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# Early Experience of Doxycycline Sclerotherapy for Lymphatic Malformations

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No potential conflict of interest relevant to this article was reported.

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## ABSTRACT

**Purpose:** Lymphatic malformations (LMs) are congenital malformations of the lymphatic system which can be effectively treated by sclerotherapy. This study aims to evaluate the efficacy of doxycycline in the treatment of LMs.
**Methods:** We retrospectively reviewed the medical records of all patients who were diagnosed as LMs and underwent doxycycline sclerotherapy in Asan Medical Center between March 2013 and February 2014. Thirty-five sclerotherapy procedures were performed on 21 patients. The procedures were performed under general anesthesia. After each treatment, the clinical and radiographic response was characterized as complete (≥80% decrease in lesion size), partial (<80% decrease of size), or no response (no decrease of size).
**Results:** There were 11 male patients and 10 female patients. The median age of sclerotherapy was 21 months (range, 2–180 months). The most common location was cervicofacial (52.3%), followed by extremity (28.6%) and truncal (19.0%). The most common lesion type was macrocystic (71.4%), followed by microcystic (28.5%). There was one (2.8%) skin necrosis which was recovered by wound management. Thirty-eight percent of patients had a complete response, 47.6% of patients had a partial response and 14.3% of patients had no response. Median frequency of treatment was one (range, 1–5). No response group consisted of all microcystic type.
**Conclusion:** Sclerotherapy with Doxycycline is safe and effective for macrocystic LMs.

**Keywords:** Lymphatic abnormalities; Doxycycline; Sclerotherapy

## INTRODUCTION

Lymphatic malformations (LMs) are rare forms of vascular anomalies, which were treated by surgical excision, as well as percutaneous sclerotherapy [1]. Surgery has been the main form of treatment, but in some cases total removal is not feasible when the extent involvement includes vital structures. Moreover, it has a risk of recurrence and multiple complications, including fistula formation, infection, damage to vascular structures, damage to nerves, and cosmetic deformity [2]. Among the treatments alternatives to surgery, the most widely practiced on in patients is to inject the lymphangioma with sclerosants. Because the endothelial lining of lymphangiomas seems to be vulnerable to infections and chemical

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irritants, and spontaneous infection of lymphangiomas can lead to total regression of the lesion, sclerotherapy was initiated in an attempt to exploit this phenomenon. Over the last decade, multiple sclerosant drugs including OK-432, doxycycline, ethanol, bleomycin, Ethibloc, and some other substances have been used for the treatment of LMs [3,4]. OK-432 is the most commonly studied sclerosant in pediatric patients and has previously been shown to be safe and effective in the treatment of LMs [4,5]. However, there were several side effects including fever, local inflammation, pain, and swelling [4,6]. It is also relatively expensive. Doxycycline is an inexpensive, widely accessible tetracycline antibiotic with an acceptable side-effect profile [5,7,8]. The goal of this study was to evaluate the efficacy of doxycycline in the treatment of LMs.

## METHODS

### 1. Subjects

We retrospectively reviewed the medical records of all patients who were diagnosed as LMs and underwent doxycycline sclerotherapy in Asan Medical Center between March 2013 and February 2014. The median follow-up period was 50 months (range, 42–54 months). Thirty-five sclerotherapy procedures were performed on 21 patients. Patients' demographic variables (age, sex), type of lesion, location, procedural data, and complication rates were collected. The number of sclerotherapy and outcome to date was also entered into a database. LM is classified into the macrocystic type, cysts larger than 1 cm with clear margins, and the microcystic type, consisting of cysts smaller than 1 cm, that appear diffuse, and grow without clear borders. When the 2 types concur, it is called the combined type.

### 2. Procedures

LMs were clinically diagnosed and confirmed by imaging with ultrasound (US), computed tomography, or magnetic resonance imaging (MRI). Follow-up imaging by sonography or MRI was carried out as needed to monitor progress and plan further treatments.

All sclerotherapy procedures were performed under general anesthesia. Prophylactic antibiotics were not given. The procedures were carried out in the operation room after standard skin preparation and draping.

