

## Intralesional bleomycin sclerotherapy for cystic hygroma in children - as alternative treatment

Sharanbasappa Gubbi<sup>1</sup>, Sangmeshwar Patil<sup>1</sup>, Chinmayee K. Reddy<sup>1\*</sup> and J.C. Rajiv Reddy<sup>2</sup>

<sup>1</sup>Department of General Surgery, Mahadevappa Rampure Medical College, Sedam Road, Kalaburagi-585105, Karnataka, India and <sup>2</sup>Department of General Surgery, Ramraj Hospitals, Shapur Nagar, Hyderabad-500055, Telangana, India

Received: 20<sup>th</sup> December 2022; Accepted: 22<sup>nd</sup> February 2023; Published: 01<sup>st</sup> July 2023

**Abstract:** *Introduction:* Although cystic hygromas can appear in any part of the body they are commonly found in the cervicofacial regions particularly in the posterior cervical triangle, axilla, mediastinum, groin and below the tongue. The optimal treatment is total surgical excision; nevertheless, the mode of treatment is gradually shifting to sclerosant therapy. Keeping this point in mind, the present study focuses on usage of bleomycin as the sclerosant of choice in the treatment of cystic hygromas. *Methods:* A prospective study conducted in Mahadevappa Rampure Medical College, Kalaburagi, over a period of 2. Cystic hygroma was diagnosed clinically with radiological supplementation of Doppler ultrasonography or MRI. The procedure was performed under IV sedation and USG guidance. All patients received 3 doses of antibiotics 1 preoperatively and two post operatively. Number of doses of bleomycin was dependent on the prognosis and clinical evaluation. *Results:* Complete resolution without induration clinically seen in 16 out of 20 patients (80%), whereas good response was observed in 4 patients (20%) who had a repeat of the session after 3 months of the first session following which we attained complete resolution of the cystic hygroma. Side effects such as fever (15%) followed by fever along with erythema in 2 subjects (10%) and erythema in one subject (5%) were observed. *Conclusion:* In conclude, we recommend Intralesional Bleomycin Sclerotherapy as the primary method of treatment in cystic hygroma to avoid the risk of inadvertent damage from surgery and for cosmetic reasons.

**Keywords:** Intralesional Bleomycin Sclerotherapy, Cystic hygromas, Children, Side effects, Surgery, Sclerosant therapy, Color Doppler USG, Outcome.

### Introduction

In Greek, hygroma means "water-containing tumour". They are lymphatic system abnormalities that occur at birth. Cystic hygroma is more common than other types of lymphangioma and can consist of a single or many macrocystic lesions with limited contact with normal lymphatic channels [1-2].

Lymphangiomas are commonly characterised as capillary, cavernous or cystic lymphangiomas. On the basis of the size of the cysts they contain, they can also be classified more readily as microcystic, macrocystic, and mixed lymphangiomas. Cysts in microcystic lymphangioma are less than 2 cm in size, but cysts in macrocystic lymphangioma are more than 2 cm. The mixed lymphangioma is

characterised by cysts of varying sizes, i.e. some cysts are greater than 2 cm in size. Cystic hygromas can occur anywhere on the body. Cystic Hygroma (CH) is a form of cavernous lymphangioma that affects the skin and superficial tissues. It is a multilocular cystic mass with cysts of varying sizes that include the head and neck in more than 70% of cases, followed by the axilla, abdomen, and extremities.

Cystic hygromas can present during pregnancy on an ultrasound or after your baby is delivered as a lump or bulge beneath their skin. A cystic hygroma can affect any kid since it is caused by a genetic mutation that changes how the lymphatic system develops during foetal development. Cystic hygromas

can form on their own or among children diagnosed with a hereditary problem. Six lymphatic sacs can be seen in the developing embryo during the eighth week of pregnancy. There are two jugular sacs, two iliac sacs, one near the base of the root of the mesentery, and one dorsal to the abdominal aorta (cysternachyli). Jugular lymphatic sacs form in the neck region, whereas iliac sacs form in the lumbar region. Later on, a network of lymphatics forms that communicates with lymphatics from different locations. These sacs are invaded by connective tissue to produce lymph nodes during the ninth week of pregnancy [2-3].

