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Intralesional Bleomycin and Ethanolamine Oleate in the Treatment of Cystic Hygroma in Children: A comparative study

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Abstract
Background: *Cystic hygroma is a congenital malformation of the lymphatic system that often poses significant clinical challenges due to its location and potential complications. Surgical excision, though traditionally preferred, carries risks of recurrence, incomplete resection, and morbidity. Intralesional sclerotherapy has emerged as a safer, less invasive alternative.*
Aim of the study: *To compare the efficacy, safety, and cost-effectiveness of intralesional ethanolamine oleate and bleomycin hydrochloride in the treatment of cystic hygroma in children.*
Methods: *This prospective, comparative study was conducted at Dhaka Shishu Hospital from January 2012 to June 2013. Sixty children (≤12 years) with clinically and ultrasonographically confirmed cystic hygroma were randomly allocated into two groups: Group A (n=30) received ethanolamine oleate, and Group B (n=30) received bleomycin. Patients were followed up for therapeutic response, adverse effects, and cost of treatment.*
Result: *Both groups demonstrated comparable outcomes in terms of lesion regression. Excellent response (91–100% reduction) was observed in 53.3% of Group A and 46.7% of Group B. The mean regression rate was 82.07% in Group A and 77.13% in Group B ($p>0.05$). Most patients required 2–3 injections. Adverse effects such as redness, fever, and vomiting were more frequent in the bleomycin group, while ethanolamine oleate showed better tolerance. Importantly, treatment cost was significantly lower in Group A (mean BDT 1,080) compared to Group B (mean BDT 3,900; $p<0.001$).*
Conclusion: *Both ethanolamine oleate and bleomycin are effective in the management of cystic hygroma in children. However, ethanolamine oleate is more cost-effective, with fewer adverse effects, making it a preferable therapeutic option in resource-limited settings. Long-term follow-up and larger multicenter studies are needed to confirm these findings.*
Keywords: *Cystic hygroma, ethanolamine oleate, bleomycin, intralesional therapy, sclerotherapy, children*

I. Introduction

Cystic Hygromas are developmental malformation of the lymphatic system that belongs to the Lymphangioma family- it is a benign hamartomatous tumors of the lymphatic system, characterized by multiple communicating lymphatic channels and cystic spaces [1]. Cystic hygroma can lead to morbidity because of its compression of adjacent organs such as respiratory obstruction, dysphasia, nerve compression, malocclusion or can result in local inflammation, infection, haemorrhage and sinus formation [2]. Surgical excision is considered by most surgeons to be the treatment of choice for lymphangioma. However, total excision with preservation of the involved vital structures is not always possible, because the lesions commonly extend into surrounding tissue or infiltrate vital structures [3]. As most of the lesions occur in the neck, during surgery there is a chance of injury to the facial nerve, phrenic nerve, recurrent laryngeal nerve, brachial plexus and great vessels like carotid arteries, jugular veins. On the other hand, income plate excision may be followed by lymphorrhoea, wound infection or recurrence of the lesion [4]. The recurrence is most likely within the first year after resection [5]. Complications of total resection, recurrence of incomplete resection and difficulties in subsequent surgery have emphasized the need to develop an effective alternative to surgical treatment of cystic hygroma [6]. Laser therapy in patients with lymphatic malformation of the upper aerodigestive tract is safe and repeatable [7]. Different agents have been used intralesionally till now, such as Doxycycline, OK-432, Fibrin glue with variable response [8]. A satisfactory therapeutic response to local bleomycin in cystic lymphangioma, incompletely resectable or with postoperative recurrence and also non resectable cystic hygroma [9]. Intralesional bleomycin has been used in different countries like Australia, Japan, and Malaysia as an effective non-surgical measure against lymphangioma with promising results and without any serious side effects [2,10, 11]. Ethanolamine Oleate is a safe agent with minimum side