The macrocysts were cannulated using sonographic guidance with a 21-gauge needle and attempt was made to aspirate the cyst of its entire content. This was frequently facilitated by the simultaneous manual manipulation of the cyst and syringe by the surgeon (**Fig. 1**). The sclerosant, a 10-mg/mL solution of doxycycline, was prepared by dissolving 100 mg of doxycycline in 10 mL of injectable saline. The doxycycline was injected through percutaneous injection without removing the aspirating needle. The dose of doxycycline injected per session ranged from 50 mg to 300 mg and was determined by the capacity of the LM, with a maximum dose of 300 mg of doxycycline (30 mL of solution). After removal of the needle, each puncture site was closed with a figure of 8 suture using 5-0 Maxon to prevent egress of the sclerosant. Patients were observed in the recovery room after the procedures.

After each treatment, the clinical and radiographic response was characterized as complete (≥80% decrease in lesion size), partial (<80% decrease of size), or no response (no decrease of size). Intraoperative US guidance was used for cyst localization.


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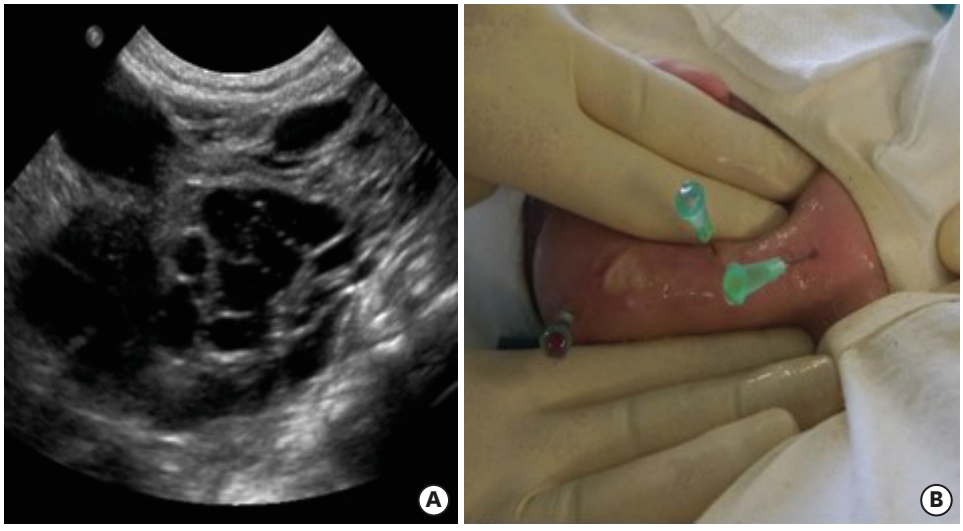

**Fig. 1.** Sclerotherapy of a neck macrocytic LM under intraoperative ultrasound. (A) Sonographic image of a LM in the operation room. (B) The macrocysts were cannulated using sonographic guidance with a 21-gauge needle and attempt made to aspirate the cyst of its entire content. This was frequently facilitated by the simultaneous manual manipulation of the cyst and syringe by the surgeon.
LM, lymphatic malformation.

## RESULTS

The patient characteristics of the study population are outlined in **Table 1.** A total of 35 sclerotherapies were performed in 21 patients with a median frequency of 1 treatment per patient (range, 1–5). The ratio of males to females was 11:10. The median age of the procedure was 21 months (range, 2–180 months). Of LMs, 71.4% were classified as macrocystic (15 of 21), and 28.5% were classified as microcystic (6 of 21). The most common lesion location was cervicofacial (52.3%), followed by trunk (19.0%) and extremities (28.6%).