A number of processes have been proposed to explain the pathophysiology of cystic hygroma. These lesions are thought to be caused by the sequestration of lymphatic tissue from lymphatic sacs during the development of lymphatico-venous sacs. These isolated tissues have no access to the lymphatic or venous systems. Later on, the sequestered lymphatic tissues dilate, giving rise to the cystic appearance of these tumours [3].

Cystic Hygroma is a multiloculated congenital lymphatic malformation bordered by endothelial cells. Cystic hygroma is more common than other kinds of lymphangioma and can consist of a single or many macrocystic lesions with limited contact with normal lymphatic channels [1]. The incidence is roughly one in per 6000-12000 births. It appears at birth in 50-60% of patients and by 2 years of age in 80-90% of cases. Cervico-facial regions (particularly the posterior cervical triangle), axilla, mediastinum, groin, and below tongue are typical places, and others are less than 2cm [3-4].

These abnormalities can arise in the liver, spleen, kidney, and intestine. Parallel lesions at these places include an omental cyst in the omentum and a mesenteric cyst in the intestine's mesentery [5-7]. The optimal treatment is total surgical removal, although the style of treatment is gradually shifting to sclerosant therapy. Therefore, the present study was undertaken to assess and evaluate the efficacy of bleomycin as a sclerosant as treatment for cystic hygroma and also the safety of bleomycin in treating cystic hygroma.

## Material and Methods

A prospective study conducted in Mahadevappa Rampure Medical College, Kalburagi, over a period of 2 years with 20 patients 12 females and 8 males. Cystic hygroma was diagnosed clinically with radiological supplementation of Doppler ultrasonography or MRI.

### Inclusion criteria:

- Ultrasonographically (USG) proven, subcutaneous, macrocystic lesions Over the neck,
- <5years of age,
- No/minimal vascularity.

### Exclusion criteria:

- Arterio venous malformations,
- Thoracic or abdominal lymphangiomas
- Cysts less than 5 cm,
- Previously surgically operated cases,
- Underlying pulmonary disease.

**Procedure:** The patients underwent preoperative evaluation after taking written and informed consent from the patient's attenders. The procedure was performed under IV sedation and USG guidance. All patients received 3 doses of antibiotics 1 preoperatively and two post operatively. The principle followed was that a minimum of the 50 % of the aspirated fluid on par with the sclerosant was reinserted with in mind the dose of 0.5mg/kg body weight (1 bottle of bleomycin containing 15 units of bleomycin diluted with 10cc of distilled water). Number of doses of bleomycin was dependent on the prognosis and clinical evaluation.

### Sclerosing Agents:

- **Detergents** : disrupt vein cellular membrane ( protein theft denaturation )  
Eg: sodium tetradecyl sulfate (sotradecol), ethanolamine oleate (ethamolin)
- **Osmotic agents**: damage the cell by shifting the water balance through cellular gradient (osmotic) dehydration and cell membrane denaturation.  
Eg: hypertonic sodium chloride solution, sodium chloride solution with dextrose (sclerodex)

- *Chemical irritants:* damage the cell wall by direct caustic destruction of endothelium  
Eg: chromated glycerin (scleromo), polyiodinated iodine

Cystic Hygromas mostly present in Neck (75%), Axilla (20%), others (5%). Being a large lesion in the neck, compression of vital structures leading to respiratory obstruction, symptoms of nerve compression, significant cosmetic deformity is observed. Surgery has usually been the preferred treatment, but due to 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.

*Non surgical methods:* Aspiration, Diathermy, Laser, Chemotherapy and Intralesional Sclerotherapy.

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

*Clinical pictures:*

**Fig-1:** Shown pre op image showing cystic hygroma over the cheek



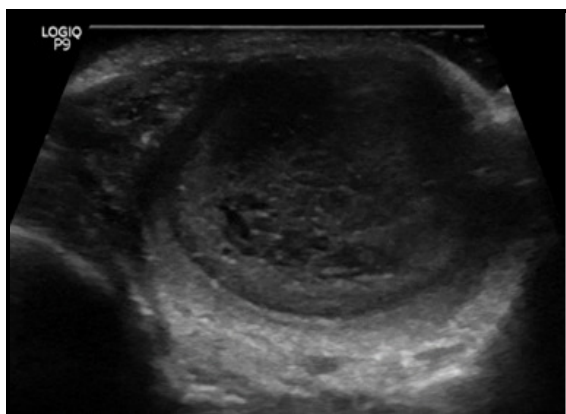
Radiological evaluation of the cystic hygromas includes sonography, CT and MR imaging [8]. Ultrasound is useful for identifying superficial lesions but is ineffective when they extend into deep structures such as the neck, thoracic cavity, or retroperitoneum. The use of MRI in cystichygroma can help with precise diagnosis and preoperative planning, resulting in successful treatment of this lesion. The advantages of MRI include greater multiplanar capabilities, the absence of bone artefacts, and the absence of ionising radiations [9].