effects like mild pain, low grade pyrexia and rarely hypersensitivity reactions. It is very cheap in comparison to other sclerosing agents and easily available in Bangladesh. It is commonly used for endoscopic sclerotherapy in the treatment of esophageal varies [12]. The basic mechanism of therapeutic effect of sclerosant is thought to involve changes resulting from reaction of tissue to the chemical agent. Inflammation, sclerosis and cicatricial contraction of lesion follow the injections. Therefore, the difference in the efficacy may be related to the ratio between cystic spaces and surrounding tissue in each lymphangioma [3]. The aim of this study was to compare the efficacy and safety of intralesional bleomycin versus ethanolamine oleate in the treatment of cystic hygroma in children, in order to identify the more effective and safer therapeutic option.

II. METHODOLOGY & MATERIALS

This was a prospective, comparative, interventional study conducted at Dhaka Shishu Hospital, Bangladesh Institute of Child Health (BICH), Sher-e-Bangla Nagar, Dhaka, during the period from January 2012 to June 2013. All newly diagnosed, untreated cases of cystic hygroma presenting to the Outpatient Department of Pediatric Surgery at Dhaka Shishu Hospital were considered for inclusion. On average, 4–6 such patients present per month (≈60 cases per year). A total of 60 patients were selected and randomly allocated by lottery method into:

Group A (n=30): Patients treated with intralesional ethanolamine oleate
Group B (n=30): Patients treated with intralesional bleomycin

Inclusion Criteria:
- Children aged ≤12 years (≤144 months).
- Clinically and ultrasonographically confirmed cases of cystic hygroma.

Exclusion Criteria:
- Immediate life-threatening lesions.
- Aspiration revealing pus or blood.
- Intra-abdominal hygroma.
- Mediastinal extension.
- Patients unable to complete the treatment schedule.

Ethical Considerations

The study protocol was approved by the Thesis and Ethical Review Committee of BICH and Dhaka Shishu Hospital. The objectives, procedures, benefits, and potential risks were explained to parents/guardians, and written informed consent was obtained prior to enrollment.

Investigations

All relevant investigations were performed to support diagnosis, determine the extent of lesions, and monitor systemic effects of the drugs. Hematological investigations included hemoglobin percentage, total WBC count, and differential WBC count. Imaging studies consisted of ultrasonography, which was done for all patients to evaluate size, septation, and extension of the lesion, while chest X-ray was performed when mediastinal extension was suspected.

Treatment

After counseling, written informed consent was obtained, and patients were admitted for the first injection. Oral cephradine (50–100 mg/kg/day in four divided doses) was started on the day of aspiration and continued for three days. Aspiration of cyst contents was done under strict aseptic precautions, and in multiloculated lesions, each cavity was aspirated separately before sclerosant injection. Patients were monitored in the hospital for at least 24 hours after the procedure.

Dose Schedule: In Group A, ethanolamine oleate was given at 0.4 ml (20 mg)/kg body weight, with a maximum dose of 20 mg, or 0.4–1 ml/cm² of lesion surface area. In Group B, bleomycin was administered at 0.2–0.6 mg/kg body weight, prepared as a 1 mg/ml solution in normal saline.

Follow-up: Patients were reviewed on day 1 and at week 1 for adverse effects, and again at weeks 4 and 8 after each injection to evaluate therapeutic response. Repeat injections were given at four-week intervals if residual swelling was present, with a maximum of four sessions allowed. Final assessment was carried out eight weeks after the last injection.

Post-procedure Care: After injection, patients were kept under observation for at least one hour. Oral cephradine was continued for three days, and paracetamol (10–15 mg/kg/dose, three to four times daily for 2–3 days) was prescribed for pain relief.

Outcome Evaluation: Response to treatment was assessed according to percentage of regression of the lesion: excellent (91–100%), good (51–90%), fair (25–50%), and poor (<25%). In addition, adverse effects such as pain, redness, vomiting, fever, and swelling were recorded, and treatment cost was estimated in both groups.

