Original Research Article

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Efficacy of intralesional bleomycin in treatment of lymphangiomas in children: an observational study

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ABSTRACT

Background: Lymphangioma, a benign slow growing tumor of lymphatic vessels, common to the pediatric age group usually presents as swelling with cosmetic deformity. Commonly affecting the head and neck region it may present with compressive symptoms like airway obstruction or dysphagia. Previously surgical excision was the treatment of choice but it involves significant risks and so sclerotherapy has gained popularity. We conducted this prospective observational study to have a quantitative analysis of the effect of intralesional bleomycin in reducing the size of lymphangiomas in children in our setup.

Methods: This observational study was conducted in the paediatric surgery department between 2014 and 2016. A total of 34 children who presented with swellings which were diagnosed to be lymphangiomas based on clinical and sonological basis were included in the study and underwent intralesional bleomycin sclerotherapy. Details like dimensions of the lesion before and after the treatment, ultrasound measurement, residual size, characteristic of the cyst like presence or absence of septation, micro or macrocytic were recorded along with demographic details like age and sex. Outcome after 4 weeks was evaluated and classified into 3 groups as in excellent response, good response or poor response. Statistical analysis was done using R statistical software.

Results: Of the 34 patients 59% were males. The median age was 18 months with inter-quartile range 4-36 months. 88% of patients had macrocystic lesions. 4 weeks after bleomycin sclerotherapy excellent response was seen in 23 (68%) of the patients, good in 8 (26%) and poor in 3 (9%) of the patients. There was statistically significant association between post procedure swelling, type of cysts and presence of septations and the number of sittings required to the outcome (p value <0.05).

Conclusions: Present study shows that intralesional bleomycin sclerotherapy is very effective in the treatment of lymphangiomas in children, with macrocystic lesions showing a significantly better response.

Keywords: Bleomycin, Paediatric lymphangioma, Sclerotherapy

INTRODUCTION

Lymphangioma is a benign slow growing tumor of lymphatic vessels, the most frequent site being in the head and neck region, axillla and rarely in the mediastinum. This tumor is usually confined to the pediatric age group. However, it has been reported in

adults as well. 3 It manifests at birth in up to 65% of cases and presents by 2^{nd} year of life in 80-90% of cases.

The reported incidence of lymphangioma is 1.5 to 2.8 per 1000 across both gender and all races. The common presentation of these lesions is swelling and cosmetic deformity. In addition, a swelling of significant size can

compress vital structures and cause airway obstruction, dysphagia, speech abnormalities.^{4,5}

Previously, surgical excision was the treatment of choice.⁶ Other options are radiation therapy and incision and drainage, with unsatisfactory results. As the lesion infiltrates the tissue planes and encircles the neurovascular structures, complete surgical extirpation is not a viable option in many cases.⁷ Moreover, Recurrences, scar formation and nerve injuries are common complications following surgery.^{1,2}

Intra lesional sclerotherapy has gained popularity as an acceptable method of treatment for lymphangiomas in children with more effectiveness in macro cystic lesions. 1,8-11 Injection sclerotherapy produces irritation of endothelial lining of the lymphangiomas which leads to inflammation and fibrosis eventually leading to involution.

There has been little quantitative analysis of the effect of intra-lesional injection of bleomycin in our setup. This prospective observational study was conducted to find out the effect of intra lesional bleomycin injection of bleomycin in reducing the size of lymphangioma in children.

METHODS

We conducted this prospective observational study at the department of pediatric surgery at government medical college kozhikode from 2014 to 2016. All consecutive patients satisfying the inclusion criteria were recruited into the study. We selected only those patients with age less than 12 years who presented with swelling diagnosed as lymphangioma based on clinical and ultrasound imaging. Only those patients with lesion containing straw-colored serous fluid on aspiration were included in the study. We excluded swellings with size less than 2 cm. Moreover, Post surgical recurrent lesions were also excluded from the study. We studied 34 patients in total. Using a predesigned and pretested data collection form, we collected demographic variables like age, sex, body weight, weight. In addition, we recorded other details like size of the lesion before and after the treatment. ultrasound measurement, residual size, characteristic of the cyst like presence or absence of septation, micro or macrocytic and outcome in terms of excellent, good or bad.

