Complications After Treatment of Head and Neck Venous Malformations With Sodium Tetradecyl Sulfate Foam

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Purpose: The aim of this study was to evaluate complications in patients with head and neck venous malformations (VMs) treated with foam sclerotherapy using sodium tetradecyl sulfate (STS).
Methods: The authors retrospectively evaluated the complications, pain. and degree of satisfaction in 69 consecutive patients affected by cervicofacial VM managed with STS using the Tessari method in a single institution.
Results: The average number of procedures for each patient was 2.1. The most frequent complication was blistering. We observed 1 patient of temporary weakness of a facial nerve branch, 1 paradoxical embolism, and 1 orbital compartment syndrome.

The average pain score was 0 (no pain at all) (51.5%). There was no statistically significant correlation between patient satisfaction and the presence of complications or the degree of pain.
Conclusions: Sclerotherapy with STS is an effective treatment that yields to very high patient satisfaction. This procedure has an overall low complication rate and is usually effective within a few sessions. However, severe complications may occur; these must be pointed out in the informed consent and the surgeon must be aware of and ready to quickly treat them to prevent long-term sequelae.

Key Words: complication, endovascular, sclerotherapy, sodium tetradecyl sulfate, vascular malformation, venous malformation

Vascular malformations are developmental abnormalities of the vascular tree present from birth. They are classified based on the vessel type (capillary, venous, lymphatic, and arteriovenous) or on their rheologic characteristics (slow-flow or fast-flow).[1] Venous malformations (VMs) are the most common vascular malformation, and their treatment remains very challenging.[2] Forty percent to 60% of all VMs involve the head and neck area. Symptoms may vary and include cosmetic complaints, pain, swelling, and functional limitations. Frequently, localized intravascular coagulopathy[3–5] can take place in larger VMs and will worsen signs and symptoms. In more "benign" patients, symptoms can be so mild that no treatment is needed, with the exception of conservative measures; in other patient, symptoms are so severe that >1 treatment can be needed and the approach has to be increasingly invasive.[6–8]

There are several options to treat VMs and these include sclerotherapy, surgery, or laser.[9] Overall, many descriptive studies are present in the literature regarding sclerotherapy. However, most focus on technical procedural aspects or short-term results only. The conclusion in many articles is that VMs are difficult to treat and that most patients require multiple therapeutic sessions before a clinically relevant effect is obtained.

Many sclerosants such as ethanol, jellified ethanol, bleomycin, polidocanol, or sodium tetradecyl sulfate (STS) are available, and they show an effectiveness of 74%, 89%, 88%, 90%, and 86%, respectively, according to a recent analysis.[6]

Ethanol is one of the most commonly used, and is a potent agent for all types of vascular malformations. It provokes a denudation of the intima layer by causing the death of endothelium. This distress produces an immediate coagulation and thrombosis that can lead to complete obliteration of vessel lumen. Differently from other sclerosants, ethanol sclerotherapy is affected by a very low rate of recanalization, which reflects a good long-term outcome. However, ethanol is hampered by major side effect, such as relevant skin, mucosal or muscle necrosis, nerve injury, and systemic complications including pulmonary hypertension, cardiovascular collapse, and death [10–12] Instead, sclerotherapy with other milder sclerosing agents is recognized as a "safer" technique. Being much less painful, it can also be performed under local anaesthesia (ethanol invariably requires general anaesthesia), in an outpatient setting. From a cost/benefit ratio point of view, the drug of choice seems to be STS.[6]

The aim of this study is to analyze the complications occurred on 69 consecutive patients with head and neck venous malformations that were treated with endovascular injection of STS with the Tessari method.[13]

MATERIALS AND METHODS

We retrospectively reviewed medical records and imaging of patients diagnosed as having VM and treated with STS sclerotherapy during the period 2011 through 2015 in a single institution. Being this a retrospective study, an institutional review board was not required. VMs were diagnosed with clinical examination and trough imaging techniques (ultrasound and magnetic resonance imaging). Inclusion criteria were: a diagnosis of head and neck VM; having received sclerotherapy to treat the VM; having used STS as a sclerosant. Exclusion criteria were: the VM being in a region different from the head and neck; the VM being treated with means other than sclerotherapy (surgery, laser); having used a sclerosant other than STS. Sixty-nine patients were enrolled (average age 34). Overall, a total of 148 sessions (average: 2.1, range: 1–6) of sclerotherapy were performed. Sclerotherapy was performed with STS adhering to the Tessari method. In detail, 0.5 to 15 mL of sclerosant was injected as foam with air in a 1:2 to 1:3 ratio. The clinical records of all 69 patients were reviewed to collect data to investigate whether a complication occurred and, if so, what kind. Then all 69 patients were contacted for a telephone interview. However, only 66 responded. In this latter, we investigated any residual sequelae and the degree of patient satisfaction. The patients were asked whether they considered the result good enough and whether he or she would accept to undergo the same procedure again.

