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Efficacy and Safety of Bleomycin Sclerotherapy for Venolymphatic Malformations in Head and Neck Region with MRI Follow Up

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Keywords:

Venolymphatic malformations; Sclerotherapy; Bleomycin

1. Abstract

1.1. Purpose: Venolymphatic Malformations (VLM) are low flow, vascular lesions that commonly occur in the head and neck. Sclerotherapy has become the mainstay of treatment for these lesions as sclerotherapy is less invasive than surgical excision. Bleomycin is one of the sclerosing agents used for these malformations. The aim of our study was to assess the efficacy and safety of percutaneous bleomycin sclerotherabpy in head and neck VLMs.

1.2. Materials and Methods: Prospectively maintained procedural records were retrospectively reviewed to identify all patients with VLM who underwent percutaneous bleomycin therapy between 2012 and 2018. Demographic information, lesion and treatment details were collected through chart review. Treatment responses were evaluated objectively by manual volume measurements of the VLM on pre and post treatment MR/CT imaging. Subjective treatment evaluations were obtained with patient satisfaction responses during their clinic visit. Paired t test was used for pre and post treatment volume comparison and $p<0.05$ was considered significant.

1.3. Results: Twenty patients (13 Female; age range 6-67 years) were treated with clinical follow up of 15±16 months and imaging follow up of 28±17 months. All patients were followed clinically and were satisfied with their treatment and improved symptomatically. All lesions reduced in size on follow up subjective evaluation. Pre and post treatment imaging, available on 13 patients, showed a mean reduction of lesion by 57% ($p= 0.02$) after treatment. No peri-procedural complication was seen except for one patient (5 %) who developed hyperpigmentation at the site of ECG leads.

1.4. Conclusion: Our study confirms long term efficacy and safety of percutaneous sclerotherapy with bleomycin for VLMs in head and neck with MRI follow up.

2. Introduction

Venolymphatic Malformations (VLM) is a developmental vascular malformation that consists of a combination of dilated, aberrant venous and lymphatic channels with disorganized endothelial cells in various proportions. VLM can occur anywhere in the body, but most frequently involve the head and neck region [1]. Of all the vascular malformations, venous and lymphatic malformations constitute 40 and 28% respectively [1]. According to ISSVA (International Society for the Study of Vascular Anomalies) classification system for vascular anomalies, VLM are classified as slow flow vascular malformations. Morphologically, lymphatic components can be macrocystic having large individually distinguishable cysts or microcystic with tiny cysts indistinguishable from each other or mixed [2]. Venous component may be distensible, non-distensible or cavernous [3]. VLMs are usually asymptomatic; however, rare complications can occur depending on the location and severity of malformation. For instance, patients with orbital involvement may present with progressive proptosis, ptosis, restriction of eye movements, swelling and in severe cases with acute visual loss due to intralesional hemorrhage or inflammation/ optic nerve compression [4]. VLMs with predominant lymphatic component of macrocystic type can expand and compress the adjacent tissues. These usually present with airway obstruction and swallowing difficulties when present in the head and neck region.

Both CT and MRI show the multicompartmental nature of the

VLMs. Imaging can be static or dynamic. Phleboliths are a common feature seen on the static imaging in slow flow lesions and reflect resolution of previous thrombosis. MR imaging is better than CT in delineating the lesion, in showing its internal structure and demonstrating the blood products in various stages of degradation [4]. Dynamic imaging helps in better understanding of the lesions physiology and pre-treatment planning [3]. In complex lesions in critical locations, an invasive angiography may sometimes be required for further characterization of the lesion. VLMs are irregular non-encapsulated lesions, making surgical management difficult [5]. Surgery can be curative for superficial VLMs, however, for deep seated lesions, where the extent of involvement cannot be defined, risk of hemorrhage and injury to surrounding vital structures makes surgery, a less favourable option. Intralesional sclerotherapy with bleomycin has emerged as a primary treatment of choice for VLMs in the recent years [6, 7]. Most commonly associated side effects of intralesional bleomycin therapy include pain, erythema, swelling, fever, hyperpigmentation and local skin necrosis at the site of injection [7]. Although rare with smaller doses of bleomycin used for sclerotherapy, few studies in the literature have associated bleomycin with lung toxicity [8-10]. The aim of our study was to objectively assess the efficacy and safety of percutaneous Bleomycin embolization in head and neck VLMs with MRI follow up.

