World J Surg (2020) 44:3616–3619
https://doi.org/10.1007/s00268-020-05667-z

Self-compounded Doxycycline Sclerotherapy for the Treatment of Lymphatic Malformations in Low-Resource Settings

David A. Shaye[2,1] · Ciersten A. Burks[1] · Shekhar K. Gadkaree[1] · Isaie Ncogoza[2] · Gratien Tuyishimire[2] · Victor Nyabyenda[2] · Aaron Gassore[2]

Accepted: 14 June 2020 / Published online: 8 July 2020

Abstract

Background Congenital anomalies are one component of the overwhelming surgical disease burden in low- and middle-income countries (LMICs). Lymphatic malformations (LMs) are a common congenital deformity of the head and neck in which the utilization of sclerotherapy may avoid surgery and yield superior outcomes. To be useful in LMICs, sclerosing agents must be widely available, inexpensive, and effective.

Methods A retrospective review of 10 pediatric patients with macrocystic or mixed LMs who were treated with self-compounded doxycycline sclerotherapy at Rwanda's Central University Teaching Hospital of Kigali was performed. Doxycycline oral tablets were crushed by hand, mixed with normal saline at a concentration of doxycycline 10 mg/mL, and injected directly into LMs of the head and neck.

Results Ten pediatric patients underwent 21 sclerotherapy sessions with a mean of 2.1 sessions per patient (SD 1.3, range 1–5). Of the 8 patients that were seen in follow-up, all achieved at least 80% resolution, 6 of 8 achieved 100% resolution, and none required surgery. One patient developed an infection at the injection site which resolved with antibiotics.

Conclusions Self-compounded doxycycline sclerotherapy is a safe, effective, and widely available treatment option for sclerotherapy of LMs in LMICs.

Introduction

Congenital anomalies are responsible for an alarming 57.7 million disability-adjusted life years (DALYs) worldwide. [1] Lymphatic malformations (LMs) are congenital, cystic lesions that occur most commonly in the head and neck at a rate of 1:2000–1:4000 live births [2–6] (Fig. 1). Abnormal development of lymphatic channels results in macrocystic, microcystic, or mixed lesions lined by vascular endothelium [7]. Spontaneous resolution is rare (3%), and without treatment, infection or hemorrhage can compress adjacent structures in the head and neck, including the airway [8, 9].

Surgical resection has historically been the mainstay of treatment, but is technically challenging and fraught with complications due to the proximity of vital neurovascular structures [10]. Sclerotherapy has emerged as a preferential therapeutic option, particularly in the management of macrocystic lesions [11]. Sclerotherapy relies on the infiltration of an inflammatory agent that scars, contracts, and eventually consolidates the vascular endothelium. A wide variety of sclerosing agents exist, including absolute ethanol [12], sodium tetradecyl sulfate (STS), acetic acid, doxycycline, OK-432 (Picibanil) [7, 13], and bleomycin

✉ David A. Shaye
david_shaye@meei.harvard.edu

[1] Facial Plastics and Reconstructive Surgery, Department of Otolaryngology, Massachusetts Eye and Ear, Harvard Medical School, 243 Charles Street, Boston, MA 02114, USA

[2] Department of Otolaryngology, Central University Teaching Hospital, Kigali, Rwanda

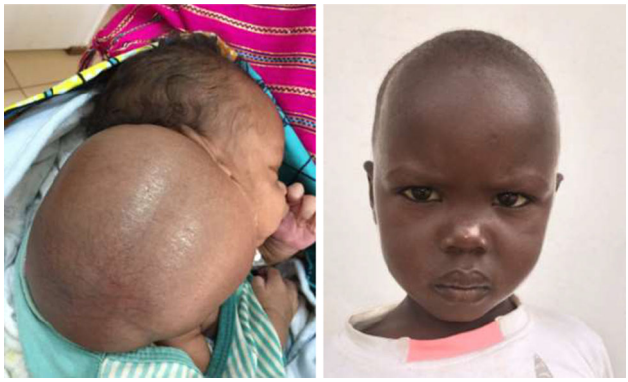

Fig. 1 A 10-day-old infant (Patient No. 1, Table 1) with a lymphatic malformation prior to treatment and after 3 treatment sessions with self-compounded "homemade" doxycycline sclerotherapy. Follow-up at 34 months

[14]. Although a variety of sclerosing agents exist, it is important to note that many agents can be exorbitant in cost or scarcely available in low- and middle-income countries (LMICs). Furthermore, in high-resource settings, LMs are treated by multi-disciplinary teams of physicians comprised of pediatric surgeons, otolaryngologists, plastic and reconstructive surgeons, interventional radiologists, psychiatrists, nutritionists, and others [14, 15]. An average admission may cost USD $30,995 [16]. Thus, in LMICs where there is an immense burden of congenital surgical disease [17], safe, effective, inexpensive, and widely available therapeutic options are of paramount importance.