Under sedation and local anesthesia and with strict aseptic precautions, the cyst was aspirated with a 18G needle. While keeping the tip of the aspiration cannula within the cyst lumen, 0.5 IU per Kg body weight of Bleomycin was injected. The calculated dose was diluted with distilled water. If multiple septations were detected on pre procedure ultrasound evaluation, the drug was injected into different cysts separately. Patients were observed for 24 hours post procedure and observed for any immediate complications.

Response was recorded after four weeks after the procedure clinically and with ultrasound measurements. This procedure was repeated after four weeks if the cystic component persisted and measured greater than 1 cm cube volume. No further attempts were made if there was a poor response to two sittings of procedure.

The response was graded based on clinical appearance and the volume reduction as per ultrasound into three categories.

- Excellent response: no obvious swelling clinically and USG showing no residual lesion or residual solid lesion or if residual cystic lesion a volume reduction >80% in size with single/multiple doses of neomycin.
- Good response: Clinically obvious swelling but with significant reduction in size clinically and with reduction in volume on USG >50% but less than 80% with multiple sittings.
- Poor response: Minimal change in size clinically after two sittings.

We had obtained institutional ethics committee clearance before conducting and recruiting patients. Informed consents were taken from parents and assent from the patients.

Statistical analysis

Statistical analysis was done in R software. We summarized continuous data as mean (\pm) and standard and categorical data as proportions. Associations were studied with chi-square test. Before and after measurements were compared with paired T test. During analysis, wherever missing data was present. We considered only complete cases for analysis. Statistically, significance was taken as p value <0.05.

RESULTS

Out of the 34 patients in present study, there was a male preponderance with 20 (59%) constituting the males. The median age was 18 months (IQR 4-36).

Table 1: Demographic features.

	(ALL) N=34
Age	18.0 (4.25; 34.5)
Gender	
Female	14 (41.2%)
Male	20 (58.8%)
Site	
Axilla	3 (8.82%)
Chest wall	3 (8.82%)
Face	1 (2.94%)
Limb	2 (5.88%)
Neck	25 (73.5%)

The mean size of the swelling was 6 cm X 5cm (± 3 X2). The median volume on sonological evaluation was 25 (IQR 15-35). The most common site affected was neck with 25 (74%) affected with face being the least affected (Table 1).

The post procedure result was excellent in 23(68%) of the patients, good in 8(26%) and poor in 3 (9%) of the patients. No other symptoms were present in 94 % of the patients.

Table 2: Baseline comparison of demographic features.

	(ALL) N=34	Excellent N=23	Good N=8	Poor N=3	p overall
Age	18.0 (4.25;34.5)	18.0 (4.00;30.0)	14.5 (9.50;39.0)	72.0 (37.0;84.0)	0.581
Length Clinical	6.00 (5.00;7.00)	6.00 (4.00;6.00)	6.00 (5.00;7.25)	7.00 (6.00;9.50)	0.378
Breadth Clinical	4.00 (4.00;6.75)	4.00 (3.50;5.00)	5.00 (4.00;7.00)	4.00 (4.00;6.50)	0.773
USG volume in cc	25.0 (16.2;35.0)	25.0 (15.0;35.0)	32.5 (18.8;37.5)	35.0 (27.5;40.0)	0.668
Length Post	2.73 (2.28)	. (.)	1.50 (0.53)	6.00 (1.73)	< 0.001
Breadth Post	2.18 (2.40)	. (.)	1.12 (0.35)	5.00 (3.46)	0.007
USG Residual	21.8 (10.4)	. (.)	12.0 (.)	25.0 (10.0)	0.377
Gender					0.155
Female	14 (41.2%)	12 (52.2%)	1 (12.5%)	1 (33.3%)	
Male	20 (58.8%)	11 (47.8%)	7 (87.5%)	2 (66.7%)	

Table 3: Association between various factors and outcome.

