

Intralesional bleomycin sclerotherapy in childhood lymphangioma

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This clinical trial was conducted to evaluate the efficacy of intralesional bleomycin sclerotherapy (IBS) in children with lymphangioma and to determine the incidence of complications in the treatment. Seventeen lymphangioma cases were treated with IBS from 2004 to 2012. Age, mode of presentation, locations and types of lesions, and results of treatment were studied. Lymphangioma was diagnosed by physical examination and imaging studies. Most of the lesions were located in the cervical region (n=8) and of macrocystic type (n=13). After the first injection, three patients were lost to follow-up. Good response was seen in 50% of the lesions, complete resolution in 35.7%, and poor response in 14.3%. No serious complications or side effects were observed after IBS. The average follow-up was 18.5 months. IBS is effective in the treatment of lymphangioma. Although no major adverse effects have been encountered, complications should be kept in mind and in the event of their occurrence be treated immediately.

Key words: lymphangioma, sclerotherapy, bleomycin.

Lymphangioma is a benign tumor of lymphatic vessels and consists of cystic spaces of varying size. The most frequent occurrence is in the head and neck, accounting for 75% of all cases^{1,2}. It is typically detected at birth in up to 65% and presents by the age of two years in 90% of cases^{1,3,4}. The incidence of lymphangioma is reported to be from 1.5-2.8 per 1000 with no predilection for either sex⁵. Swelling and cosmetic deformity are the most common symptoms.

Surgical excision is the traditional management, the goal of which is the removal of the involved tissue without sacrificing vital structures, but this may not be achieved in most cases. Due to the nature of the lesion, which has a propensity to infiltrate tissue planes and encircle important neurovascular structures, complete excision is frequently impossible³. Multiple nonsurgical therapies have been proposed, including diathermy, cryotherapy, radiotherapy, fibrin glue, and percutaneous sclerotherapy. Intralesional sclerotherapy has become a

method of treatment for lymphangiomas in children. Various sclerosing agents have been used in the treatment of childhood lymphangiomas.

A retrospective clinical trial was conducted to evaluate the efficacy of intralesional bleomycin sclerotherapy (IBS) in the treatment of lymphangiomas in children and to determine the incidence of complications during the treatment.

Material and Methods

A retrospective study of 17 children diagnosed with lymphangioma and treated with IBS from 2004 to 2012 was conducted. Age, mode of presentation, locations and types of lesions, and results of treatment were studied. The total number of lymphangioma patients in this period was 23.

Lymphangioma was diagnosed by means of physical examination and information from imaging studies such as ultrasonography,

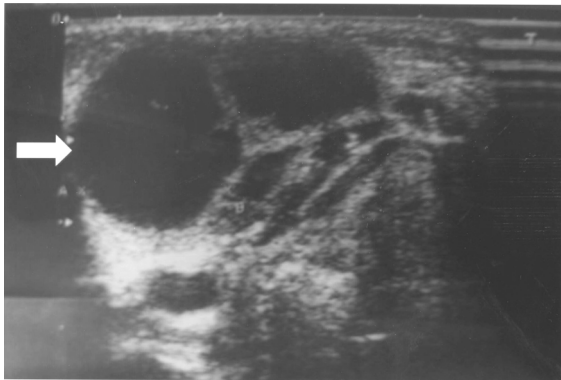


Fig. 1. Ultrasonographic view of a patient with macrocystic-type lymphangioma.

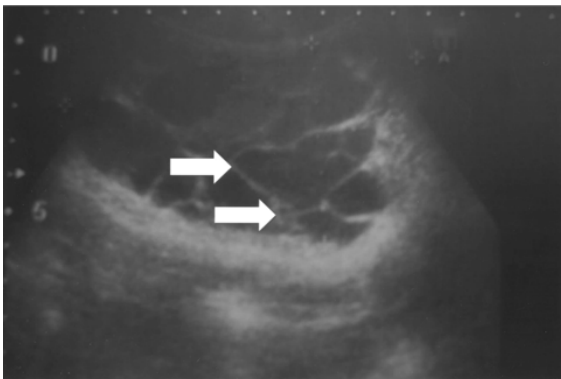


Fig. 2. Ultrasonographic view of a patient with mixed-type lymphangioma.

