

Original Article

Efficacy of bleomycin for non-operative treatment of cervical lymphangioma in University of Ilorin Teaching Hospital, Nigeria

ABSTRACT

Background: Lymphangiomas are the developmental defects of the lymphatic channels, and they are most commonly found in the head and neck regions. Late presentation, rejection of surgery, and traditional scarification result in fatal complications. Surgical excision often thought to give immediate relief and aesthetic results is associated with damage to contiguous structures and recurrence, hence, the need for less invasive treatment modality.

Objective: To assess the effectiveness of bleomycin sclerotherapy of cervical lymphangiomas.

Materials and Methods: This is a prospective study of patients with cervical lymphangioma treated with sclerosant injection between January 2008 and December 2016. Preinjection ultrasound scan and initial ultrasound-guided aspiration of the fluid in the swelling (which many times is multiloculated) using a 20G cannula into a 10 ml syringe were performed. The cannula tip is retained in the space and intralesional injection of double-diluted bleomycin 0.5 i.u./kg body weight was given as outpatient at 2–4-weekly interval. Postinjection events were documented. The clinical assessment of the pre- and postinjection of sclerosant was performed.

Result: A total of 23 patients were recruited, and six were females and 17 were males. All swellings were noticed at birth but median time at presentation was 17 days. All patients but one (95.8%) had complete clinical resolution after 1–4 courses of sclerotherapy for 4–16 weeks. Only one patient had residual nodule that required surgical excision. Redundant skin and hyperpigmentation from skin wrinkle were the early effects noticed in three patients; however, these were cosmetically acceptable to the parents. No recurrence was recorded.

Conclusion: The treatment of cervical lymphangiomas with intralesional bleomycin injection is shown to be effective. It is safe and associated with no complication. This treatment modality and outcome was found to be acceptable to the parents of these children.

Keywords: Bleomycin, cervical lymphangiomas, cystic hygroma, sclerotherapy, surgery

INTRODUCTION

Lymphangiomas are the congenital malformations of the lymphatic system resulting from failure of involution or resorption of the lymphatic saccules. They are mostly found in the head and neck regions and to a lesser extent in the axilla and trunk but can be found anywhere the lymphatic vessels are, because there have been reports of unusual location of lymphangiomas.^[1,2] Cystic hygroma is an old term commonly used to describe cystic lymphangiomas in the cervical area that is now preferably called macrocystic lymphatic malformation.^[3] When discovered before 30 weeks' gestation, it is associated with chromosomal abnormality in 70% of fetuses and this is associated with spontaneous or

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therapeutic abortion. The incidence of one in 12,000 live births has been reported^[2] but data are not available in most of Africa. Over 60% are clinically apparent at birth and up to 90% present by the age of 2 years.^[4,5]

Embryologically, they are believed to originate from the sequestration of lymphatic tissue from lymphatic sacs during the development of lymphaticovenous sacs. These sequestered tissues fail to communicate with the remainder of the lymphatic or venous system and they dilate later on resulting in the cystic morphology.^[4]

On the basis of ultrasonography, the lesion has been classified as microcystic (consists of cysts measuring less than 2 cm in size), macrocystic (cysts more than 2 cm) and mixed.^[4,6] Surgical excision and sclerotherapy are the mainstay of treatment but because lymphangiomas develop early embryologically and do not follow tissue planes, complete surgical excision is challenging and could result in the mutilation of the tissues. More so, diffuse and predominantly microcystic lymphatic malformations are difficult to eradicate by any method. There are evidences that sclerotherapy with the injections of bleomycin, OK-432, or triamcinolone (10 mg/kg) repeated at intervals provides effective treatment.^[5,7,8] Simple drainage, aspirations, radiation, and cauterization have been tried with unsatisfactory results.

Surgery has been fraught with unpleasant limitations which include damage to contiguous vital structures, difficulty in achieving complete excision, disfigurement, and recurrence which could be as high as 20%.^[9]

This study aims to evaluate the effectiveness of bleomycin sclerotherapy in the cases of cervical lymphangiomas treated in our center.

MATERIALS AND METHODS

This is a prospective study of patients with cervical lymphangioma treated with bleomycin sclerosant injection between January 2008 and December 2016 at a tertiary teaching hospital.

Diagnosis was made based on clinical evaluation [Figure 1] and ultrasound scan, which was used to confirm the diagnosis and to exclude microcystic lesion. Only macrocystic lymphangiomas were included in this study. MRI was performed for a patient that had intraoral extension and another with mediastinal extension. For huge swellings with doubtful consistency, a neck X-ray was ordered to exclude other differential diagnoses

[Figure 2]. Parents/guardians were appropriately counseled for intralesional bleomycin injection. For those that presented as neonates, parents were counseled to present their children after the first month for the commencement of the injection.

