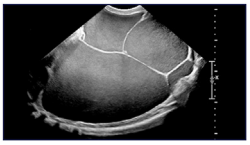

Clinical and Imaging Outcomes of Doxycycline Exchange Sclerotherapy for Lymphatic Malformations

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ABSTRACT

Purpose: To evaluate serial doxycycline exchanges (SDEs) to treat lymphatic malformations (LMs).

Materials and Methods: Retrospective chart review of patients undergoing LM sclerotherapy with SDEs at the authors' tertiary care academic institution from April 2003 through March 2023. The primary outcome measure was change in symptoms between pretreatment and posttreatment clinical notes. Secondary outcomes included percent change in lesion volume measured from imaging studies and 30-day adverse events.

Results: Forty-six patients (25 males [54.3%]; mean age at presentation, 15 years ± 22) received a mean of 1.9 treatments (SD ± 1.0) with 4.8 exchanges (SD ± 2.3) per treatment, including initial instillation, in the interventional radiology suite. Swelling (28/46, 60.9%) and discomfort (8/46, 17.4%) were the most prevalent initial symptoms. Of 46 patients, 24 (52.2%) had 1 SDE admission, 14 (30.4%) had 2 separate admissions, and 8 (17.4%) had ≥3 separate admissions. Of 44 patients with appropriate follow-up to assess clinical change, 4 (9.1%) experienced full clinical remission, 27 (61.4%) experienced improved clinical symptoms, and 13 (29.5%) experienced either unchanged or increased symptoms. LM size was reduced by a median of 63.4% (interquartile range [IQR], 63.9%) after 1 series of exchanges and by 64.4% (IQR, 69.5%) after 2 series of exchanges relative to lesion size after the first series of exchanges.

Conclusions: Most patients had improved clinical symptoms and reduced LM size at the conclusion of SDE therapy. SDE therapy is a safe and effective LM treatment that allows multiple sclerotherapy sessions with 1 procedure, which has the potential to reduce radiation-, procedural-, and anesthesia-associated risks.

ABBREVIATIONS

CT = computed tomography, IQR = interquartile range, LM = lymphatic malformation, MR = magnetic resonance, SDE = serial doxycycline exchange, US = ultrasound

Lymphatic malformations (LMs) are benign vascular lesions characterized by cystic dilatation of lymphatic ducts. LMs typically localize to areas of high lymph node density, most often in the head and neck; however, they present across other lymphatically dense areas of the body, including the groin, trunk, and extremities (1). Depending on the size and location of the malformation, the symptomatology may include discomfort, swelling, aesthetic deformity, or functional impairment. Sclerotherapy is the first-line therapy for LMs and involves aspiration of the LM followed by injection of a sclerosant into the LM with the goal of reducing its size. A variety of sclerosants have been used in the treatment of LMs, including bleomycin, picibanil (OK432), doxycycline, sodium tetradecyl sulfate, pingyangmycin, ethanol, and polidocanol (2).

Doxycycline is a commonly used and effective sclerosant; however, there is no standard protocol for its use in the treatment of LMs (3,4). Doxycycline infusion and aspiration procedures often require multiple retreatments and repeat visits to the hospital for patients. On average, pediatric patients undergo 2.9 LM treatments (range, 1–10 treatments) with percutaneous doxycycline sclerotherapy (5). Between 79.3% and 96.9% of these patients experience clinical improvement in pretreatment symptoms after their multiprocedure regimen is completed (4–6). Repeat treatment presents a scheduling and cost burden for patients and may also increase the risk of procedure-associated adverse events. The authors' institution initiated serial doxycycline exchanges (SDEs), in which a percutaneous drain is placed into the LM cavity, after which the patient is admitted to a

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RESEARCH HIGHLIGHTS

- Serial doxycycline exchange (SDE) therapy is a method of performing multiple doxycycline sclerotherapy sessions in an inpatient setting with a single drain placement procedure.
- Patients receiving SDE had improvement in symptomatology and reduction in lesion size.
- SDE is a safe and effective treatment for lymphatic malformations and has the potential to reduce procedure-, radiation-, and anesthesia-associated risks for the patient.

