio, L., et al., 2013. Consensus document of the international union of angiology (IUA)-2013. Current concept on the management of arterio-venous management. Int. Angiol. : a journal of the International Union of Angiology 32 (Issue 1), 9–36. http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23435389&retmode=ref&cmd=prlinks.

Liu, A.S., Mulliken, J.B., Zurakowski, D., Fishman, S.J., Greene, A.K., 2010. Extracranial arteriovenous malformations: natural progression and recurrenceafter treatment. Plast. Reconstr. Surg. 125 (4), 1185–1194. https://doi.org/10.1097/PRS.0b013e3181d18070.

McMorrow, L., Shaikh, M., Kessell, G., Muir, T., 2017. Bleomycin electrosclerotherapy: new treatment to manage vascular malformations. Br. J. Oral Maxillofac. Surg. 55 (9), 977–979. https://doi.org/10.1016/j.bjoms.2017.10.002.

Mir, L.M., 2006. Bases and rationale of the electrochemotherapy. European Journal of Cancer, Supplement 4 (11), 38–44. https://doi.org/10.1016/j.ejcsup.2006.08.005.

Muir, T., Bertino, G., Groselj, A., Ratnam, L., Kis, E., Odili, J., McCafferty, I., Wohlgemuth, W.A., Cemazar, M., Krt, A., Bosnjak, M., Zanasi, A., Battista, M., De Terlizzi, F., Campana, L.G., Sersa, G., 2023. Bleomycin electrosclerotherapy (BEST) for the treatment of vascular malformations. An International Network for Sharing Practices on Electrochemotherapy (InspECT) study group report. Radiol. Oncol. 57 (2), 141–149. https://doi.org/10.2478/raon-2023-0029. Sciendo.

Orlowski, S., Belehradek, J., Paoletti, C., & Mirt$, L. M. (n.d.). Transient electropermeabilization of cells in culture increase of the cytotoxicity of anticancer drugs. In Biochem. Pharmacol. (Vol. 37, Issue 24).

Queisser, A., Seront, E., Boon, L.M., Vikkula, M., 2021. Genetic basis and therapies for vascular anomalies. Circ. Res. 129 (1), 155–173. https://doi.org/10.1161/CIRCRESAHA.121.318145. Lippincott Williams and Wilkins.

Richter, G.T., Suen, J.Y., 2010. Clinical course of arteriovenous malformations of the head and neck: a case series. Otolaryngol. Head Neck Surg. 142 (2), 184–190. http://oto.sagepub.com/lookup/doi/10.1016/j.otohns.2009.10.023.

Rosenberg, T.L., Suen, J.Y., Richter, G.T., 2018. Arteriovenous malformations of the head and neck. Otolaryngol. Clin. 51 (1), 185–195. https://doi.org/10.1016/j.otc.2017.09.005. W.B. Saunders.

Schmidt, V.F., Cangir, Ö., Meyer, L., Goldann, C., Hengst, S., Brill, R., von der Heydt, S., Waner, M., Puhr-Westerheide, D., Öcal, O., Ümütlü, M.R., Mansour, N., Rudolph, J., Sint, A., Obereisenbuchner, F., Häberle, B., Ricke, J., Seidensticker, M., Wohlgemuth, W.A., Wildgruber, M., 2024. Outcome of bleomycin electrosclerotherapy of slow-flow malformations in adults and children. Eur. Radiol. 34 (10), 6425–6434. https://doi.org/10.1007/s00330-024-10723-6.

Sersa, G., Mascherini, M., Di Prata, C., Odili, J., de Terlizzi, F., McKenzie, G.A.G., Clover, A.J.P., Bertino, G., Spina, R., Groselj, A., Cappellesso, R., Gehl, J., Bisase, B., Curatolo, P., Kis, E., Lico, V., Muir, T., Orlando, A., Quaglino, P., et al., 2021. Outcomes of older adults aged 90 and over with cutaneous malignancies after electrochemotherapy with bleomycin: a matched cohort analysis from the InspECT registry. Eur. J. Surg. Oncol. 47 (4), 902–912. https://doi.org/10.1016/j.ejso.2020.10.037.

Wohlgemuth, W.A., Müller-Wille, R., Meyer, L., Wildgruber, M., Guntau, M., Heydt, S. von der, Pech, M., Zanasi, A., Flöther, L., Brill, R., 2021. Bleomycin electrosclerotherapy in therapy-resistant venous malformations of the body. J. Vasc. Surg.: Venous and Lymphatic Disorders 9 (3), 731–739. https://doi.org/10.1016/j.jvsv.2020.09.009.

Yang, X., Hua, C., Chen, H., Luo, L., Ma, G., Hu, X., Qiu, Y., Yu, W., Chang, L., Jin, Y., Lin, X., 2021. Systemic hemodynamic changes in low-dose ethanol embolotherapy for soft-tissue arteriovenous malformations. Chinese Journal of Plastic and Reconstructive Surgery 3 (1), 32–40. https://doi.org/10.1016/S2096-6911(21)00076-5.