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Intralesional doxycycline and bleomycin hydrochloride in the treatment of cystic hygroma

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Abstract

Purpose: Cystic lymphangioma is a common congenital lymphatic malformation. The aim of the study was to compare the safety and efficacy of doxycycline and bleomycin in the treatment of cystic hygroma.

Methods: A total of 60 children with cystic hygroma were included in the study after fulfillment of inclusion and exclusion criteria from July 2016 to June 2018. They were randomly assigned to the doxycycline group (group A = 30 children) or the bleomycin group (group B = 30 children). The comparative parameters between the two groups were the reduction of size of the lesion, adverse effects of both drugs, and treatment cost between groups. All patients were followed up for 6 months.

Results: Median age was 10.00 months in group A and 8.50 months in group B ($p=0.841$) Male to female ratio was 1.76:1. There was a significant reduction in the median size of the lesion in both groups after treatment ($p<0.001$). 86.7% of patients had an excellent response in group A whereas 60% in group B had an excellent response ($P=0.049$). There was more adverse effect in group B than group A (63.3% vs 36.7%, $P=0.04$).

Conclusion: Doxycycline monotherapy had a higher rate of excellent clinical outcomes with fewer side effects than bleomycin and was more cost-effective.

Keywords: Cystic hygroma, Doxycycline, Bleomycin hydrochloride

Introduction

Cystic hygroma, also known as macro cystic lymphatic malformation, is a common congenital lymphatic malformation with an incidence of cystic hygroma is 1.2–2.8 per 1000 births [1]. In about half of the patients, the disease is already obvious at the time of birth, and in 80% to 90% of cases, it is diagnosed within the first or second year of life [2]. Surgery had been the mainstay of treatment of lymphangioma and respiratory distress, recurrent infections, or cosmetic reasons are the main indications [3]. However, due to the property of the lymphangioma to infiltrate adjacent structures, incomplete resection or

inadvertent nerve injury may occur during surgery. Even in the most expert hands, it still carries a complication rate of 12–33% and a recurrence rate of 15–53% [4]. For these reasons, multiple non-surgical strategies have been attempted in order to cure the lesion with minimal complications. These include radiotherapy, combined radio-chemotherapeutic approach, and lasers. However, none of these treatments are sufficiently effective.

Bleomycin has been used as a sclerosing agent for the treatment of cystic hygroma since 1977 [5]. Studies have reported success in up to 88% of cases. However, there were several complications such as discoloration of the injection site, sudden increase in the size of cystic hygroma, fever, vomiting, cellulitis, interstitial pneumonia, and pulmonary fibrosis [16]. On the other hand, Doxycycline, a derivate of tetracycline, is a widely

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available and relatively inexpensive broad-spectrum antibiotic. Several authors have effectively used doxycycline for the treatment of cystic hygroma [6, 7]. The aim of the study was to compare the effectiveness and complications of bleomycin and doxycycline in the treatment of cystic hygroma.

Materials and method

Study design and settings

A hospital based prospective comparative study was conducted from July 2016 to June 2018 (24 months), in the Division of Pediatric Surgery, Bangladesh Institute of Child Health and Dhaka Shishu (Children) Hospital, Dhaka among children with cystic hygroma. All patients, aged below 5 years, with cystic hygroma who had clinical and ultrasonic evidence of cystic hygroma attending in the Surgical Out Patient Department (SOPD) in Dhaka Shishu (Children) Hospital within the study period were included in the study. The patients were very poor, so they could not afford CT or MRI as these procedures involve out-of-pocket expenditure. Patients who were previously treated for cystic hygroma, had lesion more than 10 cm diameter, had infected lesions, had intra-thoracic or intra-abdominal lesion confirmed by chest X-ray or ultrasonography respectively, and patients with immediate life-threatening lesions and any comorbidity or associated diseases were excluded. Patients whose guardians had refused to participate in this study were also excluded.

Group allocation

After selection of the subjects, detailed procedure and benefit of the study was explained to the legal guardian. They were encouraged to participate voluntarily and were allowed to withdraw from the study freely. Informed written consent was taken from the enrolled patients. A total of 60 patients were divided into 2 groups. Patients in whom doxycycline was used were included in group A ($n=30$) and patients in whom bleomycin was used were included in group B ($n=30$). The first case was selected by lottery and subsequent cases were selected alternatively as odd and even number cases.