STUDY DETAILS

Study type: Retrospective, observational, cross-sectional study

Level of evidence: 4 (SIR-D)

low-acuity hospital bed and multiple sessions of instillation and drainage of doxycycline are performed at the bedside. As this is performed with a single fluoroscopic procedure, this method has the potential to reduce the number of procedures and anesthesia-associated risks for the patient. In this retrospective, cross-sectional study, the clinical and imaging outcomes of LMs after SDE sclerotherapy were evaluated.

MATERIALS AND METHODS

Patient Population

This retrospective study was approved by The Johns Hopkins Medicine Institutional Review Boards. Medical records and imaging data were reviewed for all patients with LMs evaluated at the authors' institution's vascular anomalies clinic between May 2005 and December 2023. Patients meeting LM size criteria classified as a macrocystic lesion (>2.5 cm in diameter) and sufficiently large for drain placement were considered for SDE treatment. Patients were included if they received at least 1 treatment with SDE. Demographic information, procedural details, length of inpatient stay, imaging studies, and clinical notes related to the treatment of their LM were obtained and analyzed. The primary outcome measure included change in patient symptoms, determined retrospectively by the authors (P.C.G., A.J.G., D.A.S., and T.G.) by comparing pretreatment and posttreatment clinical notes before and at least 30 days after each treatment. Clinical change was assessed based on the resolution of the initial presenting symptom specific to each patient. Clinical change was categorized as resolved, improved, or stable/worsened. All evaluators (P.C.G., A.J.G., T.G., A.K., and R.W.) were trained to categorize each clinical outcome according to a preset rubric. Any disagreements were discussed and resolved by consensus.

The secondary outcome measure was estimated change in lesion volume measured on pretreatment and posttreatment computed tomography (CT), ultrasound (US), or magnetic resonance (MR) imaging. Patients with appropriate preimaging and postimaging studies for assessment were defined as those with a 3-dimensional imaging modality available prior to any doxycycline exchange procedure and after at least 1 treatment was conducted. Lesion dimensions were measured at their longest cross-sectional diameter in the axial, sagittal, and coronal planes by authors [initials removed for blinding]. Volumetric change was calculated using an ellipsoid approximation of 3 dimensions: $\frac{\left(\frac{4}{3}\cdot\pi\cdot D_{AP}\cdot D_{TR}\cdot D_{cc}\right)}{8}$

previously described for tumor volumetry (7). Change was assessed as the relative percent change between pretreatment and posttreatment scans. Patients with missing clinical or imaging follow-up were excluded from analysis of outcomes.

Doxycycline Exchange Procedure

SDE describes a protocol in which a small drain is placed into a macrocystic LM, after which the patient receives multiple doxycycline infusions while an inpatient in the hospital. Procedures were performed by C.R.W. and another physician, who have 15 and 30 years' experience, respectively. Patients underwent US-guided placement of a 6.3-F Dawson-Mueller Multipurpose Drainage Catheter (Cook Medical, Bloomington, Indiana) into the macrocystic LM with fluoroscopic confirmation of placement and adequate lesion filling. The US-only approach was preferred for superficial target lesions that were completely visualized with US alone. The LM was first drained, and a doxycycline solution, equivalent to approximately 50% of the volume of the aspirated lymphatic fluid, was infused into the malformation through the drain. Doxycycline was mixed in a 10-IU/mL saline solution. If multiple macrocystic lymph-containing lesions were characterized by imaging, usually only 1 or 2 drains were placed. These lesions were probably not truly multicystic but instead had flow in between, because the authors were often able to treat the entire lesion from 1 or 2 access points. More drains were placed during the same session if the entire lesion was not treated. Procedures were most often conducted with pediatric patients receiving general anesthesia and adult patients receiving general anesthesia or moderate sedation with monitored anesthesia care.

