CLINICAL STUDY

Doxycycline Sclerotherapy Is Superior in the Treatment of Pediatric Lymphatic Malformations

Debi M. Thomas, MD, Minna M. Wieck, MD, Christa N. Grant, MD, Avafia Dossa, MD, Donna Nowicki, RN, CPNP-PC, Phillip Stanley, MD, Chadi Zeinati, MD, Lori K. Howell, MD, and Dean M. Anselmo, MD

ABSTRACT

Purpose: To evaluate efficacy of sclerotherapy with doxycycline versus sodium tetradecyl sulfate (STS) for treatment of macrocystic and mixed lymphatic malformations (LMs).

Materials and Methods: This single-center retrospective review identified 41 children (17 boys; 24 girls; age range, 1 month to 15.4 y) who underwent sclerotherapy with doxycycline (n = 32) or STS (n = 9) for macrocystic (n = 31) or mixed (n = 10) LMs. There were 114 treatments performed, averaging 2.8 treatments (range, 1–8 treatments) per patient. Average follow-up time was 10 months (range, 1–59 months). Clinical response was deemed excellent or moderate if > 90% or > 50% of LMs resolved based on visual estimate.

Results: With doxycycline, 87% of patients (28 of 32) had excellent or moderate response with an average of 2.8 treatments (range, 1–7 treatments); 13% required subsequent resection. With 3% STS monotherapy, only 55% of patients (5 of 9) had excellent or moderate response with an average of 2.8 treatments (range, 1–8 treatments), and 33% required subsequent resection. Significantly fewer patients treated with STS responded well compared with patients treated with doxycycline ($P = .03$). Patients treated with STS had significantly longer follow-up than patients treated with doxycycline (27 months vs 6 months, $P = .0001$).

Conclusions: Doxycycline monotherapy resulted in a high rate of excellent clinical outcomes after a few treatments without increased need for subsequent operative resection. These results support use of doxycycline sclerotherapy as primary treatment for macrocystic and mixed LMs in children.

ABBREVIATIONS

LM = lymphatic malformations, STS = sodium tetradecyl sulfate

Lymphatic malformations (LMs) are defined as congenital malformations of the lymphatic system that comprise channels and cystic spaces of varying size (1,2). Because spontaneous regression is rare (3), early treatment can mitigate significant morbidity and potential mortality. Surgical resection is historically the standard treatment for LMs, but in the last 20 years, percutaneous sclerotherapy has emerged as a safe, effective, and less invasive treatment (4). The size and location of the LM determine the feasibility of various therapeutic options (1). Microcystic LMs are made up of cysts < 1–2 cm in diameter or are too small to be accessed by a needle for sclerotherapy (2,4,5). Conversely, macrocystic and mixed LMs can be treated with sclerotherapy or surgical resection (6,7).

The aim of sclerotherapy is to damage the endothelium of the cystic channels by obliterating them via inflammation and fibrosis through direct injection of a sclerosing agent (1). Commonly used agents include OK-432 (Picibanil; Chugai Pharmaceutical Co., Ltd, Tokyo, Japan), doxycycline, bleomycin, pingamycin, ethanol, and sodium tetradecyl sulfate (STS) (Sotradecol;

From the Departments of Pediatric Surgery (D.M.T., M.M.W., C.N.G., A.D., D.N., D.M.A.), Radiology (P.S., C.Z.), and Plastic and Maxillofacial Surgery (L.K.H.), Children's Hospital Los Angeles, Los Angeles, California. Received September 23, 2015; final revision received and accepted August 22, 2016. **Address correspondence to** D.M.A., Vascular Anomalies Center, Children's Hospital Los Angeles, 4650 Sunset Boulevard, Mailstop #100, Los Angeles, CA 90027; E-mail: Danselmo@chla.usc.edu

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Bioniche Teo Inverin, Co. Galway, Ireland) (6,8). There is disparity in the medical literature regarding the safety and efficacy of different sclerosants, and it is unclear which agent is most effective for the treatment of macrocystic and mixed LMs in children (4,6,9). 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 (9–11). However, it has not yet gained approval from the US Food and Drug Administration. Doxycycline is an inexpensive, widely accessible tetracycline antibiotic with an acceptable side-effect profile (12,13). STS is a detergent that helps to release transmembrane lipoproteins from LM cell membranes (6). Because of the paucity of data regarding which agent is more effective as a sclerosant for the treatment of LMs (14), the goal of this study was to compare the clinical response of macrocystic and mixed LMs to percutaneous sclerotherapy with doxycycline versus STS.

