E-ISSN: 2616-3470
P-ISSN: 2616-3462

www.surgeryscience.com
2019; 3(1): 141-144
Received: 16-11-2018
Accepted: 18-12-2018

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Intra lesional Bleomycin as an effective alternate treatment for cystic hygroma

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DOI: https://doi.org/10.33545/surgery.2019.v3.i1c.26

Abstract
Background: Cystic Hygroma is a congenital malformation of the lymphatic system, present mostly at birth and gradually increases in size. It is a benign tumor of lymphatic origin, mostly seen in neck and axilla. It is seen in 1 in 6000 to 12000 births. The Surgical excision is the main stay of treatment, but it carries a risk of neurovascular damage, scar and recurrence too. Use of Intralesional Bleomycin in Cystic Hygroma has shown effective results.
Aim: To evaluate the efficacy and safety of Intralesional Bleomycin in Cystic Hygroma and to study complications during the treatment.
Materials and methods: A prospective study was done over a period of 2 ½ years on 15 children 8 male (53.3%), 7 female (46.6%). The diagnosis of Cystic Hygroma was made on clinical examination and was supplemented with Doppler Ultrasonography. Before the procedure Haemogram and baseline chest radiograph performed. The procedure was performed after taking consent from parents. Preoperatively a single shot of antibiotic given. Under sedation, A wide bore (18G) needle used to aspirate the contents, with same needle placed in Inj. Bleomycin added at 0.5mg/kg body weight (diluted with 10cc of distilled water)
Results: Response was assessed clinically and on the basis of color Doppler USG. Complete resolution without induration clinically seen in 12 out of 15 patients (80%). Good response in 2 patients (13.3%) with 3 doses and in 1 patient (6.6%) after 4 doses. Adverse reactions include fever, redness and pain. No significant complications or recurrence in the follow up of 6 months.
Conclusion: So Intra Lesional Bleomycin is safe and effective treatment in Cystic Hygroma and can be practiced as an alternate to surgery.

Keywords: Cystic hygroma; intra lesional Bleomycin; Lymphangiomas; Sclerotherapy

Introduction
Cystic Hygroma (CH) is a multiloculated congenital malformation of the lymphatic system occurring in approximately 1 in 6000-12000 births. Cystic Hygroma is a congenital lymphatic malformation that presents at birth in 50 to 65% of cases and manifests by 2 yrs of age in 80 to 90% cases [1].
Cystic 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 [2].
A large lesion in the neck can cause significant cosmetic deformity, compression of vital structures, respiratory obstruction, dysphagia and symptoms of nerve compression [3].
Surgery has usually been the preferred treatment for lymphangiomas but due to ramifications and infiltrations of surrounding structures, the excision becomes difficult especially if vessels or nerves are surrounded. Therefore incomplete excision and inadvertent nerve injuries are not uncommon after surgical management [2].
A variety of non-surgical treatment methods have been used for cystic hygroma including aspiration, drainage procedures, radiotherapy, cryotherapy, diathermy, laser, chemotherapy and intralesional sclerotherapy. Sclerosants that have been known are sodium morrhuate, dextrose, hypertonic saline, tetracycline, doxycyline, acetic acid, ethanol, boiling water, alcoholic solution of zein (ethibloc), fibrin sealant, triamcinolone, OK-432 and Bleomycin [4].
These sclerosing agents are thought to work by ablating the endothelial cells of the disrupted lymphatic feeding into the lymphocele, decrease in lymph fluid production and eventually leading to collapse of the cyst [5]. Yura in 1977 was the first clinician to use Bleomycin solution

as a sclerosing agent for treatment of Cystic Hygroma [6]. Since then multiple studies have reported favorable results of Intralesional Bleomycin injection (IBI) sclerotherapy in management of children with lymphangiomas. Bleomycin has 88% regression rate in case of cystic hygroma and 32 to 49% resolution in haemangiomas [1].

Material and Methods

A prospective study was conducted to determine the efficacy and short term adverse effects of IBI sclerotherapy in children with Cystic Hygroma (CH) from March 2016 to December 2018. A total of 15 patients enrolled in the study. Institutional Ethical Committee approval was taken before the commencement of study.

Children with Ultrasonographically (USG) proven (Figure 1), subcutaneous, Macrocystic lymphangiomas over the neck, aged below 5years with no/ minimal vascularity was included in the study.

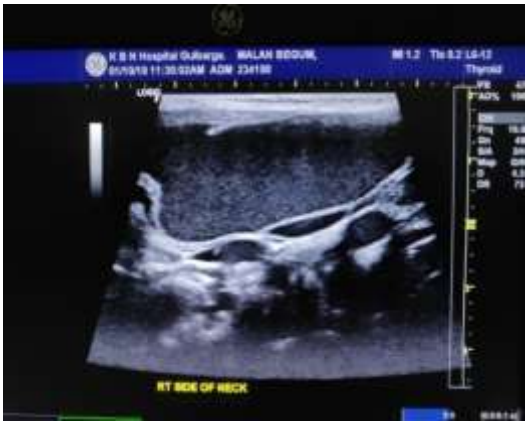

Fig 1: Large well defined cystic lesion with multiple septations and mobile internal echoes noted in posterior triangles of neck.

