Original Article

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Ear, Nose and Throat Section

Comparative Study on Efficacy of Intralesional Bleomycin Injection in Head and Neck Lymphangioma and Vascular Malformation

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ABSTRACT

Introduction: Head and neck region is the most common site of occurrence for lymphangioma and vascular malformation. The surgical modality of treatment for these conditions carries higher risk of neurovascular damages, recurrence and bad scar. Intralesional Bleomycin Injection (IBI) has been used extensively as a non surgical treatment because of its low cost, easy availability and high sclerosing effect on vascular endothelium. Most of the researches have been focused on reporting its efficacy on lymphangioma or vascular malformation or haemangioma only.

Aim: To compare the efficacy and safety of intralesional bleomycin injection in lymphangioma and vascular malformation of head and neck region.

Materials and Methods: A prospective comparative study was carried out in the Department of ENT-HNS in Kathmandu Medical College Teaching Hospital, Nepal from January 2015 to June 2016. First 15 patients of lymphangioma (Group 1) and same number of slow flow vascular malformation (Group 2) were offered IBI in the dose of 0.5 mg/kg/dose (not exceeding 15 mg/dose). The injection was repeated every three weeks, if needed. The size of the lesion was measured and serial photographs were taken. Complications were also recorded. The mean and standard deviation was calculated and results were compared using Chi-square and Student's t-test.

Results: Response rate (size reduction) between the groups was comparable (p=0.361). Mean number of injections required in Group 1 and Group 2 were 3 and 5 respectively. The number of injections required to meet the above mentioned response was statistically higher in Group 2 as compared to Group 1 (p=0.002). Apart from minor complications like fever and transient increase in swelling in both the groups (20%) and skin hyperpigmentation in Group 2 (13%), there were no haematological or pulmonary complication in due course of treatment and follow up.

Conclusion: Intralesional bleomycin injection is equally effective for lymphangioma and slow flow vascular malformation but vascular malformations require significantly higher number of injections than lymphangioma.

Keywords: Lymphovascular malformation, Non surgical, Sclerotherapy

INTRODUCTION

Lymphangioma is a common congenital lesion arising from malformed lymphatic system. About 60% of it appears at birth, 80% manifests within two years of life or may present at any time in life [1]. The most common site of occurrence of these lesions is the head and neck (75%) with no sex predisposition. It is usually a multilocular swelling and each cyst varies from 1 mm to 5 cm in diameter that may communicate with each other and contains a clear or straw coloured fluid, occasionally blood mixed [2].

Vascular anomalies are another common congenital and neonatal abnormalities, the most common site of predilection being head and neck region (60%) [3]. Mulliken JB and Glowacki J classified these pathological conditions into haemangioma and vascular malformation [4]. Haemangiomas usually manifest during the first month of life; whereas, vascular malformations are always present at birth. After rapid proliferation during first two years of life, haemangiomas regress slowly whereas vascular malformations do not. Waner M and Suen JY have classified vascular malformations into slow flow (capillary, lymphatic and venous) and fast flow (arterial, arteriovenous fistula and arteriovenous malformation) [5]. Mathur NN et al., coined the term 'haemodynamically less active' for 'slow flow' lesions [2].

Surgical excision is the treatment of choice for lymphangioma and vascular malformation. However, the vicinity of complex neurovascular structures may often be a challenge for the head and neck surgeon when they envelop the vital structures, thus inherit the chance of complications like nerve palsy, haemorrhage and bad scar or recurrence. So alternative treatment modalities like LASER, percutaneous sclerotherapy (bleomycin, OK432, ethibloc) etc. have been tried in the past. We used IBI for these conditions because of its low cost, easy availability and safety. The efficacy of IBI among the cohort of patients with head and neck lymphangioma and vascular malformation was compared.