At Rwanda's Central University Teaching Hospital, our protocol for macrocystic and mixed LMs of the head and neck has relied on self-compounding doxycycline oral tablets to formulate a sclerosing agent. The method was derived from necessity, is technically simple, cost-effective, and easily adapted to any setting. Herein, we evaluate outcomes of our initial cohort of pediatric LM patients treated with self-compounded "homemade" doxycycline sclerotherapy.

Materials and methods

Subjects

Institutional review board approval was granted by the Central University Teaching Hospital of Kigali. Medical records of LM patients with macrocystic (> 1–2 cm in size) [4–6], microcystic (< 1–2 cm in size) [18–20], or mixed lesions who were treated with self-compounded doxycycline sclerotherapy between May 2015 and October 2017 were reviewed. Patient age, sex, radiographic imaging, district, village, LM type, maximum diameter of lesion, sclerosing agent, concentration, number of treatments, and time interval between treatments were recorded. Two surgeons (DAS, AG) evaluated percent resolution on follow-up examination. Patient families were compensated for transportation fees for all follow-up visits. Statistical analysis was performed using Microsoft Excel (version 16.16.20).

Sclerosing technique

Uncoated doxycycline oral tablets (200 mg) were crushed by hand and vigorously mixed with normal saline at a concentration of doxycycline 10 mg/ml. In an operating room setting, under general anesthesia or ketamine sedation, a 30-mL syringe with an 18-gauge needle was used to aspirate and discard cystic fluid contents. A volume of

Table 1 Clinical presentations, treatment regimens, and outcomes. Treatment concentration was doxycycline 10 mg/mL (maximum dose 150 mg/patient) for each treatment session for all patients

Patient	Sex	Age at 1st treatment (months)	Imaging	Predominant lesion type	Predominant lesion size (greatest dimension cm)	Treatment sessions (#)	Complications	Follow-Up (mo)	% Resolution
1	M	0.3 mo	CT	Macrocyst	20	3	Infection	34	100
2	F	29 mo	CT	Multicystic	7	5	None	20	100
3	M	3 mo	US	Multicystic	5	3	None	20	100
4	F	13 mo	CT	Macrocyst	7	2	None	26	80
5	M	34 mo	US	Macrocyst	3	1	None	–	–
6	M	31 mo	CT	Macrocyst	10	1	None	16	100
7	F	0.5 mo	NR	NR	4	1	None	20	100
8	F	29 mo	US	Multicystic	7	1	None	–	–
9	M	3 mo	US	NR	11	2	None	22	90
10	F	16 mo	US	Macrocyst	8.5	2	None	4	100

M, male; *F*, female; *mo*, month; *d*, day; *CT*, computed tomography; *US*, ultrasound; *NR*, not recorded; *cm*, centimeter

doxycycline solution (10 mg/mL) equivalent to half of the volume aspirated was infiltrated into the LM up to a maximum dose of 150 mg. The aspiration and infiltration was performed through a single needle stick to limit violations of the skin. All children were admitted overnight for observation. Antibiotics were not routinely given.

Results

Ten pediatric patients with LMs underwent sclerotherapy, five males (50%) and five (50%) females (Table 1). The mean age at first treatment was 15.9 months (SD 13.7, range 0.3–30). Pre-treatment lesion types were classified as macrocystic for 70% ($N = 5$) of cases. The mean maximum lesion dimension was 8.3 cm (SD 4.8, range 3–20) (Table 1).

All ten patients (100%) underwent successful sclerotherapy reduction of their lesions with 10 mg/mL of doxycycline. A total of 21 sclerotherapy sessions were performed. Four patients (40%) required only one sclerotherapy session. Mean number of sessions per patient was 2.1 (SD 1.3, range 1–5) with average follow-up of 20.3 months (SD 8.4, range 4–34 months). One patient was unable to return for examination but confirmed to be fully healed, while the other was lost to follow-up. Of the 8 patients examined in follow-up, all achieved at least 80% resolution of their LM. Six of 8 patients ultimately achieved 100% resolution, 1 patient achieved 90% resolution, and 1 patient achieved 80% resolution. Complications included 1 patient with an infection at the infiltration site that resolved with antibiotics.

Discussion

Congenital anomalies are responsible for a significant portion of global surgical disease burden [1]. The vast majority (94%) of the congenital disease burden falls within LMICs where higher birth rates, nutritional deficiencies, and a surgical workforce crisis contribute to this trend [21]. LMs of the head and neck, otherwise referred to as cystic hygromas or lymphangiomas, are one such example.