They present as hypoechoic or anechoic, unilocular and septated or multilocular trans-spatial lesions on ultrasonography, with no real vascular flow on color Doppler, when large, the lesion can transverse tissue planes and generate a considerable mass effect [10]. Cystic hygroma is visible on MRI as a low signal intensity area on T1 weighted images and a high signal intensity area on T2 weighted images and STIR imaging. T1 weighted images after contrast enhancement may exhibit minor rim enhancement. In the instance of intralesional bleeding, it may appear as a high signal intensity area on T1 weighted imaging [10].

**Fig-2:** Shown Post op images after bleomycin injection



**Fig-3:** Shown follow up ultrasound, post sclerotherapy shows decrease in size of the lesion



**Results**

The study involved 20 patients, 8 of whom were male (40%) and 12 of whom were female (60%), ranging in age from 30 days to 36 months with average age was 16.1 ± 9.6 months.

Table-1: Basic characteristics		
Characteristics	Number	Percentage
Age (months)		
<1	1	5
1-12	8	40
13-24	7	35
25-36	4	20
Mean ± SD	16.1 ± 9.6 months	
Sex		
Male	8	40
Female	12	60

From the table-1, it was observed that, majority of the study subjects were belongs to age group 1-12 months (40%) followed by 13-24 months (35%), and 25-36 months (20%). In the present

study, female children (60%) were more dominant than male children (40%). The pre op image showing cystic hygroma over the cheek (Fig-1).

Table-2: Side effects		
Side effects	Number	Percentage
Fever	3	15
Erythema	1	5
Fever and Erythema	2	10
No side effects	14	70

In the present study, it was found that, 14 (70%) of study subjects were not experienced any side effects, whereas 3 subjects were experienced fever (15%) followed by fever along with erythema in 2 subjects (10%) and erythema in one subject (5%) (Table-2). The Post op images showing after bleomycin injection (Fig-2).

Table-3: Outcome based on gender			
Outcome	Male (%)	Female (%)	Total
Excellent	6 (37.5)	10 (62.5)	16
Good	2 (50)	2 (50)	4
Poor	0	0	0

From table-3, outcome was based on gender; it was observed that, in excellent outcome of treatment, female subjects (62.5%) were shown good response as compared to male subjects (37.5%), whereas equal response was observed in good outcome of treatment by both (50%) subjects (Table-3). Further, Number of doses of injection varied from 1 to 2. It was understood that, complete resolution without in duration clinically seen in 16 out of 20 patients (80%), whereas good response was observed in 4 patients (20%), whereas none was observed as poor outcome. The follow up ultrasound image showing post sclerotherapy shows decrease in size of the lesion (Fig-3).

**Discussion**

Cystic Hygroma (CH) is a form of cavernous lymphangioma that affects the skin and superficial tissues. It is a multilocular cystic mass with cysts of varying diameters, with more than 70% involving the head and neck, followed by the axilla, belly, and extremities [11]. A big neck lesion can cause substantial

cosmetic deformities, compression of important organs, breathing obstruction, dysphagia, and nerve compression symptoms [12]. Surgery has been the mainstay of treatment, but even in the most competent hands and with the most precise surgical procedure, it has markedly unfavourable outcomes, including injury to neighbouring tissues, bleeding, scarring, lymphatic drainage from the incision, and recurrence [11].

Many non-surgical treatments, such as radiation, cryotherapy, diathermy, laser, chemotherapy, and intralesional sclerotherapy, are documented in the literature. Sodium morrhuate, dextrose, hypertonic saline, tetracycline, doxycycline, acetic acid, ethanol, boiling water, alcoholic solution of zein (ethibloc), fibrin sealant, triamcinolone, OK-432, and bleomycin are examples of sclerosants [13]. The ultimate mode of treatment for cystic hygroma is surgical excision; however, many recent case reports have showed excellent results with using sclerosants for management of such lesions [1, 3-5, 14-18]. The other treatment modalities include simple aspiration, radiation, laser excision, and cauterization [2,14,18-19].