Univariate analyses were performed to determinate the incidence of complications after sclerotherapy, the association between the number of treatments, the type of complications occurred, and

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the patients' satisfaction. Chi-squared test was performed to find out correlation between type of complication and patients' satisfaction. We used Linear Regression Model to validate our results. All statistical analyses were performed using SPSS software version 20.0 (IBM Corp, Armonk, NY).

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

RESULTS

Number of Procedures

Thirty-three (47.8%) patients underwent 1 procedure, 12 (17.4%) underwent 2 procedures, 13 (18.8%) underwent 3 procedures, 5 (7.3%) underwent 4 procedures, 4 (5.8%) underwent 5 procedures, and 2 (2.9) underwent 6 procedures.

Complications

Frequent Complications

Of the 69 patients, 25 (36.2%) had blistering (Fig. 1), 11 (15.9%) patients had minor ulceration (Fig. 2), and 8 (11.6%) had minor bleeding on the site of the procedure. Sixteen (23.2%) patients had limited movements (facial expression or mouth opening) owing to oedema. Sixty-six patients responded to the phone interview. In a scale factor from 0 to 5, 34 (51.5%) patients declared that the pain was 0, 11 (16,7%) patients declared that the pain was 2, 4 (6,1%) patients declared that the pain was 3, 9 (13,6%) patients declared that the pain was 4, and 7 (10.6) patients declared that the pain was 5. None of them declared that the pain was 1.

Rare Complications

One patient (1.5% of patients, 0.6% of procedures) had a temporary palsy of a buccal branch of the facial nerve (Fig. 3), completely resolved after 6 months. This patient was treated for a VM of the right masseter muscle (Fig. 4) with 1 cc of STS. One patient (1.5% of patients, 0.6% of procedures) had a paradoxical embolism, allowed by a patent foramen ovale. The patient presented dysarthria and dysmetria, which resolved in few weeks. She was treated with 10 cc of STS for a large cervicofacial VM. A detailed description of this case was published previously.[14] One patient (1.5% of patients, 0.6% of procedures) had an orbital compartment syndrome. This patient was treated with 10 cc of STS for a VM occupying the right cheek, upper and lower lip, the hard and soft palate, and the pharynx (Fig. 5). During the procedure, under fluoroscopic guidance, a very small amount of sclerosant appeared to "leak" into the orbital fraction of the VM. The procedure was

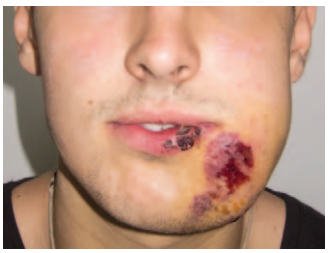

FIGURE 1. Very typical blistering occurring after foam sclerotherapy of left chin-cheek venous malformation.

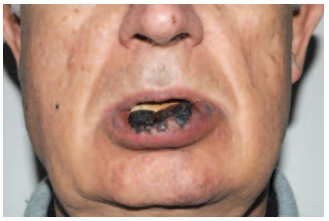

FIGURE 2. Mucosal necrosis of the lower lip few days after treatment of a venous malformation infiltrating the mucosa.

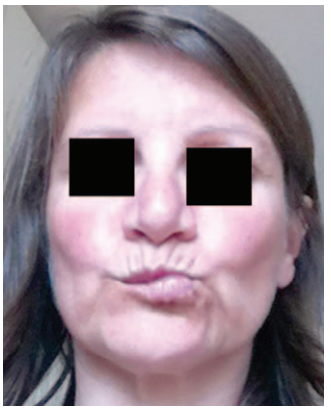

FIGURE 3. Transient paresis of a buccal branch of the right facial nerve after treatment of a venous malformation of the right masseter muscle.

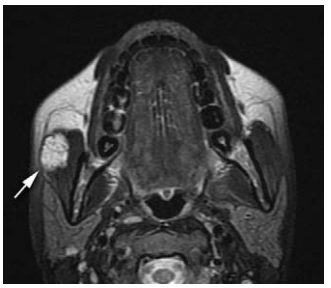

FIGURE 4. Magnetic resonance imagong of patient depicted in Fig. 3 showing a venous malformation within the lateral margin of the right masseter muscle (arrow).