Variables

Data were recorded in a predesigned case record form. Age (in months), sex, weight (in kg), location of the lesion, rate of size regression, and adverse effects of drugs such as skin pigmentation, pain, fever, and treatment cost were recorded and analyzed.

Procedure

The treatment procedure was performed as outpatient basis without local or regional anesthesia. In group

A, doxycycline solution was prepared by dissolving 100 mg of doxycycline in 10 ml of normal saline. The amount of fluid aspirated from each pocket of cystic hygroma was replaced with equal amount of doxycycline solution through percutaneous injection without removing the aspirating needle. Up to 200mg of doxycycline was given. In group B, bleomycin hydrochloride solution was prepared by dissolving 1 mg with 1 ml normal saline. Bleomycin solution was injected at a dose of 0.2-0.6 mg/kg body weight. After aspiration of as much fluid as possible, the solution was injected through the same needle of aspiration in the same place. After injecting the drugs, the patients were observed for 2 hours to assess for the development of any anaphylactic reaction. The second and subsequent procedure was performed at 4 weeks interval in necessary cases. Out of 30 patients who received doxycycline, cystic hygroma resolved 20 patients in 1st dose, 6 required 2nd dose, and 3 patients required 3rd dose. On the other hand out of 30 patients who received bleomycin cystic hygroma resolved 18 patients in 1st dose, 4 patients required 2nd dose, 4 patients required 3rd dose, 2 patients required 4th dose, and swelling of 2 patients did not resolve who showed poor response underwent surgery.

Data analysis

After completion of data collection, to maintain consistency, the data were checked and edited manually and verified before tabulation. The statistical analyses were conducted using SPSS version 22. Results were presented as frequency and percentage. Continuous variables were presented as mean and standard deviation or median and compared with Student's *t* test or Mann-Whitney *U* test. Categorical variables were presented as frequency distributions and compared with Pearson's chi-square test or Fisher's exact test as appropriate. The difference between pretreatment and post treatment size was analyzed by Wilcoxon signed-rank test. A *P* value of <0.05 was considered significant.

Table 1 Location of cystic hygroma in two groups

Location	Group A ($n=30$)	Group B ($n=30$)
Posterior triangle	15 (50.0%)	15 (50.0%)
Axilla	5 (16.7%)	5 (16.7%)
Cheek	4 (13.3%)	7 (23.3%)
Trunk	4 (13.3%)	2 (6.7%)
Buttock	1 (3.3%)	0 (0.0%)
Forearm	1 (3.3%)	1 (3.3%)

Table 2 Comparison of pre-treatment and post-treatment size in group A and group B

Group	Pretreatment size (in cm ³) (n=30)	Post treatment size (in cm ³) (n=30)	P value
Group A [median (IQR)]	12.00 (9.21,16.19)	0.75 (0.00, 1.50)	<0.001
Group B [median (IQR)]	16.75 (11.63, 22.87)	1.50 (0.69, 2.06)	<0.001

P value derived from Wilcoxon signed-rank test

Ethical consideration

Ethical clearance was taken from ethical review committee of Bangladesh Institute of Child Health and Dhaka Shishu (Children) Hospital (Memo no:BICH-ERC-8/2/2017, Dated-19/06/2017). Informed written consent was taken from all parents or legal guardians

of patients after adequate explanation of the purpose of the study. They were assured of protection of patient’s autonomy, privacy, and confidentiality.

Results

Among a total of 60 patients, 37 patients were male and 23 patients were female (ratio 1.76:1). Median age of the participants were 10 months in group A and 8.5 months in group B. The most common site of occurrence was the posterior triangle of the neck (30, 50%). The other sites were axilla, cheek, trunk (four of them intra-thoracic and two intra-abdominal) buttock, and forearm (Table 1). There were no significant differences between groups with regards to age, sex, and site of involvement (p value of age 0.841, p value of sex = 0.426),

There was a significant reduction in the median size of the lesion in both groups (Table 2) and poor response means response category <25% [6] (Figs. 1



Fig. 1 Pre and post treatment photographs in Group A (Doxycycline)



Fig. 2 Pre and post treatment photographs in Group B (Bleomycin)

and 2). In group A, 86.7% of participants showed excellent responses, whereas in group B, 60.0% of participants showed an excellent response. The degree of response was measured clinically by measuring tape. These differences in response between groups were marginally statistically significant as $p=0.049$ (chi-square test) (Table 3).