Data Collection

Data were collected using a structured data sheet. A detailed history was obtained from each patient regarding age, sex, onset and progression of swelling, history of infection, and previous treatments. Clinical examination included assessment of the site, size, color, local temperature, tenderness, consistency, fluctuation, transillumination, and fixation to skin or underlying structures. Diagnosis was confirmed both clinically and ultrasonographically. Photographs were taken before aspiration, immediately after aspiration, and during follow-ups at four and eight weeks.

Statistical Analysis

All data were entered and analyzed using SPSS version 16.0. Quantitative variables were expressed as mean ± standard deviation and compared between groups using Student's *t*-test. Qualitative variables were expressed as frequency and percentage and analyzed using the Chi-square (χ^2) test. A *p*-value of <0.05 was considered statistically significant.

III. RESULT

The mean age was 28.83 ± 29.59 months in Group A and 27.83 ± 24.06 months in Group B, with most patients falling within the 0–30 month age range. The gender distribution was nearly equal in both groups (male: 53.3% vs. 46.7%; female: 46.7% vs. 53.3%). The most common site of cystic hygroma was the neck, observed in 60% of Group A and 46.7% of Group B, followed by the axilla, trunk, forearm, and cheek. No statistically significant differences were noted in baseline age, gender, or lesion location between the two groups ($p > 0.05$) (Table 1). In terms of regression of cystic hygroma size, an excellent response (91–100% reduction) was observed in 53.3% of patients in Group A and 46.7% in Group B, while a good response (51–90% reduction) was seen in 33.3% of patients in both groups. Poor response (<25% reduction) was slightly higher in Group B (20%) compared to Group A (13.3%), though the difference was not statistically significant ($p = 0.766$) (Table 2). Analysis of swelling size showed that the mean pretreatment size was 27.67 ± 28.49 cm² in Group A and 23.53 ± 12.91 cm² in Group B. At the last follow-up, the mean size reduced to 4.19 ± 5.98 cm² in Group A and 4.53 ± 5.68 cm² in Group B. The percentage regression was 82.07 ± 26.11% in Group A and 77.13 ± 31.13% in Group B. These differences were not statistically significant ($p > 0.05$), indicating that both bleomycin and ethanolamine oleate were similarly effective in reducing cystic hygroma size (Table 3). The mean number of doses required was similar between the two groups, with Group A needing 2.40 ± 0.81 doses and Group B 2.60 ± 0.81 doses, showing no significant difference ($p = 0.345$). Most patients in both groups required 2–3 doses for effective regression (Table 4). However, a significant difference was observed in treatment cost: the mean cost in Group A was BDT 1,080 ± 366.15 (range 450–1,800), which was considerably lower than Group B at BDT 3,900 ± 1,220.51 (range 1,500–6,000), with the difference being statistically highly significant ($p = 0.0001$) (Table 5). Redness occurred in 20% of patients in Group B versus 6.7% in Group A, showing a statistically significant difference ($p = 0.038$). Other complications, including tenderness (13.3% vs. 20%), vomiting (0% vs. 13.3%), fever (13.3% vs. 26.7%), and temporary increase in swelling size (20% vs. 33.3%), were also more common in Group B, though not statistically significant (Table 6). Regarding the time required for regression of swelling, most patients in both groups achieved resolution within 8–12 weeks (80% in each group). The mean regression time was 9.60 ± 3.25 weeks in Group A and 10.40 ± 3.25 weeks in Group B, with no significant difference between them ($p = 0.345$) (Table 7).

