Original Article

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Bleomycin vs Setrol for Sclerotherapy of the Lymphovenous Malformation

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Abstract

Introduction: Lymphatic malformations are developmental anomalies of lymphatic system consisting of abnormally formed lymphatic channels and cystic spaces. Bleomycin was first developed as an antineoplastic antibiotic, and its sclerosing effect was discovered later. The mechanism involves damage to endothelial cells with a nonspecific inflammatory reaction and occlusion of vessels. Vascular malformations have devastating cosmetic effects in addition to being associated with pain and bleeding. Sclerotherapy has been used as an effective therapeutic modality for the management of vascular malformations. **Subjects and Methods :** The material for this study was gathered from the patients treated with sclerotherapy for vascular malformation in the Sapthagiri Institute of Medical Sciences and Research Centre from January 2020 to December 2020 in the Department of Interventional Radiology. The material covers for 63 consecutive patients. The journals of each patient were examined for the following factors: age, medical specialty in charge of treatment, sporadic or familiar malformation, single or multiple and anatomic lesions, any prior treatment, type of radiological imagining, nature of the malformation (venous, lymphatic, venolymphatic, capillary or arteriovenous), smoking, number of sclerotherapies, nature of the sclerosant that was used (polidocanol, OK-432, ethanol, and glue), complications, and duration (follow-up) of treatment. **Result:** The 63 patients were divided into two groups: patients that eventually underwent a surgical procedure versus patients that did not. Patients were decided to be operated on if the result of the sclerotherapy was regarded as poor. These two patient groups were compared regarding the factors presented above for statically significant differences. **Conclusion:** Lymphatic malformations are developmental anomalies of the lymphatic system that occur most commonly in the head and neck region followed by axilla and mediastinum. The precise aetiology of LMs is still unknown. In 50% of cases, they are present at birth with 80% to 90% diagnosed within the first two years of life. Initially they usually present as a painless, soft mass with wide variations in the growth rate. Rapid growth can occur as a result of trauma, intralesional haemorrhage and thrombosis. Spontaneous regression is very rare.

Keywords: Sodium tetradecyl sulphate (STS) (Setrol), Venous malformation, (VnM), Vascular malformations (VM), Sclerotherapy.

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Introduction

Lymphatic malformations (LMs) are developmental anomalies of lymphatic system consisting of abnormally formed lymphatic channels and cystic spaces. Lymphatic malformations occur primarily in the head and neck, accounting for 75% of all cases. They are typically detected at birth, and 90% is clinically apparent by the age of 2 years. [1–3] There are three morphologic types of LMs: microcystic, macrocystic and combined (combination of microcystic and macrocystic components). LMs in head and neck region cause pain, bleeding, infection, muscular atrophy, malocclusion, speech difficulties, feeding problems, airway obstruction and cosmetic deformities. [4]

Bleomycin was first developed as an antineoplastic antibiotic, and its sclerosing effect was discovered later. The mechanism involves damage to endothelial cells with a nonspecific inflammatory reaction and occlusion of vessels. Intralesional bleomycin injections have been shown to be an effective treatment for haemangiomas and vascular malformation lesions. Pulmonary fibrosis as a complication after intralesional treatment with bleomycin has never been reported. [5,6]

Vascular malformations have devastating cosmetic effects in addition to being associated with pain and bleeding. Sclerotherapy has been used as an effective therapeutic modality for the management of vascular malformations. The

purpose of this case series is to describe our clinical experience of using sodium tetradecyl sulphate (STS)(setrol) 3 % in the treatment of venous malformation lesions of head and neck. [7,8]

Subjects and Methods

The material for this study was gathered from the patients treated with sclerotherapy for vascular malformation in the Sapthagiri Institute of Medical Sciences and Research Centre from January 2020 to December 2020 in the Department of Interventional Radiology. The material covers for 63 consecutive patients. The journals of each patient were examined for the following factors: age, medical specialty in charge of treatment, sporadic or familiar malformation, single or multiple and anatomic lesions, any prior treatment, type of radiological imagining, nature of the malformation (venous, lymphatic, venolymphatic, capillary or arteriovenous), smoking, number of sclerotherapies, nature of the sclerosant that was used (polidocanol, OK-432, ethanol, and glue), complications, and duration (follow-up) of treatment.

These factors were recorded in an Excel program and analysed using the SPSS statistics program. The aim of the analysis was to find predisposing factors that was predict poor outcome in sclerotherapy.

Thirteen patients were included in this study (three male and ten females; age range between 8 months and 54 years; mean age 18.2 years, ±SD 15.71). The patients were treated by 3 % Setrol intralesional injections. Of the thirteen patients treated, complete resolution occurred in four patients (28.57 %), a good response occurred in five patients (35.7 %), a moderate response in two patients (14.28 %), a mild response in two patients (14.28 %) and no response in one patient (7.14 %). The side effects encountered in all patients were pain and edema after injection which was controlled by oral analgesics and an intramuscular injection of dexamethasone. In addition, two patients developed a superficial ulceration (11.76 %) which healed uneventfully, and one patient developed ecchymosis after injection (5.88 %).

