

Effects of Intralesional Doxycycline in the Treatment of Cystic Hygroma

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Abstract

Background: Cystic lymphangioma is a congenital lymphatic malformation. The present study was conducted to find out the effects of intralesional Doxycycline in the treatment of cystic hygroma.

Materials and methods: This prospective study was conducted among 30 children with cystic hygroma in the Division of Pediatric Surgery, Dhaka Medical college Hospital, Dhaka, from July 2019 to June 2021. All patients were followed up for six months. In every follow up size of the lesion was determined and adverse effects were also noted.

Results: More than half of the cystic hygroma (53.3%) were in neck while 5 (16.6%) in axilla. Before treatment, the median size of cystic hygroma was 12.00 cm² which significantly decreased to 0.75cm² after treatment ($p < 0.001$). After treatment, 83.3% participants showed excellent response and 16.6% participants showed good response. Out of 30 patients, 33.3% had adverse effects which included pain ($n=5$), redness of skin ($n=5$), fever ($n=5$) and skin pigmentation ($n=2$).

Conclusion: Doxycycline monotherapy resulted in a high rate of excellent clinical outcomes after a few treatments without increased need for subsequent operative resection. It was very cost effective also.

Key words: Cystic hygroma; Children; Doxycycline.

INTRODUCTION

Lymphangiomas are congenital malformation of the lymphatic system. Lymphangioma is usually classified as capillary, cavernous or cystic.¹ Cystic hygromas occurs more frequently as compared to other types of lymphangioma, and may compose of single or multiple macrocystic lesions having scarce communication with normal lymphatic channels.² In about half of the patients, the disease is already obvious at the time of birth. The incidence of cystic hygroma is 1.2 - 2.8 per 1000 birth.¹ During the first and second year of life, the occurrence of cystic hygroma is diagnosed in 80% to 90% of the cases due to clinical symptoms.³

Cystic hygromas account for approximately 90% of the lymphangiomas in the head and neck region. Other common sites, outside the head and neck, include the axilla, shoulder, chest wall, mediastinum, abdominal wall, and thigh.⁴ Although it is a benign lesion, it may lead to a complicated case due to its infiltrating nature, indefinite demarcation and involvement of vital structure. Respiratory distress, recurrent infections or cosmetic reasons are the main indications of the treatment.⁵

Surgery had been the mainstay of treatment of lymphangioma. Due to the property of the lymphangioma of infiltrating adjacent structures, incomplete resection or inadvertent nerve injury may result. Even in the most expert hands, it still carries a complication rate as high as 12-33%, and a recurrence rate of 15-53%.⁶ Because of

surgical complications, multiple non-surgical strategies have been attempted in order to cure the lesion with minimal complications. They include radiotherapy, combined radio-chemotherapeutic approach and lasers. CO₂ and Nd-YAG lasers are more extensively used for localized laryngeal lymphangiomas. However, none of these treatments are sufficiently effective.⁷

Doxycycline, a derivate of tetracycline, is widely available and relatively inexpensive broad-spectrum antibiotic. Its use as a sclerosant in the pleurodesis of malignant effusions and in the treatment of postoperative lymphoceles showed only minimal side effects. In 1995, Molitch et al. reported successful treatment of five patients with extensive lymphangiomas.⁸

Several authors prefer doxycycline because it is very effective (83% reduction in size) and safe.^{9,10} The injectable form of doxycycline is readily available from pharmacies with compounding capability and requires reconstitution in a normal saline solution at a concentration of 10 mg/mL. It is inexpensive and is comparable to the oral form of the antibiotic.¹¹ In addition, doxycycline theoretically may prevent infectious complications. Almost all macro cystic lymphangiomas have an excellent response; improvement for combined lymphangiomas is superior for lesions with a greater macro-cystic composition.^{12,13}

Most of the advanced pediatric surgical centers in Bangladesh prefer bleomycin and OK-432 as sclerotherapy.¹⁴⁻¹⁶ Ethanolamine oleate has been successfully used in Bangladesh in the treatment of cystic hygroma.^{17,18} But the cost of Doxycycline is comparatively less than those modalities. Doxycycline could be more cost effective in the treatment of cystic hygroma besides the advantages of less post treatment complications. The present study was conducted to find out the effects of intralesional Doxycycline in the management of cystic hygroma.

MATERIALS AND METHODS

A hospital based prospective study was conducted the study period from July 2019 to June 2021(24 months), in Dhaka Medical College Hospital with the complaints of cystic hygroma. Thirty patients who had clinical and ultrasonic evidence of cystic hygroma were selected purposively for the study. The Patients were very poor, so they could afford CT or MRI as these procedures involve out of pocket expenditure. Patients who were previously treated for cystic hygroma, had infected lesions, had intra- thoracic or intra-abdominal lesion confirmed by chest X-ray and ultrasonography respectively, 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.

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

The treatment procedure was performed as outpatient basis with local or regional anesthesia after taking consent from parents. Doxycycline solution was prepared by dissolving 100mg of doxycycline capsule in 10 ml of normal saline (10mg/ml solution). The volume of fluid aspirated from each pocket was replaced with equal volume of doxycycline solution through percutaneous injection without removing the aspirating needle. Upto 200mg of doxycycline could be given.

Patients were advised to return after one week of each injection. They were advised to report earlier if any complication occurred. Second and subsequent procedure was performed at 4 weeks interval in necessary cases. In each follow up, size of the swelling was measured. Any sign of complication was also recorded and treated accordingly. Out of 30 patients who received doxycycline, cystic hygroma resolved 22 patients in 1st dose, 7 required 2nd dose and only one patient required 3rd dose.

After completion of data collection, to maintain consistency they 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.