One patient had underwent prior surgical excision. She had an extensive multilocular septated cystic masses at the soft tissue of both shoulders to the mid-back area, left neck to left upper thorax wall, left entire arm and hand. It was a continuous lesion without skip area and there was no intrathoracic or mediastinal extension (**Fig. 2A**). The mass of the neck and chest might cause airway obstruction so excision was performed first when she was 1 year 3

**Table 1.** Baseline characteristics of the study group

| Characteristics | Total (n=21) |
|---|---|
| Male to female ratio | 1.1 |
| Age at sclerotherapy (mo) | 21 (2–180) |
| Type of LMs | |
| Macrocystic | 15 (71.4) |
| Microcystic | 6 (28.5) |
| Location of mass | |
| Head and neck | 11 (52.3) |
| Trunk | 4 (19.0) |
| Extremities | 6 (28.6) |
| Previous sclerotherapy | 11 (52.4) |
| Initial mass size (cm) | 5 (2.3–12.0) |

Values are presented as median (range) or number (%).
LM, lymphatic malformation.


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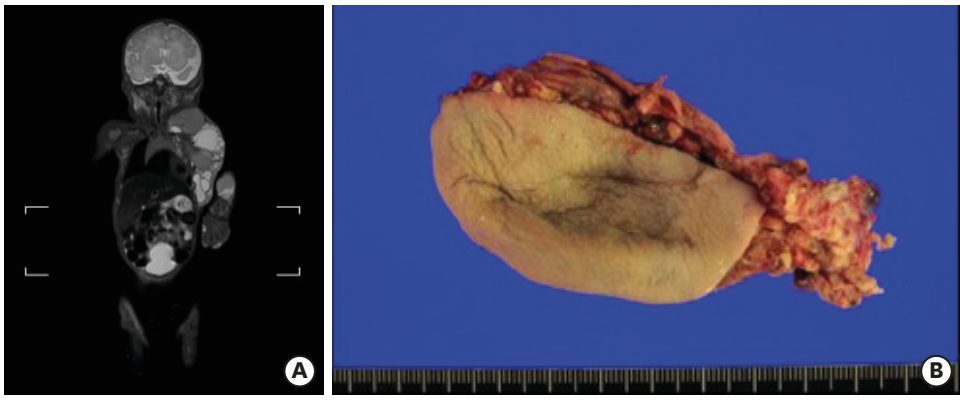


**Fig. 2.** (A) Multilocular septated cystic masses at the soft tissue of both shoulder to mid back area, left neck to left upper thorax wall, left entire arm and hand which was a continuous lesion without skip area and there was no intrathoracic or mediastinal extension. (B) The mass of the neck and chest might cause airway obstruction so excision was performed first when she was 1 year 3 months old.

months old (**Fig. 2B**). After the operation, doxycycline sclerotherapy was performed 3 times and the mass size was decreased to show partial response.

Twenty one patients received sclerotherapy, and the median frequency was one treatment per patient (range, 1–19 treatments per patient). Eleven patients (52.4%) had undergone previous sclerotherapy. Six patients had undergone only one session of doxycycline sclerotherapy and 5 patients had undergone multiple session. The average dose of doxycycline injected per procedure was 178.3 mg.

Complete response was observed in 8 patients (38%) and partial response in nine patients (47.6%). Three patients (14.3%) had no response to the therapy.

When divided by lesion type, all of the macrocystic lesion had a complete or partial response (complete=53.3%, partial=46.7%) but only half of the microcystic lesion had a partial response. No response group (n=3) consisted of all microcystic type. The analysis was performed to find out factors with good therapeutic effect (**Table 2**). There were no statistically significant differences in sex, age, number of treatments, size, and dosage. It was confirmed that the treatment effect was different depending on the type of lesion.

In this series, there was one (2.8%) complication, the development of skin necrosis which was recovered by wound management (**Fig. 3**). The lesion was microcystic type at the right upper chest. The dose of doxycycline injected was 200 mg (20 mL of solution).