Sclerotherapy with intra-lesional bleomycin, as a primary treatment modality, for cystic hygroma, has been tried. Many studies show the usage of bleomycin to be effective [16-18,20]. The other agent used as sclerosant is OK432, which is also used [2,16-18,20-21].

These sclerosing drugs are assumed to function by destroying the endothelial cells of the disturbed lymphatic supplying into the lymphocele, resulting in a decrease in lymph fluid production and, eventually, the cyst's collapse. Bleomycin is an anti-neoplastic drug that was originally used in 1966 to treat a range of malignant lesions by inhibiting DNA synthesis. Intralesional Bleomycin was used as a sclerosing drug for the first time in 1977 by Yura et al in Japan for CHs, and the results were promising [17].

Pulmonary toxicity is a significant adverse effect of bleomycin that is most commonly observed when the dose surpasses the maximum cumulative dose of 5mg/kg or 30mg/m<sup>2</sup>. According to studies, this is rarely observed with such low doses. It irritates the endothelium lining of the CHs, resulting in nonspecific

inflammation, fibrosis, and involution. This reaction is determined by the drug dose in relation to the lesion's per unit surface area.

Sclerosants are hypothesised to act by destroying endothelial cells, resulting in a decrease in lymph fluid production and cyst collapse. Bleomycin was chosen as a sclerosant because of its ease of use, low cost, and little adverse effects when taken in low doses intralesionally in cystic hygroma. The dose of intralesional bleomycin (ILB) is 0.3-3 mg/kg/session. Many research advise that the frequency of sessions should range from 1 to 6 weeks. In our study, the ILB dosage is 0.5mg/kg/ session, with each session occurring every 4-6 weeks depending on the response.

*Side effects:* Fever, transient rise in swelling size, haemorrhage, leukocytosis, and pulmonary fibrosis are the side effects. Minor adverse effects identified in our study include fever, erythema, and edoema at the injection site, as well as vomiting, which is fewer than in other studies. In our study, it was found 30% had side effects, whereas near about similar amount of complication noted in 43% patients by Niramis R et.al study [22]. The biggest worry with Bleomycin therapy is the possibility of pulmonary harm.

*Efficacy of Bleomycin:* Its effectiveness is increased when utilised as a microsphere-in-oil emulsion. The desired result of sclerosis is drug availability per unit of lesion surface area (surface area > patient weight). The intended effect of sclerosis is produced by the local action of Bleomycin, which is dependent on the drug's availability per unit of surface area of the lesion. As a result, the dose injected should be determined by the size of the lesion rather than the patient's weight, and sclerosis can be caused with a considerably lower dose than the patient's weight would suggest.

In the present study, ILB with aqueous solution was useful in achieving 80% full clearance of cystic hygroma. Similar findings were discovered by Ikram Ud Din et al in 86%, whereas Tanak et al reported 20 (43%) great response [23].

## Conclusion

Intralesional bleomycin sclerotherapy is a straightforward, safe, and effective nonsurgical treatment that delivers equivalent results to surgical techniques while posing less risks. As a

result, to reduce the possibility of unintentional injury from surgery and for cosmetic reasons, we recommend Intralesional Bleomycin Sclerotherapy as the primary technique of treatment in cystic hygroma.