All our patients had an ultrasound scan of their swellings to confirm the diagnosis but less than half of the patients had ultrasound-guided aspiration and injection of sclerosant due to additional procedure cost and logistics (delays in ultrasound appointment booking, limited sonology personnel, and space for ultrasound scanning). The procedures were performed on outpatient basis under aseptic techniques and under ultrasound guidance. Preprocedure vitals (heart rate, respiratory rate, and temperature) were recorded. A 20G cannular on 10 ml syringe was used to aspirate and decompress the cyst and 0.5 i.u./kg body weight of bleomycin double diluted was injected into the cavity and a compressive dressing held in place by an adhesive plaster [Figure 3]. The procedure was conducted at the day case bay in the ward and the children were monitored thereafter for about 4 h for any signs of complications, for example, edema, erythema, difficulty in



Figure 1: Preinjection of bleomycin

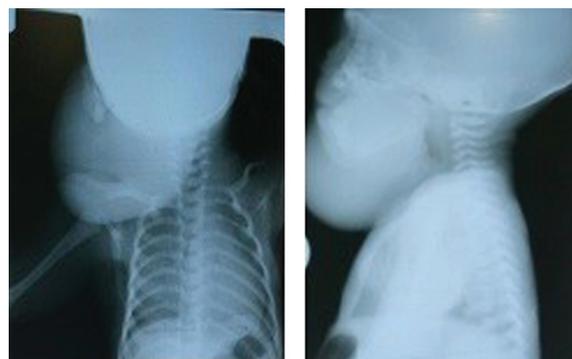


Figure 2: AP and lateral view X-rays of one of the patients with huge cystic neck swelling



Figure 3: Step by step aspiration and injection of Bleomycin sclerosant using a size 20G cannular

breathing, or restlessness. Parents were also advised to watch out for the abnormal positioning of the neck postinjection to avoid the kinking of the respiratory tract, unusual swellings, and color change of the surrounding skin. Vitals signs were repeated 15 min after the completion of injection and at 2 h before discharge.

Injections were repeated at 2–4-weekly intervals; 2 weekly for swellings >10 cm diameter and 4 weekly for those <10 cm diameter. Changes in size and skin texture were documented at each clinic visit. Clinical photographs were also taken. Surgery was performed for a patient who had significant nodular residual lesion.

Data collation was performed using standardized proforma and analyzed with Epi Info™ for Windows Version 3.5 CDC, Atlanta, GA, USA.

RESULTS

A total of 23 patients were recruited, aged between 4 h and 5 years, including six females and 17 males, with a M:F ratio of 2.8:1. All were noticed at birth with 74% (17/23) of the swellings on the left side. One patient each had hyperpigmentation of skin over the swelling, extension into the right upper aspect of superior mediastinum, and an intraoral extension displacing the tongue, which made feeding difficult. No other congenital anomalies were detected [Table 1].

The 23 patients had between one and four doses of intralesional bleomycin (median = 2.3). Treatment was over an interval of 4–16 weeks. Eleven (47.8%) patients had injection 4 weekly while 8 (34.8%) had theirs every 2 weeks because of the huge size. Four patients had single injection. All but one (95.7%) had complete clinical resolution of swelling. Only one had residual nodular mass that required surgical excision after having four doses of sclerosant injection and waiting for 1 year. The follow-up of patient was between 7 days and 26 months (median = 9.5 months).

Redundant skin [Figure 4] and hyperpigmentation (from skin wrinkling) were the immediate and early lesions noticed in three patients (13%); however, these were cosmetically acceptable to the parents. No scarring or life-threatening

complications were observed in all the patients and there was no recurrence recorded.

DISCUSSION

Cystic hygroma or cervical lymphangioma is a congenital malformation of the lymphatic system appearing as a single or multiloculated fluid-filled cavity, most often in the cervical region. Similar to the findings in previous studies that showed that most patients have their swellings at birth,^[4,5] all of the patients in our study had their lesion noticed at birth by their parents but were presented later because of ignorance about what to do, wait-and-see attitude of attending health practitioners, multiple referrals, fear of cost of care, and residence at remote areas to our facility. Some even thought the swellings were a special blessing, for the child was destined to be fat/obese. The masses were predominantly on the left side, a finding that has also been previously reported^[10,11] and were asymptomatic except for the one with lingual involvement which made feeding difficult.

The association of cystic hygroma with congenital anomalies such as Turner syndrome, Noonan syndrome, trisomies, and cardiac anomalies has been reported;^[12] however, we found none of these associations in the patients we studied. Other differentials of cystic neck swelling will include a cervical teratoma, dermoid cyst, branchial cyst, neurofibromatosis, and hemangioma.