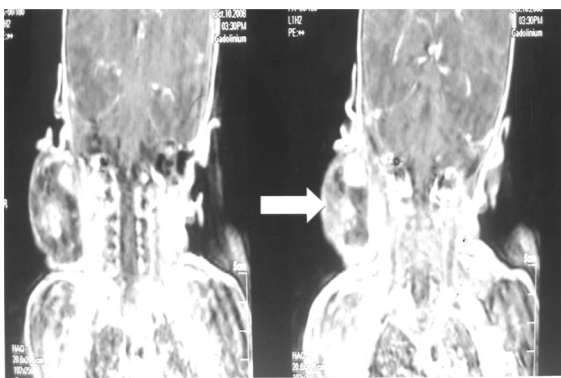


Fig.3. Magnetic resonance image of a cervical lymphangioma.

computed tomography and/or magnetic resonance imaging (Figs. 1-3). These imaging studies were also obtained to classify the type of lymphangioma and extensions of the lesion. As described by Ogita⁶, type was classified as macrocystic (>1 cm), microcystic (<1 cm) or mixed, indicating lesions containing both macrocystic and microcystic components.

As a primary mode of treatment, surgical excision was performed in six patients with lymphangiomas located in the abdominal or thoracic cavity both to confirm the diagnosis and to prevent complications that may arise from their compressive effect on vital structures. These patients were excluded in this study. In the present study, none of the patients was managed with embolization or with microbiological treatment as a first-line treatment modality, and no child was followed without any treatment. All the patients with lymphangioma received either IBS or surgical excision as the first-line therapy, and patients treated with IBS constituted the study group.

The patients were hospitalized before treatment. Injections were performed to patients under general anesthesia. The cystic components of the tumor were aspirated. While keeping the tip of the aspiration needle within the cyst lumen, 1 mg per kg body weight of bleomycin aqueous solution (1 mg/ml), described by Yura⁷, was injected. When more than one cyst was aspirated, the calculated dose was divided by the number of cysts aspirated and the divided dose was injected into each cyst. The maximum volume for replacement was 20 ml regardless of the volume of aspirated fluid. This procedure was repeated after 4-6 weeks if the cysts persisted and measured at least 1 cm in diameter.

All the patients were kept under close observation for at least 24 hours following

Table I. Sites of Involvement in Lymphangiomas

Site of lesion	n
Cervical region	8
Thoracic wall	4
Shoulder	2
Gluteus	1
Lumbar region	1
Abdominal wall	1

Table II. Response to Bleomycin Injection According to Lesion Type

Lesion type	n (Complete resolution)	n (Good response)	n (Poor response)
Macrocystic	5	4	1
Mixed	0	3	1

the procedure. They were monitored for possible immediate and late complications of the treatment. The response was evaluated as complete resolution (total disappearance), good response (showing >50% reduction in size) and poor response (showing <50% reduction in size).

Results

Patients mostly presented with swelling in the affected body regions. Most of the lesions were located in the cervical region (n=8). Other sites of involvement are depicted in Table I. With the exception of five newborn patients, the average age was 3.8 years (2 months-9 years). Most of the lesions were macrocystic type (n=13), followed by mixed type (n=4); there were no microcystic lesions in this series. The number of procedures per patient varied from one to five. After the first injection of bleomycin, three patients were lost to follow-up. Good response was seen in 50% (7/14) of the lesions, complete resolution in 35.7% (5/14), and poor response in 14.3% (2/14) (Table II). Two patients had undergone prior surgery and these patients had good response to IBS. No serious complications, side effects or recurrences were observed after the injection therapy. The average follow-up period was 18.5 months (2-46 months).

Discussion

Lymphangioma is one of the most common benign lesions of childhood, which manifests frequently before two years of age. Surgical excision has been considered the treatment of choice. Due to the property of the lymphangioma of infiltrating adjacent structures, incomplete resection or inadvertent nerve injury may result. Recurrence rates after macroscopic total excision were reported to be 15-40%⁸.