MATERIALS AND METHODS

This prospective comparative study was carried out in the Department of ENT-HNS in Kathmandu Medical College Teaching Hospital (Kathmandu, Nepal) from January 2015 to June 2016. Institutional Review Committee approval was taken before the commencement of study. First fifteen cases of lymphangioma (Group 1) and equal number of slow flow vascular malformation (Group 2) of head and neck region who consented for IBI were studied. Those who failed to respond to previous IBI or recurrence following surgery were excluded from the study. The age, sex, weight, location of the lesion, size (length and breadth), follow up duration, total number of injections, cumulative dose of the bleomycin and complications if any were recorded in a predesigned proforma. Diagnosis was made on the basis of clinical examination and Doppler ultrasound. Fine Needle Aspiration Cytology (FNAC) was needed only in doubtful cases. Very few patients needed CT scan to see the extension especially in a difficult location. The size of the lesion was measured on the basis of clinical examination and ultrasound during every follow up. All the patients were followed up with complete blood count, renal function test and chest X-ray during the course of their

treatment. Lymphangioma was classified as macrocystic (>1 cm), microcystic (<1 cm) or mixed (containing both components) as suggested by Ogita S et al., [6].

Under all aseptic precautions, the IBI sessions were always performed in the operation theatre without anaesthesia in a day case basis. The dose of injection bleomycin administered was 0.5 mg/kg body weight but varied according to the size of the lesion. A single dose of 15 mg per session and cumulative dose of 5 mg/kg was never exceeded [7]. The first author diluted one vial of bleomycin (15 mg) in a 5 mL of normal saline and a 23 gauge needle was used to inject the calculated dose at one to four site as described by Mathur NN et al., [2]. We did not aspirate and discard the cystic content in any of the cases as suggested by Regmi D et al., [8]. Local pressure was applied for 5-10 minutes after injection to prevent sudden increase in the size of the swelling or haematoma formation. Patients were discharged by evening with a mild anti-inflammatory medication. They were advised to attend the emergency, if and when required. Otherwise follow up was done every three weeks and repeat injection was offered according to the clinical response. Serial colour photographs were taken before, during and after completion of the treatment. The clinical response to treatment (size reduction) was assessed on the basis of measurements, photographs and sonographic reports. It was further graded as excellent when it was >90%, good (50-90% reduction) and poor (<50% reduction). IBI sessions were repeated until the patient was satisfied with the outcome or tolerated residual symptoms. It was abandoned when the author felt there was no role of further treatment. Surgery as alternative treatment was advised for those abandoned cases.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 16.0 software for Windows (SPSS Inc., Chicago, IL). The mean and Standard Deviation (SD) were calculated and results were compared using Student's t-test and Chi square test/Fisher's exact test. The p-value was considered significant when it was less than 0.05.

RESULTS

The age between the groups was comparable (ranged from 5-60 years). Follow up duration ranged from 2-18 months (mean 10 months). Posterior triangle of neck was the most common site for lymphangioma (67%, n=10) followed by submandibular and parotid region whereas, oral cavity and oropharynx were the most common site for vascular malformation (40%, n=6) followed by neck, cheek and parotid region. Four patients (27%) in Group 1 and 3 (20%) in Group 2 had complete recovery following IBI. Response rate (size reduction) between the group was comparable (p-value=0.361) as shown in [Table/Fig-1]. Mean number of injections required in Group 1 was 3 (range: 1-4) where as it was 5 (range: 2-7) in Group 2. The number of injections required to meet the above mentioned response was statistically higher in Group 2 as compared to Group 1 (p-value=0.002) which is shown in [Table/Fig-2]. The most common complications observed in both the groups were fever and transient increase in lesion size (~20%) and hyperpigmentation of the overlying skin in 13% patients in Group 2. None of the cases developed haematological side effects or pulmonary fibrosis in due course of treatment and follow up.