Table 1: Baseline characteristics of the study population (N=60)

Variables	Group A (n=30)		Group B (n=30)		P-value
	n	%	n	%	
Age (months)					
0–12	14	46.7	12	40	0.866
12–30	14	46.7	16	53.3	
30–120	2	6.7	2	6.7	
Mean ± SD	28.83 ± 29.59		27.83 ± 24.06		0.886
Gender					
Male	16	53.3	14	46.7	0.606
Female	14	46.7	16	53.3	
Location					

Neck	18	60	14	46.7	0.835
Axilla	6	20	8	26.7	
Trunk	2	6.7	4	13.3	
Forearm	2	6.7	2	6.7	
Cheek	2	6.7	2	6.7	

Table 2: Comparison of outcomes (percentage of regression of size) between groups (N=60)

Variables	Group A (n=30)		Group B (n=30)		P-value
	n	%	n	%	
Excellent (91–100%)	16	53.33	14	46.67	0.766
Good (51–90%)	10	33.33	10	33.33	
Fair (25–50%)	0	0.00	0	0.00	
Poor (<25%)	4	13.33	6	20.00	

Table 3: Swelling size at pretreatment and last follow up

Measurement	Group A (n=30)	Group B (n=30)	P-value
Pretreatment (Mean ± SD)	27.67 ± 28.49	23.53 ± 12.91	0.472
Regression (%)	82.07±26.11	77.13±31.13	0.509
Last visit (Mean ± SD)	4.19 ± 5.98	4.53 ± 5.68	0.819

Table 4: Total number of doses of drug required among patients (N=60)

Doses	Group A (n=30)		Group B (n=30)		P-value
1	4	13.3	2	6.7	0.721
2	12	40	12	40	
3	12	40	12	40	
4	2	6.7	4	13.3	
Mean ± SD	2.40 ± 0.81		2.60 ± 0.81		0.345

Table 5: Cost effectiveness only related to drugs and appliances

Cost (BDT)	Group A (n=30)	Group B (n=30)	P-value
Mean ± SD	1,080 ± 366.15	3,900 ± 1,220.51	0.0001
Range	450–1,800	1,500–6,000	

Table 6: Post-treatment complication at day 1 (N=60)

Complication	Group A (n=30)		Group B (n=30)		P-value
	n	%	n	%	
Redness	2	6.67	6	20.00	0.038
Tenderness	4	13.33	6	20.00	
Vomiting	0	0.00	4	13.33	
Fever	4	13.33	8	26.67	
Temporary Increase in Size	6	20.00	10	33.33	

Table 7: Time required for regression of the swelling (N=60)

Time (weeks)	Group A (n=30)		Group B (n=30)		P-value
	n	%	n	%	
4	4	13.30	2	6.70	0.721
8	12	40.00	12	40.00	
12	12	40.00	12	40.00	
16	2	6.70	4	13.30	
Mean ± SD	9.60 ± 3.25		10.40 ± 3.25		0.345

IV. DISCUSSION

Cystic hygroma is a congenital malformation of the lymphatic system, belonging to the lymphangioma family. Although it is usually a superficial lesion, it may spread along neurovascular structures, particularly in the neck, making surgical excision technically difficult. In some cases, this benign swelling behaves aggressively, mimicking malignant growth [9]. Surgical excision has long been considered the treatment of choice; however, results have often been unsatisfactory due to high morbidity, mortality, and recurrence rates. Hancock et al reported an overall complication rate of 31.3%, with neurological complications in 17% of cases [13]. The recurrence rate varies from 11.8% to 25.9% depending on lesion type and site [14], and may reach 100% if gross disease remains [5]. Furthermore, the mortality rate associated with surgery ranges from 3.4% to 5.7% [14]. Cystic hygroma does not regress spontaneously [15]. These limitations prompted the exploration of non-surgical alternatives, such as intralesional sclerotherapy with agents including bleomycin and ethanolamine oleate [2,3,11]. The presented study compared the effectiveness of Intralesional bleomycin and ethanolamine oleate in the treatment of cystic hygroma in children. In the present study, the majority of patients (93.0%) in both groups were below 30 months of age, which reflects the common age of first presentation. This finding is consistent with