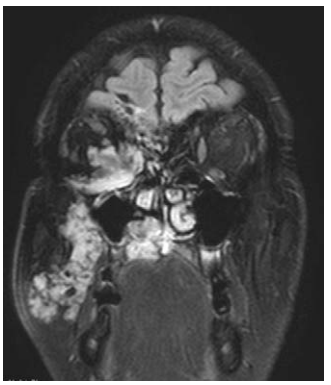

FIGURE 5. Preoperative magnetic resonance imaging of a vast venous malformation of the right face involving the cheek, the palate and the orbit.

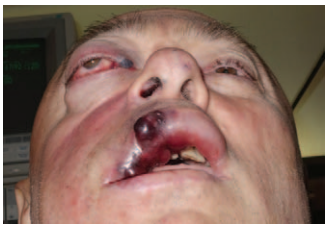

FIGURE 6. Twenty minutes after injecting the sclerosant, a right compartment syndrome took place. Note the severe proptosis of the right eye.

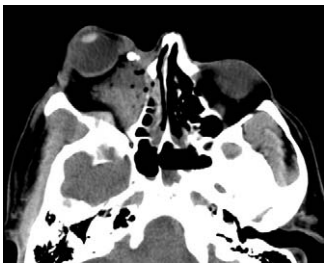

FIGURE 7. Computed tomography scan of the patient depicted in Fig. 6. Note the proptosis of the right eye and the presence, within the right orbit, of gas bubbles testifying the leakage of foam sclerosant in the orbital fraction of the venous malformation.

immediately interrupted at this point. However, in the observation room, 20 minutes after the procedure, the swelling progressively increased (Figs. 6 and 7). A bolus with 40-mg dexamethasone did not stop the event. For this reason, the patient underwent a bedside canthotomy and cantholysis (Fig. 8) and then, under general anaesthesia, a decompression by means of a lateral orbital wall osteotomy was performed (Fig. 9). Visual acuity was preserved. Ten days after, the patient was operated on again and the bony wall was repositioned and stabilized with titanium plates and screws. There was no procedure-related mortality (Fig. 10).

Patient Satisfaction

Fifty-two (78.8%) patients declared that they have reached the desired result and that they would undergo another similar procedure, stressing the high satisfaction rate. There was no correlation between the satisfaction and the type or the severity of the complication ($P = 0.336$) or the pain level ($P = 0.245$).

DISCUSSION

There is a general agreement on the fact that sclerotherapy should be the first-line treatment for clinically relevant VMs.[15] Many different sclerosants have been used for this purpose. A systematic analysis on different available sclerosants is beyond the scope of this article. Ethanol is known as the most powerful sclerosing agent and it has been considered the criterion standard for years. It possesses the highest endothelial-cydal effectiveness and it causes a complete thrombosis of the vessel lumen. However, ethanol is also known for causing a high rate of major complications such as skin or subcutaneous tissue breakdown, nerve damage, muscle necrosis, and systemic complications including pulmonary hypertension, cardiovascular collapse, and death.[10] Moreover, severe pain is perceived by the patient during injection of pure ethanol. For this reason, sclerotherapy with ethanol requires general anesthesia with constant vital signs monitoring and should be performed only in centers with very high professional expertise. Some authors recommend 24 hours of intensive care unit monitoring after a session of ethanol sclerotherapy.[16] The use of ethanol for sclerotherapy may however be preferred in some centers owing to its lower cost and availability.[17] Still, the rate of disease recurrence seems to be the lowest among sclerosing agents.[18,19] However, sclerotherapy performed with STS has a much lower rate of complications, but could be less effective and more treatment session could be needed.[20] Sclerotherapy with STS can be performed safely on an outpatient basis. STS can be used both as a pure liquid sclerosant or as a foam with air with the Tessari method.[13] Van der Vleuten et al[6] assert that the choice of treatment (between sclerotherapy, surgery and laser therapy) is a shared decision between the patient and a multidisciplinary treatment group and that, from a cost perspective, sclerotherapy with STS should be the treatment of choice. Sclerotherapy should be in any case the first-line treatment.[15,21]

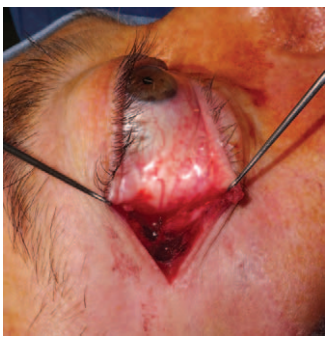

FIGURE 8. Bedside canthotomy and cantholysis.