Group	Response Rate		Total	p-value
	Poor	Good/Excellent		
1	2	13	15	0.361
2	4	11	15	
Total	6	24	30	

[Table/Fig-1]: Response rate (at least 50% or less) among the groups.
Chi-square Test

Group	Number of injection							Total
	1	2	3	4	5	6	7	
1	1	3	6	5	0	0	0	15
2	0	2	0	3	4	3	3	15
Total	1	5	6	8	4	3	3	30

[Table/Fig-2]: Number of injections required among the groups.
p-value=0.002 (Fisher's exact test)

DISCUSSION

Although, surgery is the favoured modality of treatment for head and neck lymphangioma or vascular malformation, it carries complication rate as high as 12-33% and recurrence 15-53% [9,10,11]. In order to circumvent the mortality or morbidity associated with surgery, various sclerosing agents like ethanol, bleomycin, OK432, Ethibloc, steroid have been tried in the past in order to cure the lesion with less complications [8,12].

Percutaneous sclerotherapy is an injection of sclerosing agent directly through the skin into the lesion in the lymphatic or venous malformation. Ethanol is a popular sclerosant having high efficacy ranging from 75-95% [12] but it carries high risk for skin necrosis, thrombophlebitis, nerve injury or sudden cardiovascular collapse when it enters the systemic circulation. OK432 is a low virulence strain of *Streptococcus pyogenes* cultured with penicillin-G, which is another alternative, but the availability and cost factor limit its use in our setup.

Bleomycin is a cytotoxic glycoprotein antibiotic isolated from strains of *Streptomyces verticillus*, discovered by Umezawa as antitumor agent in 1966 [13]. Later on, it was found to have sclerosing effect on endothelial cell during its treatment of malignant pleural effusion. Yura J et al., was the first to study its intralesional sclerosing effect in macrocystic lymphangioma in 1977 [14]. Sarihan H et al., was the first to use it in haemangioma in 1997 [15].

The most common site of lymphangioma was the posterior triangle of neck which was in agreement of other reports [8]. Oral cavity was the common site for vascular malformation in this series. The IBI causes destruction of vascular endothelial cells. Expected changes in the lymphangioma and vascular malformation were obvious only after three weeks. This is the reason why repeat injection was offered every three weeks in this study.

With this modality of treatment, more than 50% clinical improvement was observed in 90% of the lymphangioma and 80% of the vascular malformation. Only less than 20% patients in both the groups had to be referred to surgical modality as an alternative treatment option. Many efforts have been made to evaluate the effect of intralesional bleomycin on lymphangioma or the vascular malformation but we have compared its efficacy and safety between these two. The response rate (size reduction) was comparable between the groups and there was no statistical difference between them with regards to total size reduction at the end of therapy (p>0.05). But the number of injection required to achieve such a result was statistically higher among the vascular malformation (Group 2) as compared to lymphangioma (Group 1). Results of this series are comparable with other reports of its use in various haemangioma, vascular malformation or the lymphangioma series [8,16,17] and it is similar or even better compared to surgical modality [18]. Commonly encountered complications of the surgery like nerve palsy and bad scar were thus avoided by the use of intralesional bleomycin sclerotherapy.

Only a few complications like fever, transient increase in the size of the swelling and hyperpigmentation were encountered in our series. The most feared complication like pulmonary fibrosis was not observed in our study which is a common complication in cancer patients who have been treated with high dose of injection bleomycin. The recommended dose for IBI is 1 mg/kg/dose and the summated dose should not exceed 5 mg/kg. The dose we used

in our study was 0.5 mg/kg/dose which was much lower to cause pulmonary complications. Till date, not a single case of pulmonary fibrosis following its use as a sclerosant has been reported in the literature. IBI is the modality of choice for all head and neck lymphangioma and slow flow vascular malformation in our center before considering surgical excision.

LIMITATION

The study was conducted in only one tertiary centre with small sample size and shorter follow up. Larger study preferably a multicentre one with longer follow up is recommended.

CONCLUSION

Intralesional bleomycin sclerotherapy can be an effective and safe non surgical treatment option for head and neck lymphangioma and slow flow vascular malformation but the latter requires significantly higher number of injections than lymphangioma.

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