The patient was then admitted to the hospital floor for bedside exchanges. After the initial infusion of doxycycline (in procedure room) and for each exchange thereafter (at bedside), the drain was capped, and the sclerosant was left to dwell for 4 hours. After dwelling, the drain was uncapped and left to gravity drainage for 4 hours. The volume of drainage was recorded, and new doxycycline and saline solution was then reinfused again at 50% of this new drained volume. The same strategy was used for each patient, irrespective of patient age and size. This schedule of

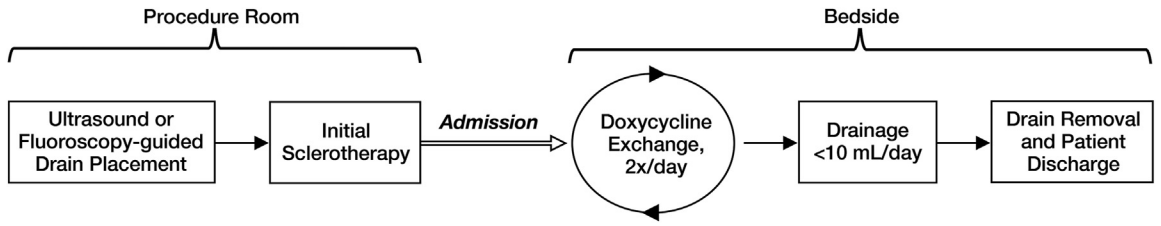

Figure 1. Doxycycline exchange protocol. Following drain placement and initial infusion of doxycycline in the interventional radiology suite, patients were admitted to the hospital floor, where subsequent exchanges were performed twice daily. Once lymphatic fluid drainage was <10 mL, the drain was removed, and patients were discharged.

dwell time allowed for 2 sessions to be completed each day, once in the morning and once in the evening. Once lymphatic fluid drainage was <10 mL, the doxycycline exchange treatment was concluded. The drain was removed at bedside, and the lesion was covered with folded gauze and secured by adhesive tape. The patient was then discharged. Typically, no pain medication was required for the doxycycline exchanges on the floor. If the patient had lingering postprocedural pain after drain placement, a dose of sedation or acetaminophen was available as necessary in the postanesthesia care unit. Bedside exchanges were performed by members of the interventional radiology team, most often a physician assistant or a resident physician. Procedural workflow is illustrated in Figure 1.

Adverse Event Assessment

Thirty-day adverse events of treatment were collected from patients following the doxycycline exchange procedures. These were then characterized according to Society of Interventional Radiology (SIR) adverse event criteria (8). There were no immediate adverse events.

Statistical Analysis

Initial chart review data were recorded on REDCap, version 13.1.33 (Vanderbilt University, Nashville, Tennessee). Data were analyzed using Excel, version 2011, software (Microsoft, Redmond, Washington) and Prism, version 9.4.1 (GraphPad Software, Boston, Massachusetts). Because of the small sample size (N = 46), the Fisher exact test was used to assess clinical and imaging outcomes.

RESULTS

Demographics

Patient characteristics and procedural summaries are described in Tables 1 and 2. This study identified 195 patients who had received treatment for LMs. Of these, 149 presented with LMs that were considered microcystic and, therefore, were not amenable to drain placement and SDE therapy. A total of 46 patients (25 males [54.3%]), underwent a mean of 1.9 treatments (SD ± 1.0) with a mean of 4.9 exchanges (SD ± 2.3) per treatment, including the initial fluoroscopic exchange. A mean of 2 drains (SD ± 1.3) were placed during each initial fluoroscopic procedure, with 16 procedures requiring the placement of >2 drains. A maximum of 6 drains were placed in a single fluoroscopic procedure. Of the 86 procedures, 51 (59.3%) were conducted with US and

Table 1. Patient Demographics and Presenting Characteristics (N = 46)

Variable	n (SD, range)
Mean age at first presentation (y)	15 (22, 0–77)
Mean age at initial treatment (y)	17 (22, 0–79)
	n (%)
Male	25 (54.3)
Race	
White	25 (54.3)
Black	11 (23.9)
Other	10 (21.7)
Age when LM first presented (y)	
Prenatal	4 (8.7)
At birth	7 (15.2)
Post birth	35 (76.1)
Main presenting symptom	
Swelling/mass	28 (60.9)
Pain	8 (17.4)
Trouble breathing	3 (6.5)
Asymptomatic	3 (6.5)
Cosmetic deformity	2 (4.3)
Decreased vision	1 (2.2)
Gastrointestinal dysfunction	1 (2.2)
LM type	
Macrocystic	35 (76.1)
Mixed	11 (23.9)
LM location	
Head and neck	31 (67.4)
Upper extremity	4 (8.7)
Lower extremity	2 (4.3)
Thorax	7 (15.2)
Abdomen	3 (6.5)
Pelvis	5 (10.9)
Previous treatment (n = 16)	
Sclerotherapy	3 (18.8)
Surgical	11 (68.8)
Medical	3 (18.8)
Presence of any cosmetic deformity	40 (87.0)
Presence of any functional deformity	11 (23.9)