Sclerotherapy is a non-surgical option to treat LMs that requires access to inexpensive, safe, and readily available sclerosing agents to be effective in LMICs. Our series demonstrates that oral doxycycline tablets can be self-compounded and used effectively as a sclerosing agent. All patients achieved at least 80% resolution, with 6 of the 8 achieving 100% resolution. This is comparable to previously reported doxycycline studies that use pharmaceutically prepared solutions to achieve 70–100% resolution [9, 13]. Furthermore, doxycycline tablets are widely available and inexpensive in LMICs. In Rwanda, parents purchased doxycycline at a cost of USD $0.04 per tablet.

Doxycycline has a low risk profile compared to other sclerosing agents. As an antibiotic of the tetracycline family, it produces an inflammatory reaction that scars and contracts the cystic endothelium [22]. While ethanol and STS are commercially available and cost-effective, their use has remained limited due to risk. Ethanol has been shown to lead to systemic toxicity, leading to cardiac arrhythmias, respiratory depression, seizures, rhabdomyolysis, and hypoglycemia in small children [23]. STS has demonstrated an increased rate of infection [20]. Bleomycin has been effective, but is associated with pulmonary fibrosis and death along with increased cost [24]. Complications associated with doxycycline include tooth discoloration, electrolyte disturbances, skin scarring, and Horner's syndrome [25–27]. In our series, complications were limited to one patient who developed a local infection that resolved with antibiotics.

Sclerotherapy is performed in the operating room setting under general anesthesia, since doxycycline infiltration has been reported as painful [28]. Therefore, while sclerotherapy treatment still consumes operating room time, it is less morbid, less invasive and requires decreased procedural time when compared to surgical resection. Also, in an effort to minimize infection risk, the entire infiltration is performed at one time and no catheters are left in place for daily infiltrations, as described elsewhere [11].

While a multi-disciplinary care team for patients with complex, congenital problems is the gold standard, it is not yet accessible to the majority of the world. Furthermore, there exists a surgical workforce crisis that drastically affects the care of pediatric patients in LMICs [29–31]. Treatment options, such as sclerotherapy, which do not include technically challenging surgical resection, are therefore essential to effectively address the disease burden in tertiary and referral level hospitals in LMICs.

This study is not without limitations. First, despite patients achieving resolution of disease comparable to previous studies utilizing doxycycline sclerotherapy [9, 13, 20], it is an underpowered, retrospective study. Also, two patients were lost to follow-up: One patient was confirmed by phone to be alive and fully healed, while the other patient's overall health and location remain unknown. Nevertheless, mean follow-up in this study exceeded that of other studies [32]. Additionally, imaging could not be relied upon as a standard outcome measure as costs incurred to patients were prohibitive. While further prospective studies are warranted, to our knowledge this is the first study to describe self-compounded doxycycline tablets for the use of sclerotherapy in low-resource settings.

LM sclerotherapy using self-compounded doxycycline tablets is a safe, effective, and low-cost therapeutic option

in LMICs. All patients who presented in follow-up demonstrated at least 80% resolution of their LMs, with the majority (6 of 8) demonstrating 100% resolution. Complications were limited to an injection site infection in one patient, which resolved with antibiotic management, and surgery was avoided in all patients. Self-compounded doxycycline for LM sclerotherapy should be considered as a therapeutic option to address the congenital surgical disease burden in LMICs.

Acknowledgements This study was granted Institutional Review Board approval by the Central University Teaching Hospital of Kigali.

Funding None

Compliance with ethical standards

Conflict of interest The author declared that they have no conflict of interest.

References

1. WHO (World Health Organization) (2013) Global health estimates for deaths by cause, age, and sex for years 2000–2011. WHO, Geneva
2. Kennedy TL, Whitaker M, Pellitteri P, Wood WE (2001) Cystic hygroma/lymphangioma: a rational approach to management. Laryngoscope 111:1929–1937
3. Ethunandan M, Mellor TK (2006) Haemangiomas and vascular malformations of the maxillofacial region-a review. Br J Oral Maxillofac Surg 44(4):263–272
4. Curran AJ, Malik N, McShane D et al (1996) Surgical management of lymphangiomas in adults. J Laryngol Otol 110(6):586–589
5. Kang GC, Song C (2008) Forty-one cervicofacial vascular anomalies and their surgical management: retrospection and review. Ann Acad Med Singap 37:165–179
6. Cahill AM, Nijs EL (2011) Pediatric vascular malformations: pathophysiology, diagnosis, and the role of interventional radiology. Cardiovasc Intervent Radiol 34:691–704
7. Smith MC, Zimmerman MB, Burke DK et al (2009) Efficacy and safety of OK-342 immunotherapy of lymphatic malformations. Laryngoscope 119(1):107–115
8. Smith RJ (2004) Lymphatic malformations. Lymphat Res Biol 2(1):25–31
9. Perkins JA, Manning SC, