Bleomycin Sclerotherapy in Lymphangiomas of Head and Neck: Prospective Study of 8 Cases

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Abstract The aim of this study is to evaluate the role of bleomycin as a primary mode of nonsurgical treatment in lymphangiomas of head and neck and study their complications. This is a prospective study of 8 patients diagnosed with lymphangioma of head and neck presenting to ENT department of Tata main Hospital from December 2014 to January 2017. They were clinically and radiologically evaluated and treated with intralesional injection of bleomycin diluted in normal saline. Complete resolution was seen in 62.5% (5/8) of patients, 25% (2/8) had good response while 12.5% (1/8) had a poor response. No major complications were noted apart from fever and inflammation. Intralesional bleomycin can be used as a primary modality of treatment.

Keywords Bleomycin · Sclerotherapy · Lymphangioma · Surgery

Introduction

Lymphangioma is a slow growing benign tumor of lymphatic vessels that are often present at birth and are usually diagnosed during early childhood (90%) [1]. They may arise in any soft tissue or organ. The most common sites are head and neck followed by axilla and mediastinum. Usually diagnosed in childhood but rare occurrences have been reported in adults also. The most common symptoms

are swelling and deformity. A large lesion may cause dysphagia and respiratory obstruction.

Diagnosis is usually based on the previous history, clinical examination followed by radiological and pathological findings. Treatment of choice is complete surgical excision; however complete removal is impossible in many cases due to infiltration of tissue and neurovascular planes. Intralesional sclerotherapy, incision and drainage and radiotherapy are other options.

Intralesional sclerotherapy was previously reserved for unresectable lesions, but it has emerged as a good option even as a primary treatment in recent years. It causes irritation of the endothelial lining of vessels which elicits severe inflammation which eventually leads to fibrosis [2]. Several studies have used bleomycin, alcohol, OK 432 and trichloroacetic acid with variable results [3].

In this study, we are sharing our experience by using bleomycin as a sclerosant since OK 432 is not yet available in India.

Materials and Methods

This was a prospective study of 8 cases of lymphangioma presented to our ENT department of Tata Main Hospital Jamshedpur. Age of our patients varied from 4 to 54 years (5 male, 3 females). Duration of our study was May 2014–December 2016.

The diagnosis of lymphangioma was made on the basis of history, clinical examination followed by radiological examinations, mainly ultrasound (done in all patients), computed tomography (CT) (3 cases) and magnetic resonance imaging (MRI) (1 case). Fine needle aspiration was used in 3 cases.

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Ultrasonography revealed the cystic nature of the lesion and its relation to surrounding tissues. It was used to classify the type of lymphangioma. Three types of lymphangioma's were seen—macroscopic (size > 1 cm), microcystic (size < 1 cm) and mixed. Lymphangioma of size less than 1 cm and extending to axilla or mediastinum were excluded from our study.

We did CT on 3 patients and MRI on 1 patient. It was to rule out hemangioma, or involvement of any blood vessel and to see the extent of the lesion. After proper diagnosis age, sex, site, size, body weight and symptoms were recorded.

General anaesthesia was used in all 5 children's and in one adult of age 48 years (failed sclerotherapy). Rest of the 3 cases were done in local anaesthesia under aseptic conditions as a day care case. Cysts were aspirated using a 24G needle and hypodermic needle under ultrasound guidance. A vial containing 15 IU of bleomycin powder was diluted by 10 ml normal saline to a concentration of 1.5 mg/ml, the dose was calculated according to body weight. The recommended dose of bleomycin is 0.5 mg/kg. Keeping the tip of the needle within the lumen 1–5 ml aqueous solution of 1.5 mg/ml bleomycin was injected under USG guidance. Same procedure was repeated in case of multiple cysts with divided doses. Aspirate was then sent for cytology.

Day care patients were observed for 5 h while others were admitted for 24–48 h to monitor and record early and late complications of the procedure.

Follow up was done until 4 weeks, clinical assessment and measurement of the lesion were done on every visit. The procedure was repeated for cysts measuring more than 1 cm at 4 weeks. Response was noted as complete resolution (total disappearance), good response (for > 50% reduction) and poor response (for < 50% reduction). Failure was noted when the lesion reappeared or did not show any reduction in size at 4 weeks. Follow up was done until 1 year.

Cases with poor response and failure were offered surgical excision. Informed consent was obtained from all individual participants included in the study (Fig. 1).

Results

Patients were aged between 4 and 54 years (5 females, 3 males). Size varied from 1.5 to 8 cm in maximum diameter. The swelling was seen in all patients ($n = 8$). Pain ($n = 4$), difficulty in swallowing ($n = 1$), Difficulty in chewing ($n = 1$), fever ($n = 1$) and skin erythema ($n = 1$). Head and neck were involved in all ($n = 8$). Cheek and supra-orbital area was involved in 1 case, only cheek in

Fig. 1 a Lymphangioma of cheek extending up to the supra-orbital area in 7 year old girl, b ultrasound guided aspiration, c ultrasound image showing the tip of the needle in the cyst, d post-operative after 6 months

($n = 2$), only neck ($n = 2$) and cheek and neck in ($n = 3$). Body weight was between 17 and 78 kg.