LM = lymphatic malformation; SD = standard deviation.

Table 2. Procedural Details and Outcomes

Variable	Value (N = 86)
No. of treatments per person, mean (SD)	1.87 (1.0)
No. of drains placed per initial fluoroscopic procedure, mean (SD)	2.0 (1.3)
Total number of exchanges per treatment including initial fluoroscopic infusion, mean (SD)	4.79 (2.3)
Image guidance, %	
US alone	40.7 (35/86)
US + fluoroscopy	59.3 (51/86)
Technical success, %	97.7 (84/86)
Duration of admission in h, mean (SD)	119.4 (160.5)
Fluoroscopy time in min, mean (SD)	1.83 (1.69)
Elapsed procedure time in min, mean (SD)	97.6 (65.4)
Treatment outcomes	
Median imaging change in volume (n = 34), % (IQR)	−62.2% (80.2)
Clinical change by patient	n=44
Resolution, %	9.1 (4/44)*
Improvement, %	61.4 (27/44)*
Stable or worsened after regimen completion, %	29.5 (13/44)*

IQR = interquartile range; SD = standard deviation; US = ultrasound.
*$P < .001$.

fluoroscopy and a mean 1.83 minutes of total fluoroscopy time. Of the 86 procedures, 63 were SDE, and 23 were standard doxycycline sclerotherapy sessions. Of 46 patients, 25 (54.3%) were Caucasian, with a mean age at first presentation of 15 years (SD ± 22); 28 (60.9%) presented with a primary symptom of swelling, with the second most common main presenting symptom being pain (8, 17.4%); 31 (67.4%) presented with head and neck LMs 4 (8.7%), had upper extremity LMs, 2 (4.3%) had lower extremity LMs, 7 (15.2%) had thoracic LMs, 3 (6.5%) had abdominal LMs, and 5 (10.9%) had pelvic LMs. The mean inpatient stay was 119 hours.

Clinical Outcomes

Forty-six patients underwent a total of 86 procedures with pretreatment and posttreatment clinical notes available for analysis. Of the 46 patients, 44 had appropriate follow-up to assess clinical change. Of 44 patients, 4 (9.1%) experienced full clinical remission, 27 (61.4%) experienced improved clinical symptoms, and 13 (29.5%) experienced steady or increased symptoms (Fig 2 and Table 2).

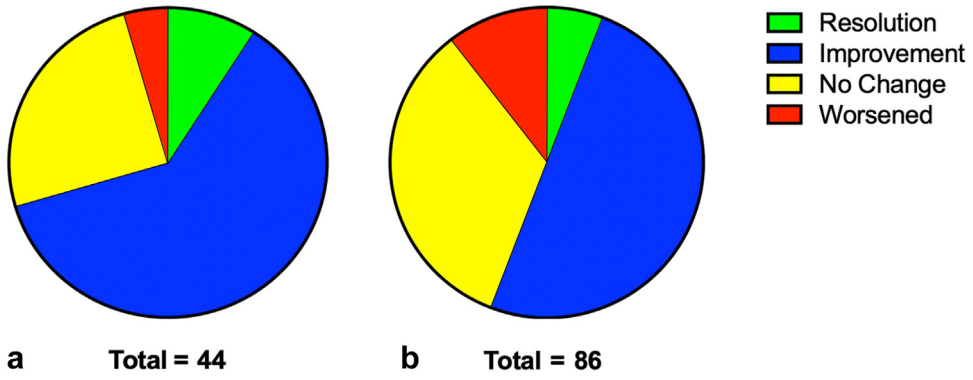

Figure 2. Change in patient symptomatology **(a)** per patient at the end of all treatments and **(b)** after each procedure. The primary outcome measure included change in patient symptoms, determined by comparing pretreatment and posttreatment clinical notes before and after each treatment. Clinical change was categorized as resolved, improved, or stable/worsened based on the resolution of the initial presenting symptom specific to each patient.