MATERIALS AND METHODS

Study Population

This study was approved by the institutional review board. A 7-year retrospective review was conducted of all patients who underwent percutaneous sclerotherapy for macrocystic or mixed LMs at a single quaternary children's hospital between January 2008 and April 2015. The review identified 41 children (17 boys and 24 girls) with macrocystic or primarily macrocystic (> 50% of lesion) LMs who underwent sclerotherapy with doxycycline or STS.

LMs were clinically diagnosed and confirmed by imaging with ultrasound or magnetic resonance (MR) imaging. All patients were treated and evaluated by a multidisciplinary team including pediatric surgery, plastic surgery, and interventional radiology at the hospital's Vascular Anomalies Center. The team consisted of 5 attending physicians and a nurse practitioner, each with > 8 years of experience in the management of vascular anomalies. All patients were required to complete at least 1 follow-up visit for study inclusion. Patients with combined vascular malformations (LMs plus venous malformations) were excluded. Data from clinical records, imaging, and photographs were collected from hospital medical records for each patient.

Patients were grouped based on the type of sclerosant used and compared with an intention-to-treat analysis (**Tables 1, 2**). Most patients were treated with the same sclerosant at all sessions. A few patients did crossover between sclerosants. Four patients in the doxycycline group were treated with both 3% STS and doxycycline at 1 session. Conversely, 4 patients in the STS group were treated with doxycycline alone at 1 session. For data analysis, these patients were grouped based on the sclerosant used at most of the treatments. Six patients who were treated exclusively with combined doxycycline and STS at all treatments were excluded.

Sclerotherapy Protocol

The choice of doxycycline, STS, or both as the sclerosant was determined according to the preference of the interventional radiologist. The doxycycline protocol initially was a dose of 100–300 mg administered in a 1:1 volume of iohexol (Omnipaque; GE Healthcare, Pasadena, California) contrast agent and 0.25% bupivacaine hydrochloride (Marcaine; Hospira, Lake Forest, Illinois) solution, equivalent to the total amount aspirated from a given lesion. In October 2013, the protocol evolved, and the doxycycline dose was 10–20 mg/kg depending on the patient's weight. Vials of 100 mg of doxycycline powder were mixed in a 1:1 volume of Omnipaque contrast agent and 0.25% Marcaine. The volume instilled was changed to one-third to one-half the volume aspirated from the lesion, performed under ultrasound or fluoroscopic guidance. 3% STS (30mg/ml) was used in liquid form. A volume equivalent to the total amount aspirated was instilled into the LM under fluoroscopic guidance.

For all sclerosants, if > 50 mL was aspirated, a drain may have been placed at the discretion of the interventional radiologist for repeated sclerotherapy over 2–3 days. This was the case for 6 of the doxycycline patients but none of the STS patients. Children with persistent lesions either progressed to surgical intervention if no change in lesion size occurred or underwent repeat sclerotherapy after 4–6 weeks if the lesions responded but persisted.

Doxycycline was primarily reported as milligrams of drug given, whereas STS was typically reported as volume injected (in milliliters) (**Tables 1, 2**). Because of the differences in units reported, the amount of sclerosant injected could not be directly compared between groups.

Clinical Endpoints

The primary endpoint was treatment response. Secondary endpoints included number of treatment sessions and need for subsequent surgery. Because of variability in lesion size documentation and differences in initial imaging modality, assessing response based on changes in lesion size was unreliable. Thus, to equally compare all patients, treatment response was subjectively recorded by the consensus opinion of the Vascular Anomalies Center physicians based on visual estimate during physical examination and follow-up imaging (**Figs 1a–f, 2a–f**). "Excellent" was defined as > 90% improvement in size, "moderate" was defined as > 50% improvement, "mild" was defined as < 50% improvement, and "none" was defined as no discernible response. Because of the subjectivity of this scale, for statistical comparison, "excellent" and "moderate" were grouped together to represent patients who had a noticeable response. "Mild" and "no response" were grouped together for a cohort of patients who had a minimal response.

Lesion location, lesion type (macrocystic, mixed/primarily macrocystic), sclerosant, and total duration of follow-up were recorded. Lesion location was classified