Original Research Article

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Ultrasound guided intralesional bleomycin therapy for cystic lymphangioma in childhood

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ABSTRACT

Background: Lymphangiomas are benign hamartomatous lymphatic tumors, characterized by multiple communicating lymphatic channels and cystic spaces. They occur in nearly all regions of the body but are most frequently seen in the neck (75%), axilla (20%), and inguinal areas (2%). This study aims to evaluate the effectiveness of intralesional bleomycin sclerotherapy in the treatment of cystic lymphangioma in children and to determine the incidence of complications in the treatment.

Methods: This is a prospective study of 36 children diagnosed with cystic lymphangioma and treated with intralesional injection of bleomycin aqueous solution from 2008 to 2015.

Results: Complete resolution was seen in (16/36) of lesions, (17/36) had a good response and (3/36) had a poor response. The tumour recurred in 3 patients. No other serious complications or side effects were observed.

Conclusions: Intralesional bleomycin therapy was very effective in the treatment of cystic lymphangioma. Our results were comparable to other published studies. Bleomycin administered as intralesional injection was found to be safe as there was no serious complication or side effect observed in this study.

Keywords: Bleomycin, Lymphangioma, Sclerotherapy

INTRODUCTION

Lymphangiomas are benign hamartomatous lymphatic tumors, characterized by multiple communicating lymphatic channels and cystic spaces. They occur in nearly all regions of the body but are most frequently seen in the neck (75%), axilla (20%), and inguinal areas $(2\%)^{1}$

Usually presents with swelling and cosmetic deformity, but a large lesion in the neck can compress vital structures, cause respiratory obstruction, dysphagia and symptoms of nerve compression. Most of them are evident at birth (65%), while 80-90% become manifest by the age of 2 years.² The incidence of lymphangioma is reported to be from 1.5-2.8 per 1000, and it has no predilection for either sex or any race.3 The mainstay of therapy is surgical excision, but due to its infiltration along the nerves and muscles, total excision is not always possible.

Extensive surgery may sometime lead to disfigurement, damage to vital structures, and ugly scar. Injection of sclerosing agents has long been used. Intralesional sclerotherapy has become an acceptable method of treatment for lymphangiomas in children to avoid the morbidity associated with surgical excision. It involves the use of a sclerosing agent that causes irritation of the endothelial lining of the lymphangioma, which leads to inflammation, fibrosis and involution.⁴ In the past, boiling water, 50% dextrose, hypertonic saline, or absolute alcohol has been employed. The results were not particularly encouraging. With the advent of agents like bleomycin, acetic acid, OK-432, doxycycline, many centers are using them as first line of therapy with satisfactory results.⁵ In the present study, we have evaluated the clinical profile of all the lymphangioma cases coming to our unit and evaluated the efficacy of intralesional bleomycin as a sclerosing agent in its management.

METHODS

Thirty-six patients with cystic lymphangioma were treated between 2008 to 2014 in the author's unit; all patients coming to the department were included in the study. The exclusion criteria were lesions infiltrating the mediastinum, lesions around the trachea, frank infection, and deep retroperitoneal lesions. Diagnosis was done mainly on clinical finding. All patients had a detailed clinical evaluation, along with pre-treatment clinical photograph.

Ultrasonography of all patients was performed Figure 2 and 5. The volume of lymphangiomas was calculated by the following formula- Length× breadth× depth×0.52 cc, where 0.52 is correction factor. CT scan was needed in a few. Fine Needle Aspiration Cytology (FNAC) was done in doubtful cases. Procedure was performed on an outpatient basis under oral / IV sedation and under local anaesthesia in the operative room after taking consent from a parent. 1 unit of bleomycin is equivalent to 1mg. The required dose was calculated as 0.5 mg/kg body weight, not exceeding 10 units at a time. After local part preparation with USG guidance cyst was aspirated and maintaining intra cystic position of the needle diluted bleomycin was injected.

If the cysts were not communicating with each other, they were aspirated at multiple sites and bleomycin was injected at multiple sites. The patient was subjected to observation till evening. Repeat dose was offered after 2-3 week intervals depending on clinical response. Bleomycin was halted when the swelling disappeared clinically, or there was no response or the swelling became stationary. When bleomycin sclerotherapy was no longer required or no longer feasible, the follow-up period was increased to 3 months, and then 6 months until the size of the lesion was stable.

Total numbers of injections needed were noted and the aggregate dosage was constrained to less than 5 unit/kg. The response to the treatment was monitored by clinical (length, breadth and area) and ultrasonography. The response was graded as excellent when complete disappearance, good (>50% reduction) and poor (<50% reduction). Mean follow-up period was 2.7 years (range 10 months to 6 years).

RESULTS

During the study period of 6 years, 36 patients with lymphangioma were included in the study. 27 were male and 9 were female. Twenty-one (58.3 %) patients were seen before 1 year of age. Nine (25%) patients presented between 1 to 2 years of age and six (16.6 %) patients presented after 2 years. Of the 36 cases, 30 (83 %) were cystic hygroma, 1 (2.7%) cavernous, and 5 (13.8%) were of mixed type. The neck region was the most common site with 26 patients, followed by axilla 7; face 2 and 1 in chest wall.

Out of the 36 patients included in the study, 3 (8.3%) required single dose, 11 (30.5%) required two doses, 14 (38.8%) required three doses, 4 (11%) required four doses, and 4 (11%) required six doses of intralesional bleomycin. The complete resolution was seen in 16 (44.4%), good in 17 (47.2%), and poor in 3 (8.3%) patients. Out of 30 patients of cystic hygroma, 15 (50%) showed complete resolution, and 15 showed good response (50%). The cavernous variety showed excellent response (100%). Out of five patients of mixed variety, two (40%) showed good response and three (60%) showed a poor response.