**Financial Support and sponsorship:** Nil

**Conflicts of interest:** There are no conflicts of interest.

## References

- Manikoth P, Mangalore GP, Megha V. Axillary cystic hygroma. *J Postgrad Med.* 2004; 50:215-216.
- Mirza B, Ijaz L, Saleem M, Sharif M, Sheikh A. Cystic hygroma: an overview. *Journal of Cutaneous and Aesthetic Surgery.* 2010; 3(3):139.
- O'Neil JA, Coran AG, Fonkalsrud E, Grosfeld J. *Pediatric Surgery.* Philadelphia, PA: Mosby. 6th ed. Elsevier. 2006; 2137-2145.
- Sanlialp I, Karnak I, Tanyel FC, Senocak ME, Büyükpamukçu N. Sclerotherapy for lymphangioma in children. *International Journal of Pediatric Otorhinolaryngology.* 2003; 67(7):795-800.
- Kaur N, Gupta A, Singh N. Giant cystic hygroma of the neck with spontaneous rupture. *Journal of Indian Association of Pediatric Surgeons.* 2007; 12(3):154.
- Kocher HM, Vijaykumar T, Koti RS, Bapat RD. Lymphangioma of the chest wall. *Journal of Postgraduate Medicine.* 1995; 41(3):89.
- Dhrif AS, El Euch D, Daghfous M, Cherif F, Mokni M, Dhahri AB. Macrocytic lymphatic lymphangioma (cystic lymphangioma) of the upper extremity: A case report. *Arch Pediatr.* 2008; 15(9):1416-1419.
- Siegel MJ, Glazer HS, St Amour TE, Rosenthal DD. Lymphangiomas in children: MR imaging. *Radiology.* 1989; 170(2):467-470.
- Sheth S, Nussbaum AR, Hutchins GM, Sanders RC. Cystic hygromas in children: sonographic-pathologic correlation. *Radiology.* 1987; 162(3):821-824.
- Bernadette L. Koch, Diagnostic imaging: Pediatrics. 3rd edition, Salt Lake City, UT: Elsevier, Inc., 2016; Section 9: 1212-1213.
- Mirza B, Ijaz L, Saleem M, Sharif M, Sheikh A. Cystic hygroma: An overview. *J Cutan Aesthet Surg.* 2010; 3:139-144.
- Camitta BM. Abnormalities of lymphatic vessels. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF eds. *Nelson Textbook of Pediatrics.* 18th ed. Philadelphia, Pa: Saunders Elsevier, 2007: chap 48.
- Acevedo JL, Shah RK, Brietzke SE. Nonsurgical therapies for lymphangiomas: a systematic review. *Otolaryngology-Head and Neck Surgery.* 2008; 138(4):418-424.
- Sobol SE, Manoukian JJ. Acute airway obstruction from a laryngeal lymphangioma in a child. *Int J Pediatr Otorhinolaryngol.* 2001; 58(3):255-257.
- Ameh EA, Nmadu PT. Cervical cystic hygroma: pre-, intra-, and post-operative morbidity and mortality in Zaria, Nigeria. *Pediatric Surgery International.* 2001; 17(5):342-343.
- Mahajan JK, Bharathi V, Chowdhary SK, Samujh R, Menon P, Rao KL. Bleomycin as intralesional sclerosant for cystic hygromas. *Journal of Indian Association of Pediatric Surgeons.* 2004; 9(1):3.
- Yura J, Hashimoto T, Tsuruga N. Bleomycin treatment for cystic hygroma in children. *Arch Jpn Chir.* 1977; 46:607-614.
- Okada A, Kubota A, Fukuzawa M, Imura K, Kamata S. Injection of bleomycin as a primary therapy of cystic lymphangioma. *Journal of Pediatric Surgery.* 1992; 27(4):440-443.
- Giguère CM, Bauman NM, Smith RJ. New treatment options for lymphangioma in infants and children. *Annals of Otolaryngology & Laryngology.* 2002; 111(12):1066-1075.
- Orford J, Barker A, Thonell S, King P, Murphy J. Bleomycin therapy for cystic hygroma. *Journal of Pediatric Surgery.* 1995; 30(9):1282-1287.
- Zhong PQ, Zhi FX, Li R, Xue JL, Shu GY. Long-term results of intratumorous bleomycin-A5 injection for head and neck lymphangioma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998; 86(2):139-144.
- Niramis R, Watanatittan S, Rattanasuwan T. Treatment of cystic hygroma by intralesional bleomycin injection: experience in 70 patients. *European Journal of Pediatric Surgery.* 2010; 20(03):178-182.
- Din IU, Rehman IU, Rasool G, Khan AR, Din SE. Intralesional bleomycin therapy of cystic hygroma in children. *J Med Sci.* 2008; 16(2):87-90.

**Cite this article as:** Gubbi S, Patil S, Reddy CK and Rajiv Reddy JC. Intralesional bleomycin sclerotherapy for cystic hygroma in children - as alternative treatment. *Al Ameen J Med Sci* 2023; 16(3): 249-254.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial (CC BY-NC 4.0) License, which allows others to remix, adapt and build upon this work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

\*All correspondences to: Dr. Chinmayee K. Reddy, Junior Resident, Department of General Surgery, Mahadevappa Rampure Medical College, Sedam Road, Kalaburagi-585 105, Karnataka, India. E-mail: chinmayee.k.reddy@gmail.com