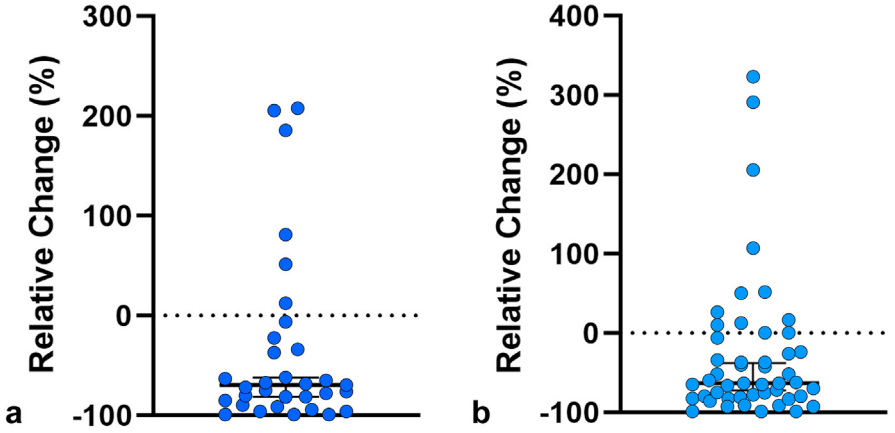

Figure 3. Relative change in lymphatic malformation volume **(a)** per patient, comparing preprocedural imaging with imaging at the end of all treatments and **(b)** after each procedure. The majority (79.4%) of patients had a reduction in lesion volume at the conclusion of their treatment, with 20.6% demonstrating no change or an increase by the end of all procedures.