The first case of lymphangioma treated by sclerotherapy with sodium morrhuate was reported in 1933⁹. Since then, various sclerosing agents have been used. Bleomycin

is an antitumor agent discovered in 1965. Besides its antineoplastic effect, it has an irritant effect on endothelial cells of the cyst wall of lymphangiomas. It seems that bleomycin causes non-specific inflammatory reaction leading to fibrosis of the cysts. The first report of intralesional bleomycin therapy was reported in 1977 with good results⁹. Since then, various studies have produced promising results⁹⁻¹³. Our study indicated that bleomycin was effective in our patients (12 of 14 with complete resolution or good response), and the results were comparable to the published series. Success rates of 36-63% for complete tumor regression, of up to 88% for significant lesion regression, and poor response of 12-18% using bleomycin were reported^{5,9-13}.

In this study, the procedure was performed in children under general anesthesia in the operating room. Bleomycin aqueous solution at a dosage of 1 mg/kg described by Yura⁷ was injected directly into a cyst after aspiration of the cyst content. The total dose never exceeded 15 mg. There has been no uniformity about the dose of this drug in the reported series. Doses of 0.3-0.6 mg/kg for each injection, with a total amount of bleomycin injected of up to 50 mg or 5 mg/kg, and up to 16 injections at intervals of 2 weeks to 2 months have been reported^{4,9,12,14,15}.

Most of the patients with lymphangioma in this series presented with macrocysts (10/14). It may be that the high rate of satisfactory response to IBS in our patients was related to the fact that lesions consisting of macrocysts respond well to local injection therapy, as reported in the literature, while response is lower in microcystic lymphangioma¹⁶⁻¹⁸. There was good response in 3 of 4 patients with mixed lymphangioma; no patients with microcystic type were observed in this series.

Poor response to IBS was observed in two patients. Sites of involvement in these patients were the cervical and gluteal regions. In the patient with cervical involvement, lesions extended into the anterior mediastinum, and

only the neck components were aspirated and injected with bleomycin. With this approach, it was hoped that as the neck component reduced in size, the mediastinal component would retract into the neck. The mediastinal component was not directly aspirated and injected for the fear that it could cause mediastinitis and compromise adjacent vital structures. The other non-responder to bleomycin was a 2.5-year-old boy with a macrocystic lesion in the gluteal region. Repeat injection is to be planned for future resolution in this patient.

No serious complications were seen after IBS. Most patients complained of skin erythema, local swelling, and induration, but these symptoms did not prolong their stay in the hospital. Although fever was reported as the most common side effect, with an incidence of 30%¹⁹, it was not observed in any of our patients. The primary concern of bleomycin therapy is the risk of pulmonary toxicity. The risk is dose-related, and at total doses of below 150 mg or 450 U, life-threatening pulmonary toxicity is rare^{20,21}. It is reported that two children who underwent bleomycin therapy died posttreatment from pulmonary complications, although a definitive link to the bleomycin therapy was not established³. Clinical studies from different centers, in which a total of 104 patients were treated with IBS, did not report pulmonary fibrosis as a complication⁹⁻¹³.

Nevertheless, there are limitations to the present study. The retrospective design and relative short follow-up period in the treatment group may undermine the strength of this study. Although there was no recurrence in the children treated with IBS during the follow-up period, the relative short duration of surveillance in this series (18.5 months) should prevent us from drawing clear conclusions concerning the recurrence. Further prospective studies involving more patients with longer follow-up periods may provide fundamental information on this matter.

The majority of our patients (12/14) who underwent sclerotherapy with bleomycin achieved satisfactory response. No serious side effects from IBS were observed. Though the sample size in this series was limited, local injection of bleomycin is recommended as a first-line therapy, and surgical excision should be reserved for refractory cases or lymphangiomas that present a diagnostic

difficulty. However, literature regarding sclerotherapy for lymphangiomas has a low level of evidence. With randomized clinical trials focused on local bleomycin therapy, standardized dosing protocols and reliable outcome reporting, it is anticipated that the heterogeneity of the literature will be decreased and future development of treatment guidelines will be possible.

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