Result

The 63 patients were divided into two groups: patients that eventually underwent a surgical procedure versus patients that did not. Patients were decided to be operated on if the result of the sclerotherapy was regarded as poor. These two patient groups were compared regarding the factors presented above for statically significant differences.

Demographics

In this study, neither gender nor age was associated to be a predisposing factor for a poor result in sclerotherapy. The treatment of the 63 patients was divided between branches of surgical specialties. Majority of the patients, 37 (59%), were treated by plastic surgeons, nine (14%) were treated by paediatric surgeons, six (10%) were treated by hand surgeons, two (3%) were treated by neurosurgeons, and one (2%) was treated by ENT surgeon. The surgical specialty that managed the treatment of the patient was not associated to be a predisposing factor for a poor result in sclerotherapy.

Data was collected from 13 patients (ten female and three males; mean age 18.2 years, ±SD 15.71, age range between 8 months and 54 years). All patients except one reported that the VnM was present at birth. One patient had the lesion develop at age of 40 years. The lesions involved the following locations lips (n = 1), cheek (n = 3), buccal mucosa (n = 2), tongue (n = 3), combined lesions of labial and buccal mucosa (n = 2), combined lesions of buccal mucosa and tongue (n = 2) and left parotid region (n = 1). The patient's chief complaint mostly centered on the cosmetic disfigurement caused by the lesion. No prior therapeutic interventions were recorded except in one patient who reported undergoing intralesional steroid injection. The size of the vascular malformations ranged from 1 to 8 cm in its widest diameter with an average size of 3.2 cm. The number of injections of STS per lesion ranged from one to three at different visits with a typical dose of 0.5–2 ml per injection, well under the maximum recommended dose of 0.5 ml/kg. An average of 0.5 ml of Setrol for each 2 ml volume of lesion was administered. Among the 13 patients, the responses to treatment were complete response in four patients (30.8 %), good response in 4 patients (30.8 %), moderate response in two patients (15.4 %), mild response in two patients (15.4 %) and no response in 1 patient (7.7 %). No hypersensitivity reactions were observed. The side effects encountered in all patients were pain and edema after injection. Two patients had a superficial ulceration (15.4 %) which healed without scarring. One patient had mild ecchymosis after the injection (7.7 %).

Discussion

Management of VnM is dependent on size, location, and often surgeon preference and comfort. Small VnM's can be completely excised. However, complete surgical eradication of extensive oral or facial venous malformation is rarely possible without jeopardizing function or causing additional disfigurement and/or severe hemorrhage. [8] Other modalities of treatments includes the use of Nd:YAG laser therapy. The disadvantage of this treatment is due to its limited use for superficial cutaneous lesions and the risk of damaging the close vital structures in the face. Sclerotherapy is a safe

Table 1: The efficiency of sclerotherapy in the treatmentof vascular malformations: A retrospective study of 63 patients

Gender	
Male	23 (37%)
Female	40 (63%)
Operated on patients (all)	12 (19% out of high- and low-flow malformations combined)
Operated on males	4 (17% out of women)
Operated on females	8 (20% out of men)
Operated on low-flow malformations	8 (14% out of all low-flow malformations)
Average age of all patients	36
Median age of all patients	33
Range of age of all patients	3–88
Average age of operated on patients	30
Median age of operated on patients	30
Range of age of operated on patients	6–67

and effective treatment with minimal morbidity. There are many other agents used for sclerotherapy: sodium morrhuate, bleomycin, ethanolamine oleate, ethanol, hypertonic saline, and various combinations of these medications.[9] The most common side effects were skin necrosis and ulceration, hypersensitivity, and swelling. STS is a widely used sclerosant agent which has been available in Canada and Europe for many years and is primarily used in the treatment of varicose veins. STS has been approved by the US Food and Drug Administration FDA for sclerotherapy of varicose veins. In this case series, our clinical experience with the use of STS 3 % solution tends to validate STS as a minimally invasive, safe, and effective treatment of head and neck VnM. The responses to therapy were very satisfactory in 61.6 % of the treated patients who showed good to complete response. The best response to STS injection was demonstrated clearly in VnM smaller than 2.5 cm due to the fact that the efficacy of the sclerosis depends on the caliber of the feeder vessels and the blood flow. Alternatively, the lower efficacy of sclerotherapy of larger caliber or faster flow lesions was seen as a result of less sclerosant agent making contact with the endothelial cells of the lesional walls.[10] The conclusions for this study are consistent with the previous literature in which the best results were obtained with low volume lesions. Stimpson et al. used 3 % STS foam to treat 12 patients who had VnM in the head and neck. They found that a single treatment may be adequate for small lesions, but the injections may be safely repeated until a satisfactory result is obtained in large lesions. The patients in this case series were treated in an office setting without any radiological guidance. Similarly, Khandpur et al. reported 90–100 % regression in the size of lesions by direct intralesional injection of 3 % STS without radiological guidance into VnM and lymphatic malformations [Table 2].