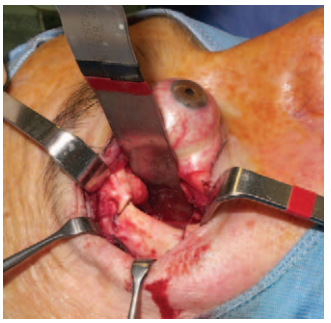

FIGURE 9. Lateral orbital wall osteotomy and lateral displacement to decompress the orbit.

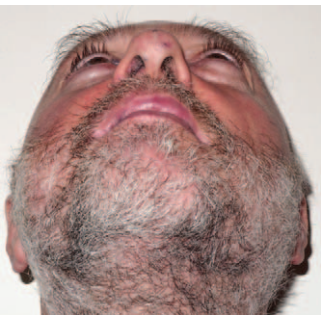

FIGURE 10. Postoperative appearance of patient depicted in Figs. 5–9.

Comparison of This Case Series With Other Published Results

The first discrepancy that is noted is that the average number of sessions performed in our cohort was 2.1, which is lower than an average 2.63 found in a review of the literature focusing on ethanol sclerotherapy of VMs.[22] The reason behind this could be the fact

that the average follow-up of this case series is just 2 years and we could face relapses needing further treatment.

Analysis of Complications

The most frequent complication was blistering, and this is coherent with other reports. Ulceration, on the contrary, was more frequent in our case series than on average. The reason behind this could be the fact that we have treated patients affected by head and neck VMs only. Here, oral involvement is almost invariably jeopardized by ulceration if the VM infiltrates the mucosa. Edema, causing impaired facial expression and mouth opening was the rule when major VMs of the face were treated. Swelling though should not be regarded as a complication but rather as a very reliable sign of long-term treatment effectiveness.[23] Pain was a relatively minor issue. Most patients say they did not feel pain at all. However, an overall 25.7% of patients reported a high or very high degree of pain during or after the procedure. Still, even these patients declared that they would accept to undergo the same procedure if needed and this underlines a very high degree of acceptance of the procedure by the patients. There were, although only episodically, major complications.

Nerve Impairment

We have observed 1 patient of temporary weakness of a buccal branch of the facial nerve. Peripheral nerve injury after ethanol sclerotherapy is a known complication. However, even with STS transient or permanent nerve impairment can happen. In a recent retrospective analysis of 204 patients, Stuart et al[24] reported 7 patients of transient and/or permanent nerve dysfunction. This means an average 3.4%. We had just 1 patient (2%) of transient nerve damage, which is lower. However, the same authors observed 3 patients of permanent injury (1.5%), whereas we had none. Detergents are not intrinsically neurotoxic, so the pathophysiology should be explained differently. A damage to the ''vasa nervorum'' or an indirect injury caused by intense swelling or by extravasation of the sclerosant causing tissue necrosis could be hypothesized. It is important, however, to underline the fact that there is no study in literature that focuses on complications after sclerotherapy with ethanol of VMs involving just head and neck region.

Orbital Compartment Syndrome

One patient suffered from intense swelling of the right orbit after injecting a palatal VM. In the literature, there is another report of a patient who lost sight after sclerosing a vast facial VM involving the orbit.[25] When a sclerosant reaches part of a VM inside the orbit, a compartment syndrome can be predicted. This must be treated in the same way a retrobulbar hemorrhage would be managed. Prompt administration of high doses of steroids, bedside canthotomy and cantholysis and, if needed, lateral and/or medial wall decompression, must be carried out within 120 minutes to preserve sight.[26,27]

We observed 1 (2%) paradoxical embolism,[14] because of a patent foramen ovale. This is a very rare complication; according to a 2012 review[28] from 1994 to 2014, there have been only 13 published patients of paradoxical embolism, and in most patients, a patent foramen ovale was present. The procedure is very frequent and this complication is very rare; therefore, a preoperative echocardiographic study is theoretically not indicated.

The majority of patients would undergo again similar treatments; this underlines how patient satisfaction is very high. In addition, according to the statistical analysis, the satisfaction of the patient is not in any way affected by the presence of complications. No type of complication is indeed correlated with the degree of patient satisfaction. Probably the satisfaction of the patient is correlated with the effectiveness of the procedure, especially in case of venous malformations localized at the level of the head & neck, where the aesthetic aspect is undoubtedly important, owing to the fact that the lesions cannot be hidden.