3. Methods

The study was approved by institutional research ethics board. A prospectively collected database of the procedural records was retrospectively searched to find patients with VLMs of the head and neck region who underwent percutaneous bleomycin therapy between 2012 and 2018. Patients with bleomycin treatment in infantile hemangiomas or other vascular tumors, those who choose surgery instead of, or in combination with bleomycin therapy and other types of neoplasms not eligible for sclerotherapy were excluded from the study. Variables collected for each case included: Patient demographics (age, sex, location of the VLM), symptoms, pre and post treatment imaging, clinical result, potential complications from treatment, total dose of bleomycin used and months of follow-up. Pre and post treatment radiological imaging of the VLMs was performed by MRI. MR imaging sequences used were T2 fat suppression and T1 with contrast. All MRI were performed using Signa GE 1.5-T scanners. All images were analyzed on a PACS workstation.

3.1. Sclerotherapy technique

Preprocedural MRI was reviewed. Informed consent was obtained. All procedures were performed as day procedures, i.e, patients were discharged home on the day of procedure. Procedures were performed under general anaesthesia in most patients except 2 patients by an interventional neuroradiologist. The malformations were accessed under live fluoroscopy using 25 gauge angiocatheters. The access ot VLM was confirmed by the observation of slow flow blood in the angiocath. Intra-lesional contents were aspirated in predominantly lymphatic components when clear fluid came out of the angiocath. Contrast angiography was then performed to confirm intra-lesional access and presence of any shunt. Following confirmation of safe needle/angiocatheter placement for sclerotherapy, bleomycin (1mg/ml concentration) was injected under negative roadmap technique to fill the malformation. Maximum intra-lesional injection was 15ml per session. Light pressure was applied for 1-2 minutes at the puncture site to restore hemostasis. Patients were then observed in the recovery area for 1-2 hours. All patients were discharged home on the day of the procedure. If multiple procedures were required, these were spaced at least 4-8 weeks apart.

3.2. Treatment Response

It was assessed through objective and subjective reduction of the lesion. Objective reduction of the lesions was assessed by manual volume measurements of the VLM on MRI or CT, pre and post treatment. Subjective reduction was reported by the patient and assessed by the neurointerventionist (JS) during their clinic visit.

3.3. Statistical Analysis:

Mean, median, standard deviations and percentages were calculated to report the central tendency of the data. Paired t-test for pre and post treatment volume comparison, P value less than 0.05 was considered significant.

4. Results

A total of 20 patients (13 females, 7 males; age range 6-67 yrs) met the criteria for inclusion in this study (table 1). Presenting symptoms were most commonly vision change (50%, e.g. blurry vision, scotoma) and proptosis (30%). Other symptoms included pain (40%), diplopia (10%), palpable mass (10%), ecchymosis (10%), bleeding (10%), and ptosis (10%). The patients had 15±16 months (median 10; range- 3-67) of clinical and 28±17 months (median 24; range- 5-52) of imaging follow up. On clinical follow up, all patients were satisfied with their treatment and improved symptomatically. All lesions reduced in size on follow up subjective evaluation. On imaging available for 13 patients, there was a mean reduction of lesion by 57% (p= 0.02) after treatment (Figure 1). No peri-procedural complication was seen except for one patient (5 %) who developed hyperpigmentation at the site of ECG leads (Figure 2).

Table 1: Table showing patients demographics, location of the lesion, pre and post volume of the lesion and volume of the bleomycin used.

Total number of patients	20
Female:Male	13:7
Age (Mean, Median, range)	36.2; 38; 6-67 years
Location of VLM	Lips, nasal bridge, scalp, cheeks, chin, base of tongue, orbits
Clinical presentation	Vision change (50%, e.g. blurry vision, scotoma) and proptosis (30%), pain (40%), diplopia (10%), palpable mass (10%), ecchymosis (10%), bleeding (10%), ptosis (10%).
Clinical follow up (Mean, Median, range)	15; 10; 3-67 months
Imaging follow up (Mean, Median, range)	28; 24; 5-52 months
Volume of Bleomycin (Mean, Median, range)	20.4; 12; 4-114 ml
Pre-treatment lesion volume	22738.7; 4898.4; 198.4-221784.5 cmm
Post treatment lesion volume	17008.08; 2281.5; 16.2-201044.8
Lesion volume reduction (Mean, Median, range)	57%; 60.3%; 9.4-91.9%
Complications	5% (One patient had hyperpigmentation)