The findings of this case series demonstrated excellent to good results in 61.6 % of the patients, and moderate to mild results in 30.8 % of the patients with direct percutaneous and permucosal intralesional injections of the 3 % STS solution. In this series, one patient who was previously treated by intralesional steroid injections showed no response to therapy; these results were comparable to those results which were obtained from the use of a foam technique (Tessari's method) in which the sclerosing agent foam was formed using a three-way stopcock and two syringes, mixing air with liquid sodium tetradecyl sulfate to create a foam.[11,12]The optimal formulation was found to be one-part sclerosant solution to four parts air. The aim of this method was to verify the safety, feasibility, and efficacy of different doses and concentrations of a sclerosing drug; variations in the preparation of the foam according to several variables, such as dilution, and volume of syringes. The concentrations used ranged from 0.1 to 3 % of STS depending on the caliber of the veins, with the larger caliber lesion, the higher concentration of STS used. The advantage of this method is minimal extravasation of sclerosant foam making it less harmful than the liquid solutions. Tessari's foaming method had been originally used for sclerotherapy of varicose veins of lower limbs where increased hydrostatic pressure might enhance extravasation of the sclerosant agent.[13] Foaming reduces extravasation related side effects and provides sclerosant rich milieu resulting in severe intimal damage. From the authors' perspective however, foaming is not required in preparation of a sclerosant agent for head and neck low flow VM due to relatively low hydrostatic pressure in the head and neck vessels compared to lower limb vessels. Furthermore, to provide a sclerosant-rich milieu inside the lesions, our approach was to increase the concentration of the injected drug and the application

Table 2: Review of studies examined the role of percutaneous and per-mucosal intralesional Setrol injection alone of venous malformations of head and neck

Studies	Sclerosant agent	Number of patients	Average age	Median and range of follow up duration	Average no. of injection	Type of study (controlled vs. uncontrolled)	Method of drug preparation (foaming vs. direct)	Results	Complications
Kok 2012	3 % STS	51	10.9	2.7 years	1.45	Retrospective uncontrolled	Foaming	23 % excellent results 60 % improved	Skin necrosis
Stimpson, 2012	3 % STS	12	7	28 months	4	Retrospective uncontrolled	Foaming	33 % complete resolution improve 50 %	Minor bleeding
Bajpai 2012	3 % STS	8	15	2–3 years	5	Prospective comparative	Direct	Overall RR: 62.5 %	Blister, ulcer
Siniluoto TM 1997	33–67 % STS mixed with CM	38	28	NR	2.2	Uncontrolled	Direct	Excellent or good in 23 patients (68 %)	Edema, infection, scarring and transient facial nerve paresis
O'Donova 1997	3 % STS	5	NR	24 months	NR	Retrospective	Direct	Improve	NR
Current study	3 % STS	13	18.2	6.6 months	3.1	Prospective case studies	Direct	Complete resolution in 30.8 % and improvement in 61.6 %	Pain, edema, ulceration and ecchymosis

of a compression dressing after intralesional injection.[14,15] Follow up of the patients was scheduled every 2 weeks and repeated injections were scheduled after 4 weeks in those patients with unsatisfactory results. Four of the patients in this series had two or more repeated injections. The results were monitored by clinical observation, documented and compared by serial photographs as well as clinical measurements. Unfortunately, the continuity of treatment varied among patients due to limited availability of the sclerosant agent, poor patient compliance with the regular follow up, and in some cases the patient's satisfaction with their results. In the present study, the reported side effects were mild in nature and healed spontaneously. In this series, no serious complications occurred such facial nerve palsy and blindness which have been reported by others.[16] Post injection inflammatory reactions and pain were recorded in all patients. One patient developed a small ulceration at the injection site and another patient developed ecchymosis. Soft-tissue swelling generally

increases in the region of the malformation immediately after the injections. Subsequently, necrosis and inflammation induced by the sclerosis subsides with fibrous tissue formation, culminating in progressive reduction in the lesion size. The complete clinical effect of the therapy may not be evident for several months. Patients and their families must be informed about these expected side effects and outcomes so the patient has realistic expectations.[17]

Conclusion

A number of treatment methods are available for LMs of the head and neck region. Surgical treatment of LMs can be associated with significant morbidity. Intralesional injection of bleomycin has minimal and controllable local and systemic adverse effects. Sclerosation of LMs with bleomycin in our case was highly effective compared to several surgical resections.

Sclerotherapy with direct intralesional injection of 3 % Setrol solution is simple, safe, and effective therapy for managing head and neck VnM that can be done as an office procedure. Smaller lesions have a more favourable response. Further controlled studies need to be performed to determine the overall efficacy of STS in the management of VnM of the head and neck, as well as long term follow-up to observe results.

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