Children with arterio venous malformations, thoracic or abdominal lymphangiomas and cysts less than 5 cm, previously surgically operated cases were excluded from the study.

Out of 15 patients enrolled to the study, 8 were male (53.3%), 7 female (46.6%) in between age of 30days to 5years. The patients details including age, sex, weight, size and location of lesion (Figure 2 and 3), clinical history, dosage of Bleomycin, clinical response, side effects and follow-up were recorded.

Fig 2: Before sclerotherapy.

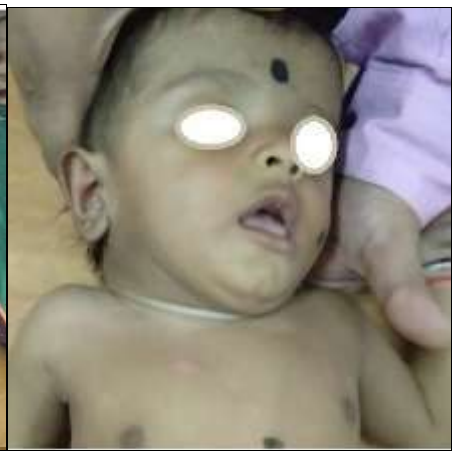

Fig 3: After 1st dose of sclerotherapy.

Data was collected after informed consent of the parents and they were counseled regarding use of IBI sclerotherapy and its effects. Before the procedure Haemogram and baseline chest radiograph were performed. Preoperatively a single dose of antibiotic given and shifted to operation theatre (OT). Sedated either by oral chloral hydrate 25mg/kg or intravenous (IV) diazepam. Under aseptic precautions An 18 gauge needle was passed through the lesion and fluid was aspirated from the cyst. Injection Bleomycin in a dose of 0.5 mg/kg diluted in 10-15 cc of distilled water was injected into the lesion by rotating the same needle in 3-4 directions. The required dose was calculated as 0.5 mg/kg body weight, not exceeding 10 units at a time. ILB was injected in a ratio of 5:1 (aspirated volume: Bleomycin volume). A compression dressing, if feasible, was applied after the procedure. The patient was kept under observation till evening. If fever occurred, oral paracetamol was prescribed. Oral antibiotics and analgesics were advised for 3 days.

The parents were instructed to review with the child after 2 days in the outpatient department for removal of dressing and evaluation of any adverse effects. Patients were again reexamined at the end of 3 weeks (Figure 3 and 4) and need for repeat injection assessed.

Minor side effects like fever, redness and swelling at the site of injection are seen in 5 patients (33.35%) No significant complications or recurrence in the follow up of 6 months after completion of planned ILB sclerotherapy. Clinical outcomes were reviewed and analyzed.

Results

Out of 15 children 8 male (53.3%), 7 female (46.6%), age of presentation, no: of doses of ILB given, its response and adverse effects are mentioned in Table no: 1.

Table 1: Age of presentation, no: of doses of ILB given, its response and adverse effects.

S. No	Age (months)	No: of injections (ILB)	Side effects
1.	06	4	Nil
2.	11	2	Erythema over injectional (inj) site.
3.	01	3	Fever with vomiting of 1 episode.
4.	12	4	Nil
5.	01	2	Fever and swelling with erythema at injectional site.
6.	08	2	Fever.
7.	16	4	erythema.
8.	18	3	Fever.
9.	60	4	Nil.
10.	24	2	Erythema and swelling.
11.	08	5	Fever with vomiting of 3 episodes.
12.	36	3	Nil.
13.	14	2	Nil.
14.	22	4	Nil.
15.	36	2	Erythema only.

The children who are at the age of 1 month have been intervened as its obstructing their airway and discomfort to the baby. ILB sclerotherapy response was assessed clinically and on the basis of color Doppler USG as:

1. Excellent - complete regression without induration,
2. Good - >50% regression and
3. Poor - <50% regression.

Number of doses of injection varied from 1 to 5. Complete resolution without induration clinically seen in 12 out of 15 patients (80%). Good response in 2 patients (13.3%) with 3 doses and in 1 patient (6.6%) after 4 doses. Outcome of ILB is mentioned in Table no: 2.

Table 2: Outcome of Intra Lesional Bleomycin injection.

Sex	Excellent response	Good	Poor	Total (%)
Male	6	2	0	53.33
Female	5	1	1	46.66
Total (%)	11(73.3)	3(20)	1(6.66)	15(100)

Discussion

Lymphangioma is a common developmental anomaly of the lymphatic system. It is characterized by the formation of a multilocular cystic mass of variable size. Lymphangioma are thought to arise from a combination of the following [7]:

1. Failure of lymphatic's to connect to the venous system,
2. Abnormal budding of lymphatic tissue, and
3. Sequestered lymphatic rests that retain their embryonic growth potential.

These lymphatic rests can penetrate adjacent structures or dissect along fascial planes and eventually become canalized. These spaces retain their secretions and develop cystic components because of the lack of a venous outflow tract. The nature of the surrounding tissue determines whether the lymphangioma is capillary, cavernous, or cystic [7].