CONCLUSION

Foam sclerotherapy with STS confirms to be a very well tolerated procedure. It should be noted though that major complications can occur, especially when dealing with major VMs. For these reasons, it is imperative that this particular cohort of patients is treated in a highly protected setting, where emergent procedures can be readily adopted to protect the airways or the orbital content. Although the patient who had paradoxical embolism eventually healed without consequences, the likelihood of this event must be discussed with patients having large VMs and in these patients we prefer to have a preoperative trans oesophageal ultrasound examination excluding right to left shunts.

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Botulinum Toxin Conjugated With Silk Fibroin and 4-Hexylresorcinol

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Purpose: The objective of this study was to evaluate whether silk fibroin (SF) incorporated into 4-hexylresorcinol (4HR) could increase botulinum toxin-A (BTX-A) activity.

Material and methods: In total, 30 rats were used for this study. The animals were divided into 6 groups according to the injected materials (SA: saline only; SF; 4HR; B2: 2 units of BTX-A; B2 + SF + 4HR: combination of B2, SF, and 4HR; B5: 5 units of BTX-A). Serial sonography was used for the evaluation of muscle thickness after injection. Immunohistochemical staining was used for the evaluation of myosin type II (myo2) and Bcl-2 protein expression.

Results: The relative thickness of the masseter muscle in B2 group was 66.14% ± 4.55% to the preinjection level; in B2 + SF + 4HR group was 54.59% ± 4.83%, and in B5 group was 56.19% ± 8.28%. Any BTX-injected group showed significantly lower value of the relative muscle thickness compared to SA, SF, or 4HR group ($P < 0.001$ for all). The difference of relative muscle thickness between B2 group and B2 + SF + 4HR group was statistically significant ($P < 0.001$). The intensity of myo2 immunostaining in B5, B2, and B2 + SF + 4HR group was significantly higher than those in the other groups ($P < 0.05$).

Conclusions: When 2 units of BTX was incorporated to SF and 4HR, combination formula showed similar activity to those of 5 units of BTX.

Key Words: 4-Hexylresorcinol, botulinum toxin, silk fibroin

Botulinum toxin (BTX) is a neurotoxin and mainly blocks the neurotransmission of cholinergic nerve.[1] There are several subtypes of BTX.[1] BTX-A has been mainly used in clinical fields.[2] BTX-A has been used for the correction of facial esthetics[3] and the treatment of temporomandibular disorder.[4] As the cholinergic nerve innervates into salivary gland, BTX-A injection can be considered for the correction of Frey syndrome[5] and hypersalivation.[6] BTX-A therapy also has been used for the correction of post-traumatic open-bite.[7] As the indication for BTX-A injection has been widen rapidly, the usage of BTX-A will be increased accordingly.

BTX is composed of heavy chain (100 kDa) and light chain (50 kDa).[8] Between 2 components, several disulfide bonds are found.[8] As free form of BTX is fragile to the attack of protease and low pH, bacteria produces BTX as a high molecular weight of progenitor toxin complex containing protector protein.[8] Therefore, commercially available BTX-A is usually provided as freeze-dried toxin with albumin as protector protein. After reconstitution with normal saline, the manufacturer recommends that BTX-A should be stored in refrigerator (2°C–8°C) and used as soon as possible.[9] Storage beyond 4 hours after reconstitution has decreased the efficacy of BTX-A.[10,11] Some authors claimed that residual BTX-A could be stored in room temperature for 4 months without significant loss of activity.[12] Generally, 2 weeks of storage in refrigerator without freezing seems to be safe, not affecting the efficacy of BTX-A.[9,13] However, repeated usage of BTX-A after reconstitution is not recommended by manufacturer because of increased contamination risk.[9] Commercially available BTX-A is produced from bacteria or from eukaryotic cells. The price for BTX-A is generally expensive.[9]

4-Hexylresorcinol (4HR) is a well known antiseptics[14] and can be used for the structural stabilization of protein.[15,16] Low concentration of 4HR can increase the activity of lysozyme.[16] Therefore, 4HR may stabilize the structure of BTX-A and increase the activity of BTX-A. Silk fibroin (SF) is produced by *Bombyx mori* and considered as drug carrier.[17] SF and 4HR combination has been widely studied in tissue engineering for the development of soft tissue augmentation material[18] or membrane.[19] 4HR can influence gene expression and protein function in cancer cells[20] and macrophages.[21] As the light chain of BTX has protease activity,[8] 4HR-incorporated drug carrier may influence BTX activity.

The objective of this study was to evaluate that SF-conjugated 4HR could increase BTX-A activity. The serial sonography was

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