Doxycycline was more cost-effective than bleomycin. The cost of doxycycline was 2.00 taka per capsule and the overall cost in four sessions in 4 weeks was 20 taka (0.25 USD). On the other hand, the total cost of bleomycin in four sessions was 125 USD.

Adverse effect of treatment was noticed in 11 patients in group A and 19 patients in group B. A total of 18 (30%) patients developed fever (38.5–39 °C) that lasted between 24 and 48 h; 16 (26.7%) patients presented with redness which disappeared within 1–2 weeks post treatment. Mild anti-inflammatory analgesic was sufficient to control the symptoms. Nine (15%) patients developed pain and only two (3.3%) patients developed skin pigmentation. Fever and redness of the lesion developed more in group B and pain and skin pigmentation was more in group A (Fig. 3).

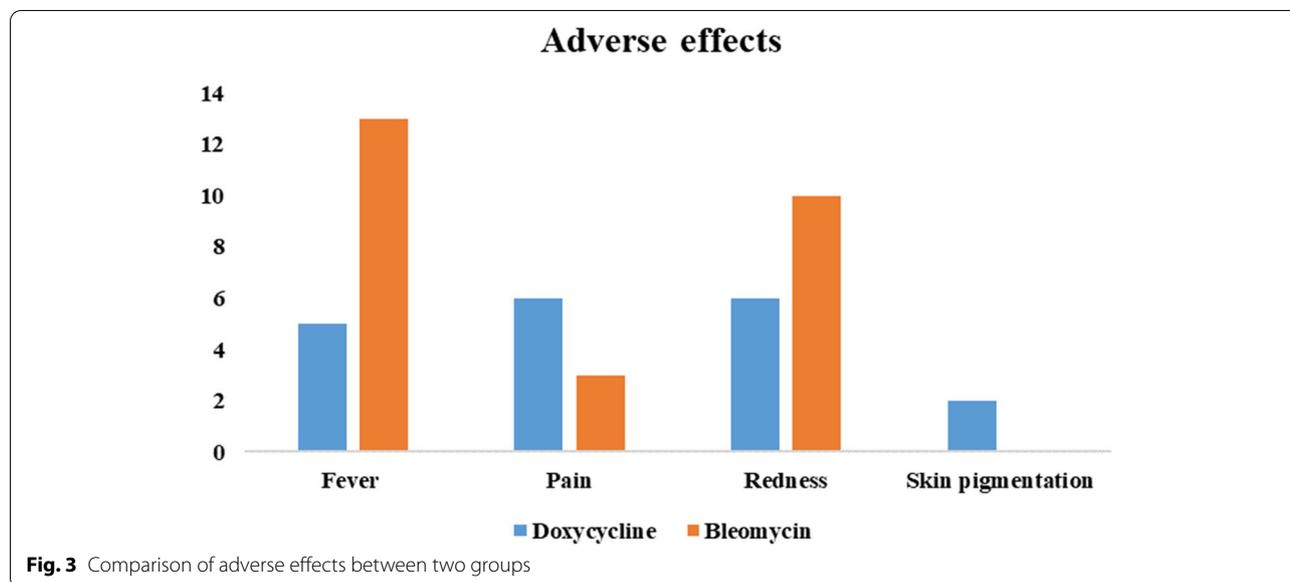
Discussion

This study compared the effectiveness of doxycycline and bleomycin in the treatment of cystic hygroma and it was found that both were equally effective. Fever and redness were noticed in fewer patients with Doxycycline whereas pain and skin pigmentation were noticed in respectively 6 and 2 patients treated with Doxycycline. There were no significant differences with regards to age, sex, weight, location of anomaly, and pretreatment between these two groups. However, a slight male predominance was found in the current study, which is consistent with other studies [6–9]. In the current study, in both groups, half of the lesions were found in the posterior triangle of the neck which is similar to other reports. Hygromas usually reside in close proximity to large veins and lymphatic ducts, in the neck (75%), axilla (20%), and others (5%) such as mediastinum, retroperitoneum, pelvis, and groin [10]. Rawat et al. found 57.9% of lesions were in the neck region [8].