Lymphangioma has been categorized into three varieties [7]:

a) Lymphangioma simplex, composed of capillary sized thin walled lymphatic channels,
b) Cavernous lymphangioma and
c) Cystic lymphangioma composed of cysts of few millimeters to several centimeters in diameter.

Cystic Hygroma (CH) is the cavernous type of peripheral lymphangioma, involving skin and superficial tissues. It is a multi locular cystic mass; cysts may be of variable sizes, involving head and neck in more than 70%, followed by axilla, abdomen and extremities. A large lesion in the neck can cause significant cosmetic deformity, compression of vital structures, respiratory obstruction, dysphagia and symptoms of nerve compression [8].

Surgery has been the main stay of treatment but even in very skilled hands and with meticulous surgical technique, it carries significantly unfavorable results, including damage to adjacent structures, hemorrhage, scar, lymphatic discharge from wound and recurrence [9].

Many alternative non-surgical treatments are described in literature including radiotherapy, cryotherapy, diathermy, laser, and chemotherapy and intralesional sclerotherapy. Sclerosants that have been known are sodium morrhuate, dextrose, hypertonic saline, tetracycline, doxycyline, acetic acid, ethanol, boiling water, alcoholic solution of zein (ethibloc), fibrin sealant, triamcinolone, OK-432 and Bleomycin [10].

These sclerosing agents are thought to work by ablating the endothelial cells of the disrupted lymphatic feeding into the lymphocele, decrease in lymph fluid production and eventually leading to collapse of the cyst [11]. We preferred Bleomycin as a sclerosant because of its easy availability, low cost, and minimal side effects when used in low dose intralesionally in cystic hygroma.

Bleomycin is an anti-neoplastic agent, which was first used in 1966, in a variety of malignant lesions where it works by inhibition of DNA synthesis. Intralesional Bleomycin as a sclerosing agent was used for the first time by Yura *et al* in Japan in 1977 for CHs and produced promising results [12].

The recommended dose of Intra Lesional Bleomycin (ILB) is 0.3-3 mg/kg/session. The frequency of session may be different from 1 week to 6 weeks as suggested in many studies [13-15]. In our study ILB dosage is taken of 0.5mg/kg/session like most of the studies and each session after every 4-6 weeks depending upon the response.

Excellent response is seen in 11 out of 15 children (73.3%) → complete regression by 2 doses in 6 patients, 3 doses in 3, and 4doses in 2 patients.

Good response seen in 3 patients (20%) → >50% regression by 4doses in 3 patients.

Poor response in 1 patient (6.66%) → < 50% response seen in 1 patient after 5 doses of ILB.

Side effects of Bleomycin are fever, transient increase in size of the swelling, hemorrhage, leukocytosis, infection, and pulmonary fibrosis [13]. The minor side effects which we have seen in our study are fever, erythema and swelling at the site of injection and vomiting seen in 5 patients (33.3%) lower

compared to other studies which is less than some studies where complications were noted in about 43% of patients [15].

The primary concern of Bleomycin therapy is its risk of pulmonary toxicity. The risk is dose related with an increased incidence associated with a total dose exceeding 400 units. or a single dose exceeding 30 mg/m2 of body surface area given intra-venous [16].

In our study, ILB with aqueous solution has been effective in complete resolution of cystic hygroma was 73.3% which was efficient and it was compared with other studies in Table no: 3. [1, 17-19].

Table 3: Intralesional Bleomycin efficiency in comparing to other studies.

Author / study	No:of patients	Excellent response
Tanaka *et al*	47	20(43%)
Okada *et al*	45	16(55%)
Muir T *et al*	95	46 (49%)
Ikram ud din *et al*	08	6(86%)
Our study	15	11(73.3%)

Bleomycin activity is enhanced if it is used in the form of micro sphere-in-oil emulsion and thus retained in the tumor for a longer period of time [20, 21].

The most important factor in intralesional Bleomycin is the concentration of the sclerosant available to the endothelial lining of the cystic hygroma. In lesions that are aspirated completely the Bleomycin available per unit area of the lesion is higher and so is its sclerosing effect [22].

Another factor, which would influence the dose to be injected, is the completeness of the aspiration of the lesion. If the cystic hygroma can be aspirated completely, the concentration of the drug required per unit of surface area would be much less as compared to the lesions that are incompletely aspirated [23, 24].

The desired effect of sclerosis is achieved by the local action of Bleomycin, which in turn would depend upon the availability of the drug per unit of surface area of the lesion. Hence the dose injected should depend upon the size of the lesion rather than weight of the patient and sclerosis can be induced by a much smaller dose than the weight of the patient would warrant.

Conclusion

Intralesional Bleomycin sclerotherapy is simple, safe and efficient non surgical method with results comparable to surgical technique with minimal complications. So we suggest intralesional Bleomycin sclerotherapy as primary method of management in cystic hygroma to avoid the risk of inadvertent damage by surgery as well as for cosmetic reasons.

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