Nine patients who developed side effects, 3 (33.3%) developed fever, 3 (33.3%) had a transient increase in size of swelling, 2 (22.2%) developed mild tenderness and fever, and 1 (11.1%) showed skin discoloration at injection site. No patient developed excessive scarring as a result of the procedure (Figure 1, Figure 4 and Figure 3, Figure 6).



Figure 1: Before bleomycin injection.



Figure 2: USG.



Figure 3: After complete resolution.



Figure 4: Before bleomycin injection of patient.

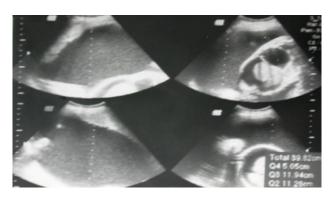


Figure 5: USG of patient.

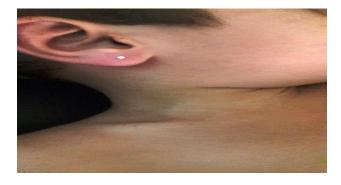


Figure 6: After complete resolution of patient.

Intralesional bleomycin therapy failed in 3 patients. Patients who failed sclerotherapy had six injections and minimal reduction in size was achieved. Further, sclerotherapy could not be performed because this patient

had a mixed type of lymphangioma. After six injections, there were not any further cysts large enough for aspiration and injection.



Figure 7: Scar and recurrence after surgery.

This patient subsequently underwent surgical resection. There were three (8%) reappearances of swelling, presented at 8, 10 and 14 months after the last received injections. 2 had good response after 2 injections of bleomycin and third had complete resolution after another injection of bleomycin.

DISCUSSION

Lymphangioma is a common developmental anomaly of the lymphatic system. It is characterized by the formation of a multilocular cystic mass of variable size. Lymphangioma are thought to arise from a combination of the following: failure of lymphatic's to connect to the venous system, abnormal budding of lymphatic tissue, and sequestered lymphatic rests that retain their embryonic growth potential. These lymphatic rests can penetrate adjacent structures or dissect along fascial planes and eventually become canalized. These spaces retain their secretions and develop cystic components because of the lack of a venous outflow tract. The nature of the surrounding tissue determines whether the lymphangioma is capillary, cavernous, or cystic.6 Lymphangioma has been categorized into three varieties: (a) Lymphangioma simplex, composed of capillary sized thin walled lymphatic channels, (b) Cavernous lymphangioma and (c) Cystic lymphangioma, composed of cysts of few millimeters to several centimeters in diameter. Different varieties frequently co-exist.

Surgery had been the mainstay of treatment of lymphangioma. However, even in the most expert hands, it still carries a complication rate as high as 12-33%, and a recurrence rate of 15-53%. (Figure 7). Owing to surgical complications, multiple non-surgical strategies have been attempted in order to cure the lesion with minimal complications. Unlike in hemangiomas, spontaneous resolution of lymphangioma is rare. Sclerotherapy provides a viable alternative to surgery in patients with macro cystic lymphatic malformations. §

Various sclerosing agents have been used, namely iodine, ethanolamine oleate, alcohol, tetracycline and cyclophosphamide. Bleomycin and OK-432 are currently the most popular sclerosants. The sclerosant damages the epithelium lining the cystic spaces, with subsequent decrease in lymph fluid production and collapse of the cysts. Desired effect of sclerosis is achieved by local action of bleomycin, which depends on availability of drug per unit surface area of the lesion. Side effects of Bleomycin are fever, transient increase in size of the swelling, hemorrhage, leukocytosis, infection, and pulmonary fibrosis.

The primary concern of bleomycin therapy is its risk of pulmonary toxicity. The risk is dose related with an increased incidence associated with a total dose exceeding 400 I.U. or a single dose exceeding 30 mg/m² of body surface area given intra-venous. However, the doses used in sclerotherapy were much smaller and authors in their series with intralesion albleomycin therapy reported nil pulmonary fibrosis as a complication. Current study used 0.5 mg/kg of dose. Others have used it in doses ranging from 0.3 to 3 mg/kg. In this study, complications were found in 9 (28.5%) patients, which is less than some studies where complications were noted in about 43% of patients. Others have noted fewer complications as opposed to this study.

In this prospective study, we found the response satisfactory in almost 86% of cases (complete resolution in 16 and good in 17). Studies using bleomycin have produced promising results. Rozman et al noted excellent and good response in 63% and 21% patients.8 Okada et al, reported significant results in 25 of 29 patients (86%) and complete disappearance in 55%. Niramis et al noted 83% of response whereas Baskin et al noted about 95% of response, suggesting good activity of bleomycin for the purpose. 16-18 Two recurrences were seen in this study. The study defined recurrence as the reappearance of the tumour after complete resolution or increase in size after initial significant reduction in size was seen. Others have also not found a recurrence to be of much concern.¹⁹ Although mortality has been reported, it was not seen in this series.14

CONCLUSION

Intralesional bleomycin therapy is an effective alternative to surgery where there are chances to endanger vital structures. Use of bleomycin as an intralesional agent for lymphangioma appears to be safe and gratifying. Sclerotherapy is recommended in place of surgery as the first line treatment modality. The latter must be limited to those lesions where sclerotherapy had failed.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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