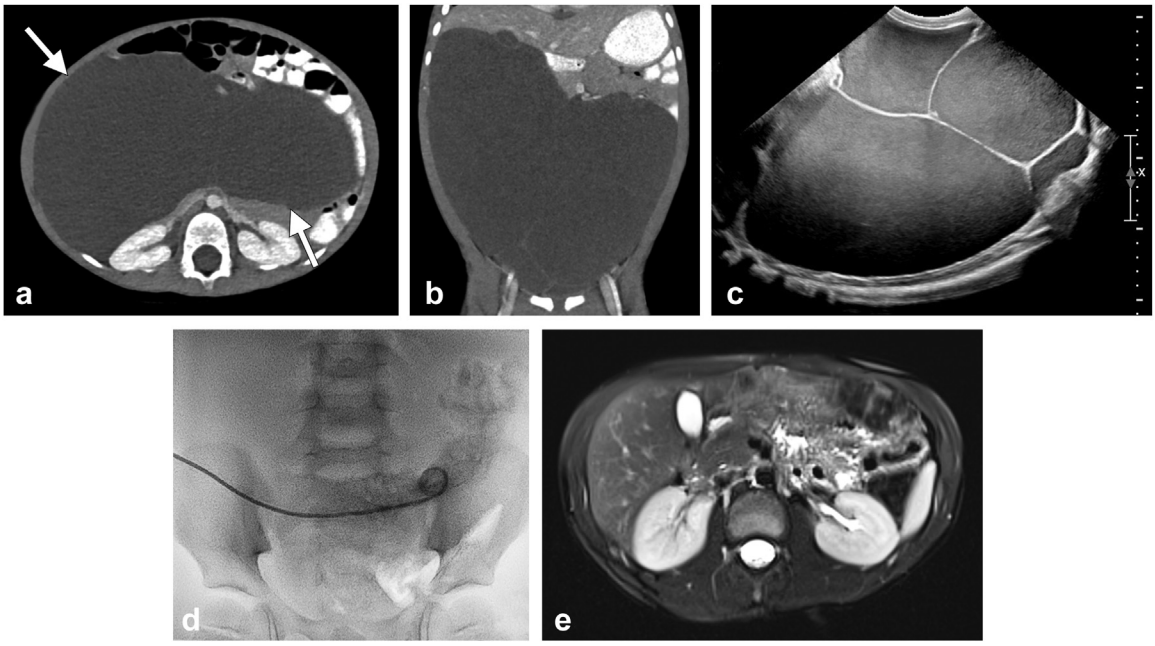

Figure 4. Doxycycline exchange therapy of a lymphatic malformation in the abdomen. **(a, b)** Transverse and coronal views of a 21.7 × 13.4 × 23–cm lymphatic malformation (LM; white arrows) demonstrating mass effect displacement of abdominal organs to the periphery. **(c)** Left upper quadrant ultrasound (US) demonstrating multiseptated quality of LM. **(d)** Fluoroscopic image of a 6.3-F Dawson-Mueller Multipurpose Drainage Catheter (Cook Medical) placed in the right lower quadrant portion of the LM. **(e)** Postprocedural T2-weighted fat-saturated image demonstrates small residual lesion.

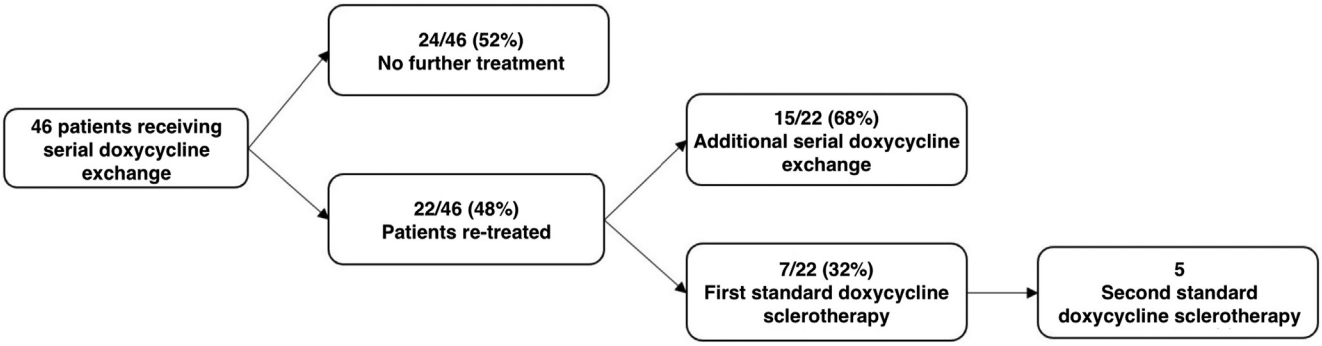

Figure 5. Patient retreatment flowchart. Of the 46 patients receiving serial doxycycline exchanges, 24 (52%) required no further treatment, and 22 (48%) were re-treated, of whom 15 (68%) received an additional serial doxycycline exchange and 7 (32%) received a first standard doxycycline sclerotherapy. Five of the patients subsequently had a second standard doxycycline sclerotherapy.

Imaging Outcomes

Of 46 patients, 34 (73.9%) had appropriate preimaging and postimaging studies for assessment. The median pretreatment lesion volume was 85.0 cm^3 (interquartile range, 155.4 cm^3); the median posttreatment lesion volume was 31.2 cm^3 (interquartile range, 135.4 cm^3). Twenty-seven of 34 patients (79.4%) had a reduction in lesion volume overall, with 7 (20.6%) of 34 patient studies demonstrating no change or an increase by the end of all procedures (Fig 3). Example pretreatment and posttreatment imaging is provided in Figure 4.

Clinical Follow-Up

Of the 46 patients receiving SDEs, 24 (52.2%) required no treatment beyond their initial SDE session. Of the remaining 22 requiring further treatment (47.8%), 15 (68.2%) required an additional SDE, and 7 (31.8%) required a first standard doxycycline sclerotherapy. Five of the patients subsequently had a second standard doxycycline sclerotherapy. Patient retreatment workflow is illustrated in Figure 5. The median follow-up from first treatment to last imaging was 328 days.