Bleomycin acts by two ways first through cytotoxic effect and second by sclerosis. It is a DNA synthesis inhibitor and its exact mechanism of action in cystic hygroma is not known; however, it is believed that it may produce a non-specific inflammatory process that results in the fibrosis of the cysts. Intralesional Bleomycin microsphere in oil emulsion has been reported to have a good response as it is retained for a long period of time. Pulmonary fibrosis is associated with treatment with a high dosage of bleomycin. The safe upper limit for the dosage of bleomycin in a single session is 30 mg/m². In most published studies, where small doses of bleomycin were used, there was no pulmonary fibrosis in any of their patients [4]. Nonetheless, bleomycin is expensive and is not easily available in many countries.

Table 3 Regression of size between groups

Size regression	Group A N (%)	Group B N (%)	P value
Excellent response	26 (86.7%)	18 (60.0%)	0.049
Good response	4 (13.3%)	10 (33.3%)	
Fair	0 (0.0%)	0 (0.0%)	
Poor response	0 (0.0%)	2 (6.7%)	



Doxycycline is an inexpensive and easily available antibiotic. The exact mechanism by which doxycycline is effective as a sclerosant is unknown, but an inflammatory process that results in fibrosis and involution of cysts is speculated [14]. It also functions as an angiogenesis inhibitor by interfering with cell proliferation and migration via inhibition of matrix metalloproteinase (MMP) and suppression of vascular endothelial growth factor (VEGF)-induced angiogenesis and lymphangiogenesis [6]. The injectable form of doxycycline is also readily available with compounding capability and requires reconstitution in a normal saline solution at a concentration of 10 mg/ml. In addition, doxycycline theoretically may prevent infectious complications. Doxycycline has an established safety profile. Adverse effects associated with doxycycline are reported as local erythema, edema at the injection site, and pain [7, 14]. Mild swelling occurs following injection and typically improves after 24–48 h [6]. Burrow et al. reported that doxycycline caused severe discomfort on injection, requiring general anesthesia in most patients. Pain requiring narcotic analgesia is common for 1 to 3 h post procedure [6]. In this study, the procedure was performed on outpatient basis with local anesthesia (Injection 2% lignocaine) after taking consent from the parent. Local anesthesia was given as patient's guardian did not give consent for general anesthesia and in other study procedures were done by local anesthesia [11].

Doxycycline showed excellent response in 86.7% of participants in contrast to 60% with Bleomycin in this study. Several studies evaluated the efficacy of sclerotherapy with doxycycline for the treatment of

macrocytic lymphatic malformations. They reported that 85–93% of patients had excellent to moderate responses with doxycycline [6, 7, 12, 14]. There was no patient with a poor response in this study which is similar to some other studies [6, 7, 14]. Here excellent response means response category >90%, good response means response category 60–90%, fair 25–50%, and poor <25 % [6]. Rawat and Saxena found 42–57% complete resolution of cystic hygroma treated with intralesional bleomycin, which is also similar to our study [8, 13]. Partial response with bleomycin was in 33% in this study, which was similar with Saxena and Hajela (36%). However, but Saxena and Hajela noted 22% with no response after repeated injection of bleomycin for 4 times, while in this study, no response was found in 6.7% of patients which was later treated by surgery. Saddal also reported that 6% of patients had no response in his study [15].

Adverse effects of doxycycline and bleomycin were compared in the current study. In group A, one third of the respondents (33.3%) had fever and redness whereas in group B, the majority of the respondents (43%) had fever and 33% of respondents had redness. Moreover, doxycycline was found very cost-effective as the overall cost of doxycycline was almost 20 taka (0.25 UD\$) in 4 weeks of treatment whereas the overall cost of bleomycin in four sessions was 125 US\$. Bleomycin is also rarely available in our market nowadays. For these reasons, doxycycline may be considered as a safe, effective, and cheaper alternative for bleomycin in the treatment of cystic hygroma in low- and middle-income countries.

Limitation

A limitation of the study is that it had a short-term follow-up of 6 months. For this reason, long time follow side effects could not be evaluated. Further long-term follow-up studies are needed to assess these.

Conclusion

Doxycycline monotherapy resulted in a higher rate of excellent clinical outcomes compared to Bleomycin in the treatment of cystic hygroma. It was very cost-effective also.

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None.

Authors' contributions

Conceptualization, methodology, and investigation: AN; Format analysis: NAK and MNH; Writing the original draft and preparation: AN and KMNF; Review and supervision: MKI. The authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available upon reasonable request from the following orchid id: 0000000280399722

Declarations

Ethics approval and consent to participate

Obtained from institution and parents of the children.

Consent for publication

Obtained from the parents of the children.

Competing interests

The authors declare that they have no competing interests.

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