Alcoholic solution of zein (Ethibloc) sclerotherapy for treatment of lymphangiomas in children

Mohammad Ali Emran\textsuperscript{a}, Josée Dubois\textsuperscript{b,*}, Louise Laberge\textsuperscript{a}, Ayman Al-Jazaeri\textsuperscript{a}, Andreana Bütter\textsuperscript{a}, Salam Yazbeck\textsuperscript{a}

\textsuperscript{a}Division of Pediatric Surgery, Sainte Justine Hospital, Montreal (Quebec), Canada H3T 1C5
\textsuperscript{b}Division of Radiology, Sainte Justine Hospital, Montreal (Quebec), Canada H3T 1C5

\textbf{Abstract}

\textbf{Purpose:} The aim of this study was to report the experience and efficacy of Ethibloc sclerotherapy as treatment of lymphangiomas.

\textbf{Methods:} Between 1992 and 2004, 63 patients had Ethibloc sclerotherapy for lymphangiomas at our institution. Computed tomographic scan or magnetic resonance imaging and clinical evaluation determined efficacy of the treatment. Results were classified as excellent (≥95% decrease in lesion volume), satisfactory (≥50% decrease and asymptomatic), or poor (<50% decrease or symptomatic).

\textbf{Results:} Sixty-three patients with 67 lesions underwent sclerotherapy with a median of 2 treatments per patient. Thirty-five involved the neck; 10, the head and face; and 22, the thorax or limb. Thirteen were predominantly microcystic; 28, macrocystic; and 26, mixed. Of the 63 patients, 6 underwent sclerotherapy for postsurgical residual lesions. Results were classified by type: of the 54 macrocystic/mixed cases, 26 (49%) had excellent, 19 (35%) had good, and 9 (16%) had poor results; in the 13 predominantly microcystic lesions, 3 (23%) had excellent, 7 (54%) had good, and 3 (23%) poor results.

Five patients (7.7%) required surgery for complications; 2, for scar revision; 2, for persistent drainage; and 1, for a salivary fistula. Infection occurred in 4 patients (6.2%) after sclerotherapy. Follow-up averaged 3.5 years (range, 12 months to 12 years).

\textbf{Conclusion:} Ethibloc sclerotherapy is a safe and effective alternative to surgical excision of macrocystic lymphangiomas and can be used for postsurgical recurrences.

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Lymphangiomas are congenital development defects of lymphatic channels [1]. Sixty-five percent present at birth or 90% within the first 2 years of life [2], mainly in the head and neck region. The lesions are usually asymptomatic, but their size increases with the child’s growth. Sudden enlargement may occur after bleeding or infection. Spontaneous regression has been reported in 1.6% to 16% of cases [3]. Although benign, complications arising from compression of surrounding structures as well as cosmetic appearance and risk of infection mandate treatment. Anatomically, lymphangiomas are subdivided into macrocystic, microcystic, and mixed forms.

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* Corresponding author. Tel.: +1 514 345 4637; fax: +1 514 345 4816. E-mail address: jseee-dubois@ssss.gouv.qc.ca (J. Dubois).
Traditionally, treatment of lymphangiomas has been surgical, but damage to surrounding structures, along with incomplete resection owing to adjacent organ infiltration and high recurrence rate, present an ongoing challenge and have encouraged the search for alternative mode of treatment as sclerotherapy [4,5].

Numerous agents have been used in percutaneous sclerotherapy such as 50% dextrose, bleomycin, OK-432 (Picibanil, Chugai Pharmaceutical, Tokyo, Japan), doxycycline, alcohol, and Ethibloc (Ethicon, Norderstedt, Germany). US Food and Drug Administration has not approved the alcoholic solution of zein for use in the United States. In this study, we report our experience with Ethibloc sclerotherapy for the treatment of lymphangiomas in children.

1. Patients and methods

After institutional review board approval, the charts of 79 children presenting with lymphangiomas at l'Hôpital Ste-Justine, Montreal (Quebec), Canada, between 1992 and 2004 were reviewed. Of these, 63 patients had Ethibloc sclerotherapy and are included in this study. The charts were reviewed for the type of lesion, location, number of sclerosing injections, complications, and outcome to date, including the need for the eventual surgical intervention. Ethibloc was chosen as the sclerosant of choice because of institutional concerns about the use of bovine serum for injection, as with OK-432.