Adverse Events

Of the 86 total procedures, 8 30-day adverse events (9.3%) (4 mild adverse events, 3 moderate adverse events, and 1 severe adverse event) were observed. The mild events were pain, ulceration, and transient neurological deficit. The moderate events were pain, and acute kidney injury (AKI) that resolved during the inpatient stay. Of note, the AKI was in a pediatric patient who had feeding and hydration challenges that were long-standing prior to the intervention. The AKI may have been due to poor oral hydration in that setting; however, the authors cannot be certain.

The severe event involved a patient requiring post-discharge hospitalization due to intractable postprocedural pain. The patient underwent placement of 1 drain and doxycycline exchanges were planned. However, after placement, he developed severe pain that required multimodal pain control therapy, including intravenous hydromorphone, fentanyl, gabapentin, acetaminophen, and ketorolac, all given in the postanesthesia care unit. On postprocedural Day 1, the patient underwent an initial SDE session but was unable to tolerate further exchanges because of pain, and SDE was aborted. The drain was subsequently removed, and the patient's pain had resolved on postprocedural Day 3. He was discharged on the same day.

DISCUSSION

The present study has described SDE therapy as practiced at the authors' tertiary care academic institution and has presented the results of a retrospective, single-center chart review of patients undergoing SDE therapy from April 2003 through March 2023. Patients had an overall improvement in their LMs through both improved symptoms and a reduction in volume on imaging. Of 44 patients, 9.1% experienced full clinical remission, 61.4% experienced improved clinical symptoms, 25% experienced steady symptoms, and 4.5% experienced increased symptoms. A majority of patients also experienced a reduction in lesion volume overall.

The use of doxycycline has been well established for the effective treatment of LMs, especially in pediatric patients. For example, Maleux et al (9) reported an 85% improvement of head and neck LMs with repeated standard doxycycline sessions. Overall, clinical improvement has been reported to range from 66% to 92% after a complete series of fluoroscopic doxycycline treatments (5–7). However, the study protocol may reduce the number of procedures necessary to achieve resolution of patient symptomatology compared with the standard method of repeat US or fluoroscopic sclerotherapy sessions. For example, Shergill et al (6) reported the largest cohort, consisting of 50 patients, treated with doxycycline sclerotherapy and with one of the best aggregated clinical improvements, with 90% of patients seeing substantial improvement in their LMs. These patients underwent a total of 146 procedures, or 2.92 procedures per patient, with a range of 1–7 sclerotherapy treatment sessions.

Table 3. Cost Analysis for 3 Repeat Treatments

Treatment modality	Procedure visit ($)*	Inpatient hospital stay ($)	Total ($)
Standard therapy	10,500 × 3 31,500	0	31,500
Serial doxycycline exchange	10,500 × 1 10,500	3,600 × 5 18,000	28,500

*From CMS.gov. (10).

Of the 50 patients in the study, only 8 required a single treatment, with 42 requiring a second treatment and 13 requiring at least 5 treatments. This is comparable to the present study, in which 24 patients required a single SDE session, with 22 requiring an additional SDE session or a first or second standard doxycycline sclerotherapy.

This study highlights the use of SDE therapy to reduce the number of image-guided procedures necessary to reach complete response. Moreover, this analysis highlights that SDE could be an effective treatment for LMs with large volumes, such as abdominal LMs in pediatric patients that may otherwise require a significant number of retreatment procedures. Image-guided procedures incur procedural costs and pose potential safety risks due to sedation, anesthesia, and radiation to the patient, which are pertinent to LMs as they predominantly affect children. This may also work to conserve the availability of fluoroscopy suites at busy interventional radiology services. Furthermore, by reducing the number of repeat sessions, patients have lower rates of LM reemergence postprocedurally, reducing patient symptomatology and the overall duration of disease burden.