	(ALL) N=34	E N=23	G N=8	P N=3	p overall
No. of sittings					< 0.001
1	20 (58.8%)	19 (82.6%)	0 (0.00%)	1 (33.3%)	
2	12 (35.3%)	4 (17.4%)	7 (87.5%)	1 (33.3%)	
3	2 (5.88%)	0 (0.00%)	1 (12.5%)	1 (33.3%)	
Site					0.088
Axilla	3 (8.82%)	3 (13.0%)	0 (0.00%)	0 (0.00%)	
Chest	3 (8.82%)	2 (8.70%)	0 (0.00%)	1 (33.3%)	
Face	1 (2.94%)	0 (0.00%)	1 (12.5%)	0 (0.00%)	
Limbs	2 (5.88%)	0 (0.00%)	2 (25.0%)	0 (0.00%)	
Neck	25 (73.5%)	18 (78.3%)	5 (62.5%)	2 (66.7%)	
Other symptoms					0.005
Absent	32 (94.1%)	23 (100%)	8 (100%)	1 (33.3%)	
present	2 (5.88%)	0 (0.00%)	0 (0.00%)	2 (66.7%)	
Macro/Micro					< 0.001
Macrocystic	30 (88.2%)	23 (100%)	7 (87.5%)	0 (0.00%)	
Microcystic	4 (11.8%)	0 (0.00%)	1 (12.5%)	3 (100%)	
Septations					< 0.001
Absent	19 (55.9%)	18 (78.3%)	1 (12.5%)	0 (0.00%)	
Present	15 (44.1%)	5 (21.7%)	7 (87.5%)	3 (100%)	
Post procedure swelling					< 0.001
Absent	23 (67.6%)	23 (100%)	0 (0.00%)	0 (0.00%)	
Present	11 (32.4%)	0 (0.00%)	8 (100%)	3 (100%)	

Most of the patients (88%) presented with macrocytic swellings.

Septations were present in 44% of the patients. Of the patients who underwent the procedures, only 11 (32%) had residual swellings. Baseline comparison of various demographic features across the outcome group is given in Table 2. There was a statistically significant difference between the breadth of the swelling before and after the study (Table 2). The mean difference was 3.27cm (CI 4.7-1.8). Similarly, there was a statistically significant

difference between the length of the swelling before and after the study (Table 2).

The mean (±) difference in length was 4 cm (CI 5.6 to 2.5). Only in 22 patients full information was available. There was no association between gender and type of cysts like macroscopic or microscopic or septations. There was statistically significant association between post procedure swelling, type of cysts and presence of septations to the outcome (p value <0.05) (Table 3). There was a statistically significant association between

number of sittings and outcome with patients with poor outcome requiring more sittings (Table 3).

DISCUSSION

The purpose of this study to determine whether intra lesional injection sclerotherapy with bleomycin is effective in treating the lymphangioma in the pediatric age group. The result from the study showed that the outcome was excellent in the majority of the patients. There was a reduction in the overall size of the swelling before and after the injection of intra lesional bleomycin. There was excellent response in majority of the patients. Both sonological and clinical assessment confirmed this. There was a statistically significant difference in the measurements both clinically and sonologically.

The reduction in size could be due to aspiration of the fluid. Thereafter, the sacrosanct injected would have caused apposition of the collapsed walls thereby reducing the overall size. Simple aspiration alone will result in recurrence. However, in present study, the follow-up result showed an excellent outcome in the majority of the patients. Several studies using bleomycin as an intralesional sclerosant have shown favorable results compared to surgery. Tanigawa N et al described the effective use of bleomycin fat emulsion for treatment of cystic hygromas. 12 In a study by Orford et al. intralesional bleomycin showed an excellent response in 44% and good response in another 44% of patients with minor transient side effects.¹³ Studies conducted in Malaysia showed complete resolution in 63% where as 21% showed good response.8 66% of children showed a complete response with only 11% needing a second sitting for resolution.14

A retrospective study with intralesional bleomycin showed a complete response in 63% of children with a good response in 21% and poor response in 16% without any serious side effect or complication. Most authors have quoted success rates of between 36 to 63% for complete tumor regression and up to 88% for significant lesion regression without significant side effects. Poor response varied between 12 -23%. Most published data show a good response to macrocystic forms of lymphangiomas. In the present study, 68% of the patients showed an excellent outcome. The increased proportion of macrocystic swellings in present study could explain the better results compared to the reported response rate in other studies in the literature.

One of the limitations in present study is the low sample size and its observational nature. In addition, there were lost to follow up and missing data in present study. Properly designed randomized controlled trial s will address the limitations in the present study.

Present study has shown there is excellent response rate for macrocystic swellings. Moreover, multiple sittings are needed for swelling presented with poor outcomes.

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