Several options proffered for the treatment of lymphangiomas including surgery, simple drainage, aspirations, radiation, and cauterization gave unsatisfactory results.^[9] Sclerotherapy was first used to manage lymphangioma successfully in 1933 using sodium morrhuate.^[5] Sclerosing agents that have been used since then include OK-432 which is an inactivated strain of *Streptococcus pyogenes*, a monoclonal antibody that is expensive and not readily available; others are absolute ethanol, doxycycline, iodine, ethanolamine oleate, cyclophosphamide, and bleomycin. OK-432 and bleomycin are the most commonly used. These agents cause the inflammation of the endothelial lining of the lymphangioma leading to fibrosis and involution.^[13] Complications of sclerotherapy to be avoided include injury to adjacent nerves, necrosis of overlying skin, and cardiotoxicity related to the overall dose. Ethanol, sodium

Table 1: Clinical data and outcomes of bleomycin injection sclerotherapy

Case no.	Age at presentation, sex, weight (kg)	Size, side	No. of injections, frequency	Total duration of follow up from 1 in. injection (months)	Outcome (resolution)
1	4 h, F, 2.25	5 cm × 6 cm, right	3, 4 weekly	17	Complete
2	2 years, M, 12	14 cm × 16 cm, right	4, 2 weekly	18	Partial, surgery
3	2 months, M, 3.6	12 cm × 14 cm, right	3, 2 weekly	3	Complete
4	5days, M, 4.15	12 cm × 14 cm, left	2, 2 weekly	11	Complete
5	16 h, M, 2.7	8 cm × 9 cm, left	2, 4 weekly	19	Complete
6	10 months, M, 8.15	6 cm × 9 cm, left	3, 2 weekly	3	Complete
7	2 weeks, M, 4.5	10 cm × 12 cm, right, intraoral extension	3, 2 weekly	3	Complete
8	3 years, M, 12	14 cm × 16 cm, right, extension into the upper chest	3, 2 weekly	12	Complete
9	3 weeks, M, 3	7 cm × 9 cm, left	2, 4 weekly	6	Complete
10	4 months, M, 5.2	8 cm × 11 cm, left	2, 4 weekly	5	Complete
11	5 weeks, M, 3.8	7 cm × 9 cm, left	2, 4 weekly	8	Complete
12	15 days, M, 3.4	8 cm × 8 cm, left	1	25	Defaulted after 1 in. injection
13	5 years, M, 20	9 cm × 12 cm, left	1	1	Defaulted-lost to follow up
14	14 days, F, 3.3	8 cm × 9 cm, left	1	7	Defaulted after 1 in. injection
15	10 days, M, 3	6 cm × 7 cm, left	1	5	Complete
16	4 days, M, 2.8	10 cm × 13 cm, left	2, 2 weekly	7	Complete
17	2 months, F, 4	7 cm × 10 cm, left	2, 4 weekly	6	Complete
18	10 weeks, M, 4.1	8 cm × 10 cm, left	2, 4 weekly	12	Complete
19	5 months, F, 5.8	7 cm × 9.5 cm, left	2, 4 weekly	5	Complete
20	15 days, F, 3.6	6 cm × 10 cm, left	2, 4 weekly	7	Complete
21	24 days, M, 3.8	8 cm × 10 cm, left	1, 4 weekly	4	Complete
22	3 months, F, 5.4	13 cm × 15 cm, left	2, 2 weekly	5	Complete
23	3 days, M, 2.9	6 cm × 10 cm swelling, right	2, 4 weekly	26	Complete



Figure 4: Redundant skin postbleomycin injection sclerotherapy. This disappeared as the child grows

tetradecyl sulfate, and doxycycline are known to produce scarring.

Several studies have shown promising results with the intralesional bleomycin therapy of lymphangiomas with up to 63% complete resolution in some studies and over

80% showing significant reduction in size.^[5,8,14-16] Our study similarly demonstrated bleomycin sclerotherapy for cervical lymphangioma as very effective with more than 95% complete resolution rate found in our patients.

The observation of the patients in our facility postinjection was to ensure that sclerosant was not inadvertently injected into vessels or vital structures with spontaneous hemorrhage or allergic reaction. Systemic injection of bleomycin should be avoided as cumulative dose may endanger the patient and lead to adverse effects such as pulmonary fibrosis. It is recommended that tracheostomy precedes any attempts at sclerotherapy for cervicofacial lymphangiomas as reactive inflammatory swelling can be dramatic in the initial period after sclerotherapy and can exacerbate partial oropharyngeal obstruction.^[17] None of our patients needed a tracheostomy but we were prepared to offer one in case it became necessary.

We deferred the commencement of the injection sclerotherapy in neonatal period to avoid interference with the transition and adaptation of the babies and also because there were no features of systemic compromise to warrant urgent intervention. There was ready acceptance of

the use of injection sclerotherapy by most parents, because they preferred this approach to surgical excision in their newborn. Though successful treatment with sclerosant injection was welcomed, surgery would play a significant role in the management of cervical lymphangiomas associated with obstructive symptoms, bleeding, recurrent infections, ulcerated/ruptured lesions, and microcystic and mixed lesions.^[5,8,15] Excision of residual lesion after sclerotherapy as with one of the patients in our study also demonstrates the role of surgery.

CONCLUSION

The treatment of cervical macrocystic lymphangiomas with intralesional bleomycin injection is very effective. It is safe and associated with no serious complication. This treatment modality and outcome was found to be acceptable to the parents of these children. Surgical excision should only be considered in complicated cases possibly from infection or a rupture and in microcystic lymphangiomas.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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