Rahman (2001) and Chakraborty (2003), who reported 87.0% and 90.0% of cases under 3 years of age, respectively [16,17]. Male-to-female distribution was nearly equal in both groups. Study commonly report no strong gender predilection [18]. The most common site was the neck (60.0% in Group A and 46.7% in Group B), consistent with reports by Mahajan et al, and Bepari (2006) [19,20]. Regarding treatment outcomes, excellent regression (91–100%) was achieved in 53.3% of Group A and 46.7% of Group B patients, while good response (51–90% regression) was observed in 33.3% in both groups. Poor response (<25%) was slightly higher in Group B (20.0%) compared to Group A (13.3%). Overall, 86.0% of Group A and 80.0% of Group B achieved >50% regression, showing no statistically significant difference. These findings are in line with previous studies. Okada et al reported >50% regression in 86% of bleomycin cases [11], while Bepari (2006) found >50% regression in 83% of ethanolamine oleate–treated patients [20]. The mean pretreatment swelling size was comparable between groups (27.67 cm^2 in Group A vs. 23.53 cm^2 in Group B). At last follow-up, the sizes were reduced to 4.19 cm^2 and 4.53 cm^2, respectively, with regression rates of 82.07% and 77.13%. These results demonstrate significant regression in both groups, similar to the findings of Bepari (2006), who reported mean pretreatment surface area of 29.43 cm^2 reduced to 5.08 cm^2 post-treatment [20]. Most patients required 2–3 doses for effective regression. In Group A, 4 patients needed only 1 injection, while 2 patients required 4 doses. Similarly, in Group B, 2 patients required 1 injection and 4 patients required 4 doses. The mean number of doses was similar between groups (2.40 vs. 2.60). Chakraborty (2003) also reported that repeated injections were often necessary, especially for larger lesions [17]. Cost analysis revealed a significant difference between groups. Group A (ethanolamine oleate) had a mean treatment cost of 1,080 BDT, whereas Group B (bleomycin) had a mean cost of 3,900 BDT ($p<0.001$). This demonstrates that ethanolamine oleate is far more cost-effective, which is an important consideration in resource-limited settings like Bangladesh. Minor complications were observed in both groups, including redness, tenderness, fever, vomiting, and transient swelling increase. Complications were more frequent in Group B (66.7%) compared to Group A (40.0%). Redness was significantly higher in Group B (20.0% vs. 6.7%). Vomiting was noted only in Group B. All complications were temporary and resolved with conservative management within one week. Similar findings were reported by Bepari (2006), who observed transient swelling increase after injection that subsided within a week [20]. The mean time required for regression was 9.6 weeks in Group A and 10.4 weeks in Group B, with no significant difference. The majority of patients in both groups showed regression by 8–12 weeks. This is consistent with other reports where regression occurred within 2–3 months of therapy [11,17]. This study revealed that both the drugs are equally effective in the treatment of cystic hygroma in children but ethanolamine oleate is cost effective and less adverse effects than bleomycin. There was no recurrence of the swelling within the study period however, longer follow up is required before any final comment regarding the recurrence of the lesion can be made.

Limitations of the study:

The study follow-up lasted only eight weeks after the last injection, which was insufficient to assess long-term recurrence rates. Only clinical regression and short-term adverse effects were studied; long-term cosmetic outcomes, quality of life, and functional implications were not evaluated. Diagnosis and outcome assessment were based on clinical and ultrasonographic findings without histopathological confirmation.

V. CONCLUSION AND RECOMMENDATIONS

Cystic hygromas are congenital lymphatic malformations, most commonly in the neck. While surgical excision is the traditional treatment, risks of complications, recurrence, and technical difficulties highlight the need for alternatives. This prospective study found intralesional ethanolamine oleate and bleomycin hydrochloride equally effective, with ethanolamine oleate showing better tolerance, fewer complications, and lower cost. These findings suggest ethanolamine oleate as a safe, effective, and economical option. Further large, multi-center studies are recommended to confirm these results, assess long-term outcomes, and explore efficacy across different age groups and anatomical sites.

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