**Table 2.** Prognostic factor for the doxycycline sclerotherapy

| Factors | Response | | | p-value |
|---|---|---|---|---|
| | Complete (n=8) | Partial (n=10) | No (n=3) | |
| Sex (male) | 4 (50) | 5 (50) | 2 (66.7) | 0.867 |
| Age (mo) | 22 (2–34) | 20 (2–180) | 12 (9–30) | 0.814 |
| Previous sclerotherapy | 4 (50) | 6 (60) | 1 (33.3) | 0.709 |
| Macrocystic type | 8 (100) | 7 (70) | 0 (0) | 0.001 |
| Microcystic type | 0 | 3 (30) | 3 (100) | 0.001 |
| Size | 5 (3–8) | 7 (2.3–12) | 4 (4–5) | 0.952 |
| Dosage | 150 (50–300) | 200 (100–300) | 200 (100–200) | 0.154 |
| No. of sclerotherapy | 1.5 (1–2) | 1.5 (1–5) | 1 (1–3) | 0.224 |

Values are presented as number (range) or number (%).


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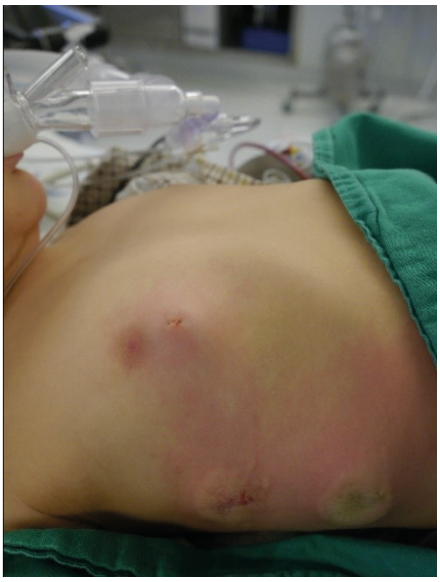

**Fig. 3.** Skin lesion after doxycycline injection which developed skin necrosis.

## DISCUSSION

Treatment of LMs is still challenging. Most of the cases of LMs show progressive growth regardless of the growth of the child, and natural decline is very rare [9]. Percutaneous sclerotherapy of LMs was introduced to avoid surgical removal, which is frequently associated with significant scar formation, and risk of complications due to the size and localization of the LMs. Moreover, surgical treatment is often not curative because of the widespread and infiltrative growth of the LMs [10]. Sclerotherapy seems to be especially recommended for macrocystic lymphangiomas and macrocystic components of mixed lesions with the current trend toward the use of OK-432. However, recent reports have demonstrated that microcystic lymphangiomas may respond very well to doxycycline [3].

Doxycycline, a derivate of tetracycline, is a widely available and relatively inexpensive broad-spectrum antibiotic. Its use as a sclerosant in the pleurodesis of malignant effusions and in the treatment of postoperative lymphoceles showed only minimal side effects. For this reason, its usefulness in lymphangioma therapy was evaluated and Molitch et al. [11] demonstrated the efficiency of doxycycline in the therapy of lymphangiomas for the first time [3]. Several studies have found that doxycycline sclerotherapy is effective [7,12,13]. Burrows et al. [7] stated that doxycycline seems to be more effective in treating microcystic lymphangiomas than OK-432. Shiels et al. [14] also reported good result about doxycycline sclerotherapy of microcystic lymphangiomas. In this study, half of the microcystic lesion have shown partial response. All of the macrocystic lesion had decreased in size.

The exact mechanism by which doxycycline is as effective as a sclerosant is unknown, but an inflammatory process that results in fibrosis and involution of cysts is speculated [12]. Doxycycline therapy seems to be associated with an inhibition of matrix metalloproteinases, which may be a cause of its effectiveness [3]. Moreover, doxycycline suppresses the vascular endothelial growth factor-induced angiogenesis and lymphangiogenesis [15].


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Skin necrosis occurred as a side effect in this study. Since other related studies have not reported any side effects of skin necrosis, this is considered to be a very rare case. The exact mechanism is unknown but theoretically, doxycycline is a low-pH drug [16], so in case of high concentration injection into the skin may cause a high risk of skin necrosis.

Even though there are some studies reporting the efficacy of other sclerosants including bleomycin, OK-432, and acetic acid [17-23], Korean studies on sclerotherapy with doxycycline are very rare. This study is the very first paper reporting the effects of doxycycline in Korea.

In conclusion, sclerotherapy with Doxycycline is one of the effective treatment methods in the treatment of LMs.

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