Informed written consent was taken from all patients or legal guardians of patients after adequate explanation of the purpose of the study. They were assured of protection of patients autonomy, privacy and confidentiality.

RESULTS

Table 1 Baseline characteristics of the patients (n=30)

Characteristics	No. of patients (%)
Age group	
Within one month	3 (10.0)
1-6 months	7 (23.3)
6-12 months	9 (30.0)
> 12 months	11 (36.7)
Sex	
Male	20 (66.7)
Female	10 (33.3)
Location of cystic hygroma	
Neck	16 (53.3)
Axilla	5 (16.6)
Cheek	5 (16.6)
Trunk	3 (10)
Buttock and fore arm	1 (3.3)
Pretreatment size of cystic hygroma (In cm²)	
Up to 10	9 (30.0)
11-20	17 (56.7)
>20	4 (13.3)

Among the 30 patients, 11 (36.7%) were from more than one year age group while 9 (30.0%) were from 6-12 months age group. Two third of the patients (66.7%) were male. more than half of the cystic hygroma (53.3%), were in neck while 5 (16.7%) in axilla. Majority of the cystic hygroma (56.7%) was 11-20 cm² in size (Table 1).

Table II Comparison of size of cystic hygroma before and after treatment (n=30)

Size of cystic hygroma (In cm ²)	Median (IQR)	p value
Before treatment	12.00 (9.21,16.19)	<0.001
After treatment	0.75 (0.00,1.50)	

Before treatment, the median size of cystic hygroma was 12.00 cm² which significantly decreased to 0.75 cm² after treatment (Obtained by Wilcoxon signed rank test) (Table II).

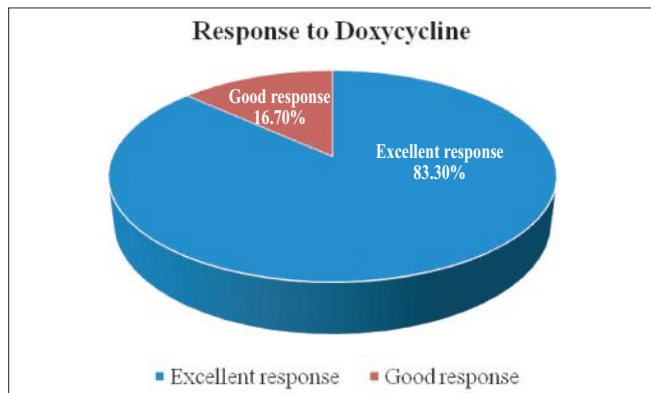


Figure 1 Response of cystic hygroma to Doxycycline according to size of regression

After treatment with Doxycycline, excellent response was observed in 25 (83.3%) patients while 5 (16.6%) had good response. No patients had poor response (Figure 1).

Table III Adverse effects after treatment with Doxycycline

Complications	No. of patients (%)
Absent	20 (66.6)
Present	10 (33.4%)

Among the 30 patients, 10 (33.4%) respondent had adverse effects which included pain (n=5), redness of skin (n=5), fever (n=5) and skin pigmentation (n=2) (Table III)



Image 1 Pre treatment Post treatment



Image 2 Pre treatment Post treatment

DISCUSSION

Cystic hygromas are rare tumors which can lead to morbidity because of cosmesis, compression of adjacent organs or can result in local inflammation, infection, sinus formation and hemorrhage.¹⁴ The present study was conducted to find out the effects of intralesional Doxycycline in the management of cystic hygroma.

A slight male predominance was found in the current study. Other studies also found male predominance regarding cystic hygroma.^{7,14} Half of the lesions were found in posterior triangle, others were in axilla, cheek, trunk, buttock and forearm. Hygromas usually reside in close proximity to large veins and lymphatic ducts, in neck (75%), axilla (20%) and others (5%) e.g. mediastinum, retroperitoneum, pelvis and groin.

After treatment, 83.3% patients showed excellent response and 16.70% participants showed good response. No participant showed poor response. This result was consistent with the study of Thomas et al who evaluated the efficacy of sclerotherapy with doxycycline for the treatment of macrocystic and mixed lymphatic malformations²⁰ They found 87% patients had excellent to moderate response with doxycycline. A report on 41 patients who were treated with doxycycline sclerotherapy was published by Burrows et al. (2008) showing encouraging results, with a mean reduction in lesion size of 83%.⁹ They stated that doxycycline seems to be more effective in treating microcystic lymphangiomas than OK-432. This result was approved by Shiels et al, who reported about doxycycline sclerotherapy of microcystic lymphangiomas. They achieved complete cyst ablation in all treated microcysts of 17 patients.²¹ The exact mechanism by which doxycycline is as effective as a sclerosant is unknown, but an inflammatory process that results in fibrosis and involution of cysts is speculated.¹¹ 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 Gactor (VEGF)-induced angiogenesis and lymphangiogenesis.⁹

Doxycycline has distinct advantages over other sclerotherapy agents including that it is inexpensive and widely available and has minimal side effects.²² Risks associated with doxycycline are local erythema, edema at the injection site, and pain.¹¹ Pain requiring narcotic analgesia is common for 1 to 3 hours post procedure. The present study found that 33.3% participants had adverse effects like fever, pain redness after treated with doxycycline. As Doxycycline was given within the cavity (not given in systemic circulation), there was no chance of effects on tooth development in children.

Cost of treatment is an important issue in a country like Bangladesh. Doxycycline was found very cost effective as the cost of doxycycline per capsule was 2.00 taka.

CONCLUSION

Doxycycline monotherapy resulted in a high rate of excellent clinical outcomes. It was very cost effective also. It can be used as sclerotherapy as primary treatment for macrocystic and mixed LMs in children.

DISCLOSURE

All the authors declared no competing interest.

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