VLM- Venolymphatic malformation; ml- millilitres; cmm- cubic millimeters

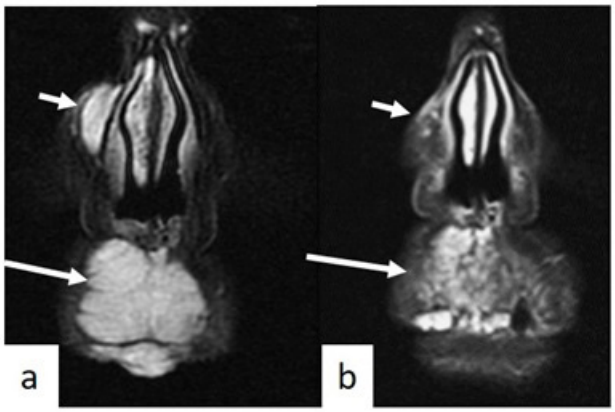

Figure 1: T2 fat sat images in coronal plane shows venolymphatic malformation (VLM) of upper lip (long arrows) in a patient who underwent 4 surgeries and 4 laser therapy before (a) and after (b) bleomycin sclerotherapy. The small VLM at right nasal bridge (small arrow) showed near complete resolution before (a) and after (b) bleomycin treatment.

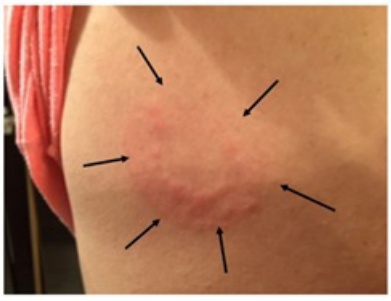

Figure 2: Peri-procedural complication was seen in one patient who developed hyperpigmentation at the site of chest ECG leads (arrows).

5. Discussion

Our study confirms the efficacy and safety of bleomycin sclerotherapy for head and neck VLMs. We report significant (p=0.02) objective reduction in size by 57% on imaging and subjective reduction in all patients with VLMs after bleomycin sclerotherapy. Only 1 patient (5%) showed complication. This was seen on long term clinical follow up of 15 months and imaging follow up of 28 months. Management of VLMs in the head and neck region require clear understanding of their vascular composition, internal flow and drainage pattern, anatomical localization and relation with distant vascular components. Main options for treatment include surgical excision or sclerotherapy or combination of both treatments. In a study by Russin et al [11] the recurrence rate after surgery was reported to be 71.4% with new or worsening cranial nerve deficits in 37.5 % of the patients.

Extremely high likelihood of recurrence and the risk of perioperative morbidity makes surgery less favorable option in such cases. Moreover, these lesions typically interdigitate within the head and neck contents making total resection challenging. Sclerotherapy involves intralesional injection of a sclerosant that causes irritation, endothelial damage and ultimately fibrosis and involution of the lesion. This treatment is particularly suitable for non-disten-

sible lesions with slow flow [12]. Historically various sclerosing agents have been used in the treatment of vascular anomalies, ethanol being the most widely used because of its availability and low cost. However, it has the risk of nontargeted embolization, adjacent tissue damage, and alcohol intoxication [13]. Inflammation and scarring in the head and neck region has significant cosmotic implications. Bleomycin is an antibacterial and a cytotoxic antitumor agent that causes a sclerosing effect on the endothelial cells via non-specific inflammatory reaction and occlusion of the vessels [13]. Many studies in the literature have reported good clinical and radiological outcomes using intralesional bleomycin sclerotherapy in the treatment of VLMs [14-18]. In a recent study by Raichura et al [19], a dramatic response after bleomycin use was seen in 13 cases and none of the patients experienced recurrence or significant complication.

Local complications of bleomycin sclerotherapy include erythema, ulceration, hyperpigmentation and scarring [20]. The most common systemic side effects reported are nausea, vomiting, mucositis, alopecia, transient fever and pulmonary toxicity [8-10, 20]. In the closed compartment space of orbit, there remains a potential risk of vision loss after the sclerotherapy procedure [20]. We only encounter the rare complications of local hyperpigmentation at the site of ECG leads in one of our patients. Our study further supports the use of bleomycin sclerotherapy as a viable option for treatment of head and neck VLMs. All lesions reduced in size on follow up subjective evaluation and mean reduction of the lesions by 57% was seen on post treatment images. None of the patients showed any systemic complications. This may be related to the much smaller dose used in our study (not exceeding mg) and limited systemic distribution of local injections compared with systemic bleomycin chemotherapy for other malignancies. One patient developed a minor complication of local hyperpigmentation at the site of ECG leads (Figure 2). Our study was limited due to small sample size. However, reports a long term prospective follow up with both subjective and objective evidence of reduction of VLM in the head and neck region following bleomycin sclerotherapy.

6. Conclusion

Our study confirms long term efficacy and safety of percutaneous sclerotherapy with bleomycin for VLMs in head and neck on imaging follow up.

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