Number of procedures varied from 1 to 3 with total dose of bleomycin 1–15 mg. Dark chocolate colour aspirate was of 1–12 ml.

Complete resolution was seen in 62.5% (5/8) of patients, 25% (2/8) had good response while 12.5% (1/8) had poor response at the end of follow up. 1 patient opted for surgical excision at the end (Fig. 2).

Erythema, pain were the most common early complications ($n = 6$), fever ($n = 2$) and restricted movement of the neck was seen in 35-year-old diabetic ($n = 1$) who eventually developed an abscess for which incision and drainage was done and was admitted for 3 days for intravenous antibiotics and insulin. No hypersensitivity or respiratory problems was noted with bleomycin (Tables 1, 2).

Discussion

Lymphangioma is a slow growing congenital malformation of lymphatic vessels that are often present at birth and diagnosed in childhood. The first case of lymphangioma treated by sclerotherapy was reported in 1933, using

Fig. 2 **a** Lymphangioma of cheek extending up to neck in a diabetic patient, **b** ultrasound showing macrocystic type of lymphangioma, **c** MRI image showing extension in neck

Table 1 Results

Results	Complete resolution ^a	Good response ^a	Poor response ^a
Age 1–15 years	4/5 (80%)	1/5 (20%)	0
Age 16–54	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)
Total	5/8 (62.5%)	2/8 (25%)	1/8 (12.5%)

^aComplete resolution 100% resolution, good response > 50% resolution, poor response < 50%

Table 2 Complications

Complications	Total %
Erythema, pain	6/8 (75%)
Fever	2/8 (25%)
Restricted neck movement	1/8 (12.5%)
Abscess	1/8 (12.5%)

sodium morrhuate. In that complete tumour regression was noted in 6 weeks following intralesional injection [4]. The idea of using sclerotherapy in the treatment of lymphangioma occurred when it was noted that lymphatic malformations spontaneously involute when they became infected and the infection resolved leading to fibrosis. After that, various sclerosing agents have been used like iodine, ethanolamine oleate, OK-432, alcohol, ethibloc, tetracycline, cyclophosphamide and bleomycin. Since OK-432 was introduced by Ogita et al. [5], reports have focused on the use of OK-432 as a first-line treatment for lymphangioma.

US, CT and MRI should be used to define the relationship of the lesion with the neighbouring structures and to help plan surgical or non-surgical strategies.

Spontaneous or traumatic haemorrhage of the cysts is the most common complication of a neglected lesion.

Bleomycin is an anti-neoplastic antibiotic, produced by streptomyces verticillus. Discovered in 1965, this drug was found to cause single- and double-strand DNA breaks and inhibition of DNA and RNA synthesis [4]. Since then bleomycin has been used for its anti-neoplastic property to treat malignancy. In the treatment of malignant pleural effusion, it was observed that bleomycin caused marked fibrosis and scarring. This sclerosing property was first put into use in the treatment of lymphatic malformation in 1977. In that series, 8 patients who either had incomplete surgical resection, recurrent or non-resectable tumour were treated with bleomycin. Good results were reported in these patients [4].

Various studies using bleomycin have shown promising results [4, 6–8]. Our study indicated that intralesional bleomycin therapy was very effective as a primary therapy for large lymphangioma's (1.5–8 cm) and the results were comparable to these published series. Different authors have quoted success rates of between 36% to 63% for complete tumour regression, of up to 88% significant lesion regression, and poor response of between 12 and 23% using either bleomycin or OK432 [8] which is comparable to our study (Table 3).

Table 3 Previous studies on intralesional bleomycin

Study	No. of patients	Complete resolution ^a (%)	Significant response ^a (%)	Poor response ^a (%)
Tanigawa [9]	33	39.4	82	18
Zulfiqar [10]	11	36	82	18
Rozman [6]	24	63	84	16
Porwal (this study)	8	62.5	87	12.5

^aComplete resolution 100% resolution, significant response (good + complete) i.e. 51–100% resolution, poor response 0–50%

Poor response (12.5% or $n = 1$) in our study was due to poor long term glycaemic control in a 35-year-old diabetic with a large lymphangioma (6.5 cm) of cheek and sub-mandibular region, which lead to abscess formation and then recurrence. It was finally removed by surgical excision under general anesthesia (Fig. 2).

In our study, no serious complications were seen as a result of intralesional bleomycin therapy. Most patients complained of skin erythema, local swelling, pain, mild tenderness and fever. These symptoms lasted only for a day or two.

Conclusion

Bleomycin can be used as a primary treatment in cases of macrocystic lymphangioma. Results of our study are comparable to other published series [4, 6, 9]. In our study, no major complications were observed showing its safety in both children's and adults. Our recommendations are to use intralesional bleomycin as a primary modality of treatment and save surgical interventions for failed or complicated cases. Our limitations were small sample size and limited resources.

Compliance with Ethical Standards

Conflict of interest Dr. Prateek Kumar Porwal, Dr. K.P. Dubey, Dr. Amit Morey, Dr. Harshita Singh, Dr. Pooja. S and Dr. Alokendu Bose declare that they have no conflict of interest.

Informed Consent Informed Consent was taken from each of the participants, Additional informed consent was obtained from all individual participants for whom identifying information (pictures) is included in this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of

Tata Main Hospital Ethical committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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