In this approach, there is a substantial increase in inpatient hospital time for the hospital, which would need to be weighed against the benefits of reduction in invasive procedure sessions and the associated risks of anesthesia and repeated imaging. In addition, patients may find it more convenient and preferable to schedule a single inpatient treatment rather than multiple outpatient sessions to achieve robust results. To compare the cost of a single placement procedure followed by a 5-day (119-hour) inpatient stay to an estimated 3 separate outpatient procedures that may be required per patient with LMs amenable to SDE (**Table 2**), the authors compared publicly available data for costs per inpatient day and Medicare reimbursement per outpatient procedure. An individual outpatient procedure for the sclerotherapy of an LM was estimated to cost $10,500 (10), whereas the mean cost for inpatient stay in the authors' home state was estimated to be $3,600 per inpatient day (11). This may represent a small cost savings when comparing the total cost of a SDE procedure ($28,500) against the total cost of the estimated 3 outpatient procedures required for a robust response ($31,500) (**Table 3**).

Exchange procedures were not associated with an increase in incidence or severity of procedural adverse events. In the present cohort, there were 4 mild, 3 moderate,

and 1 severe adverse event, which was intractable pain requiring hospitalization, according to the SIR adverse event criteria. Similar rates and qualities have been reported in other single-treatment studies (5,12). Sclerotherapy adverse events are generally uncommon but may be partially attributed to needle access. Therefore, it would be reasonable to assume that during exchange procedures, where percutaneous access is obtained only once, there would be a reduced risk of injury.

This study is limited in its generalizability because of its retrospective and single-center design. Because of retrospective data collection, there may have been bias in the reporting of 30-day adverse events, especially if the patient was seen at a different institution for these complaints or if the patient was lost to follow-up appointments after the procedure. The comparison of SDEs against the standard multisession treatment protocol needs to be validated in a randomized controlled trial. A future study may assign patients with macrocystic LMs into SDE and standard therapy treatment arms. However, given that doxycycline is often the preferred treatment agent for LMs, the improvements in this study may be considered largely logistical, decreasing separate sessions into a single admission.

The volumetric approximation used in imaging quantification is also a source of bias, especially if the LM is not ellipsoid in shape. This calculation was used because preimaging and postimaging sequences were often multimodal, such as CT, US, or MR, or used different acquisition protocols and were incongruent to direct volumetric comparison. A few patients also may not have received follow-up imaging, as they had resolution of their initial symptoms. Moreover, patients may have received additional treatments after data collection concluded in December 2023; that is, patients reported to have an increase in median lesion volume were potentially not finished with their regimen. Future prospective investigations may seek to quantify these changes with thin-slice MR and a pre-established segmentation protocol to more precisely compare volume before and after the procedure.

The present study has described the use of SDE therapy as a safe and effective treatment of LMs. Patients experienced a substantial reduction in the symptoms and size of their lesions. SDE allows for multiple sessions of sclerotherapy with a single fluoroscopic procedure, which has the potential to reduce radiation-, procedural-, and anesthesia-associated risks.

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STROBE Statement—checklist of items that should be included in reports of observational studies			
	Item No	**Recommendation**	**Page, Line #**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1, Line 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1, Line 4-18
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2, Line 2- 21
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2, Line 19-22
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3, Line 3-13
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3, Line 3-13
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 3, Line 4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 3, Line 8-23
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 3, Line 11-23
Bias	9	Describe any efforts to address potential sources of bias	Page 3, Line 20
Study size	10	Explain how the study size was arrived at	Page 3, Line 4-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 3, Line 14-23
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 4, Line 12-13
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	Page 3, Line 16-18 and Page 4, Line 2-3
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Page 4, Line 2-3
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 6, Line 8-10, 15	
		(b) Give reasons for non-participation at each stage Page 6, Line 8-10, 15	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 5, Line 19. **Table 1 and 2**	
		(b) Indicate number of participants with missing data for each variable of interest Page 6, Line 8-10, 15	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **Table 1**	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Page 6, Line 7-20	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 6, Line 7-20	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Page 7, Line 7-12	
Discussion			
Key results	18	Summarise key results with reference to study objectives Page 7, Line 15-21	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Page 9, Line 21 to Page 10, Line 15.	

continued

STROBE Statement—checklist of items that should be included in reports of observational studies *(continued)*			
	Item No	**Recommendation**	**Page, Line #**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 7, Line 22 to Page9, Line 20	
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 9, Line 21 to Page 10, Line 3	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Title Page	

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.