Patients were assessed, treated, and followed up in a multidisciplinary lymphatic and vascular anomalies clinic after initial surgical consultation. Sclerotherapy pretreatment workup included ultrasonography to determine the type of lymphangioma and computed tomography or magnetic resonance (MR) to determine the extent of each lesion. Lesions were classified as macrocystic, predominantly macrocystic mixed lesions, or predominantly microcystic mixed lesions according to the predominant component of the lesion. The only microcystic lesions included in our study were mixed lesions with a predominantly microcystic component in which the macrocystic component was injected. No attempt at sclerosing purely microcystic lesions was undertaken.

Sclerotherapy is performed under general anesthesia or sedation depending on the extent and the location of the lesion. The average procedure length was 30 minutes. An experienced interventional radiologist performed the treatment. Details of this technique have already been published [6]. Under ultrasonography guidance, direct puncture of the lesion with a 22- to 24-gauge polytef sheath needle is performed, the lesion is emptied as much as possible, and the fluid is sent for cytology for diagnostic confirmation. The lesion is then opacified with contrast medium for evaluation of the volume and the connections of the lesion. Communication between cysts existed in most cases. The amount of Ethibloc injected varied with the volume of the lesion. Ten percent of the volume was elected as the quantity of Ethibloc to be used. The volume of injections varied from 1 to 10 mL (mean, 5 mL ± 1 SD). Ethibloc is available in sterilized 7.5-mL syringes.

All procedures were performed on an outpatient basis except for children younger than 4 months who were observed overnight for postanesthetic apnea monitoring. Follow-up clinical examination was performed every 4 to 6 months after the procedure. Lesion size was checked with routine computed tomography or MR 1 year after completion of the treatment. The lesion was measured, and regression noted by comparing measurements on follow-up studies. Results were classified as excellent if there was a decrease in lesion volume greater than or equal to 95%, satisfactory if decrease in lesion size was greater than or equal to 50%, and asymptomatic or poor if there was less than 50% decrease or the patient remained symptomatic. This was in keeping with previously published methods of reporting results [6]. All patients were followed up in the vascular anomalies clinic, and the need for additional

![Fig. 1](image1.png) Results of sclerotherapy based on predominant type of lesion.

![Fig. 2](image2.png) Four-year-old girl with cervicofacial lymphangioma. (A) Presclerotherapy treatment: T2-weighted sequences demonstrate a septated mass with high signal intensity. (B) Eight months post sclerotherapy, MR T2-weighed sequences show a satisfactory result with regression in volume greater than 80%.
treatment and the progress were discussed with the multidisciplinary team. Results of treatment of mixed lesions were grouped with macrocystic lesions if a predominantly macrocystic component was present.

2. Results

No sclerotherapy was attempted on purely microcystic lesions. Sixty-three patients with 67 lesions underwent sclerotherapy with a median of 1.5 sessions per patient (range, 1 to 6). Thirty-five involved the neck; 14, the head and face; and 18, the thorax or limb. Thirteen lesions were predominantly microcystic; 28, purely macrocystic; and 26, mixed (predominantly macrocystic). Of the 63 patients, 6 underwent sclerotherapy for postsurgical residual lesions.

All patients developed a moderate, localized inflammatory reaction lasting 2 to 4 days. Fever (38.5°C-39°C) was frequently noted and lasted 24 to 48 hours. Sixteen percent of patients presented a second inflammatory reaction 2 to 4 weeks post treatment. Mild anti-inflammatory analgesic was sufficient to control the symptoms. After sclerotherapy, lesion volume increased in size slightly and then regressed over several months (2-12 months). External leakage of Ethibloc occurred in 80% of cases 2 weeks to 3 months (mean, 2 months) after injections and was considered as a predictor of favorable results.

Results were classified by type of lesion. Of the 54 macrocystic/mixed lesions, 26 (49%) had excellent results, 19 (35%) had satisfactory results, and 9 (16%) had poor results, whereas of the 13 predominantly microcystic lesions, 3 (23%) had excellent results; 7 (54%), satisfactory; and 3 (23%), poor results (Fig. 1). Five patients (7.7%) required surgery for complications. These included 2 for scar revision, 2 for persistent drainage, and 1 for a salivary fistula. Culture-proven infection occurred in 8 patients (12.3%). Four of these occurred before injection, and 4 occurred 2 to 6 weeks after sclerotherapy around the time the sclerosing agent began to extrude from the skin. The mean follow-up was 3.5 years (range, 12 months to 12 years).

3. Discussion

Vascular malformations are embryonic anomalies of the vascular system; they are subdivided into high-flow arteriovenous malformations and low-flow capillary, venous, lymphatic malformations. Mixed forms of these structures are frequently encountered. Sudden enlargement can be observed after bleeding, trauma, or infection or hormonal changes. Lymphatic malformations result from a failed connection of the lymphatic system with the venous system or to abnormal development of lymphatic vessels [7].

They are most often located in the head and neck area and can be associated with many syndromes such as Turner, Noonan, multiple pterygium, fetal alcohol syndrome, and trisomies.

Many treatment modalities have been described. Surgical excision has been the gold standard for many years.
However, the mortality rate associated with surgery for this benign condition ranges from 3.4% to 5.7% [8,9]. Hancock et al reported a series of 263 operations for lymphangiomas over a 10-year period. The overall complication rate was 31.3% with a local complication rate of 50%, mostly seromas or hematomas. Their neurologic complications were observed in 17% of cases. The recurrence rate varied between 11.8% and 52.9%, depending on the type of lesion and its location [10].

These results prompted many authors to search for alternatives to surgery. Simple puncture, irradiation, and chemotherapy have been tried and abandoned. Intracystic injection of sclerosing agents has been used in recent years [6,11-19]. The main substances used were bleomycin, doxycyclin, OK-432, Fibrin sealant, and Ethibloc.

Okada, et al [12] followed by others [11] used intraluminal bleomycin and reported partial regression in 86% and complete regression in 55% of cases, with a recurrence rate of 10%. No serious side effects were reported with a total dose of 5 mg/kg administered at intervals of not less than 2 weeks. Complications were minor, including fever, vomiting, cellulitis, and skin discoloration. Although bleomycin can induce pulmonary fibrosis and can be lethal [20], this was never reported with its use percutaneously. The experience with doxycycline is limited to 5 patients reported by Molitch et al [21].

OK-432 is produced from a lyophilized mixture of a low virulence Su strain of Streptococcus pyogenes of human origin, incubated with penicillin G and bovine serum. Ogita et al reported excellent results in 22 of 24 cystic lesions [14]. Some authors have reported disappointing results [22], whereas others have been very enthusiastic about its use [23,24] Good results have been reported with the addition of bleomycin to OK-432 [25].

Ethibloc has been used successfully for many years by European groups and by the authors [6,26]. This agent is biodegradable and thrombogenic. The associated complications are minimal, there are no neurologic sequelae, and the results are encouraging. However, the leakage rate is very significant and, although it indicates favorable outcome, is a cause of distress for parents.

In most series, the reported results are based on clinical assessment only. No imaging is performed. We are convinced of the necessity to evaluate the outcome with sophisticated imaging techniques to assess the importance of the residual lesions and to be able to compare treatment modalities. Fig. 2 represents a patient treated with sclerotherapy with a satisfactory result on MR. Fig. 3 demonstrates a mixed lesion treated with sclerotherapy with poor regression of the macrocystic component and no effect on the residual microcystic component. This can be contrasted with Fig. 4, which demonstrates an excellent response to sclerotherapy. Anecdotally, surgeons who resected lymphangiomas after Ethibloc sclerotherapy felt that dissection had been made easier. This was similarly described in another series using OK-432 [4].

In conclusion, this series shows that sclerotherapy for lymphangiomas in children is well tolerated. It is associated with excellent or satisfactory results in 84% of macrocystic lesions and in 77% of the predominantly microcystic lesions with a macrocystic component. The relatively low complication rate of sclerotherapy (13%), as compared with surgical treatment (31%), makes it a good alternative to surgical intervention. Moreover, it does not preclude surgery if needed. The microcystic component of lymphangiomas, however, does not respond to any form of sclerotherapy.

References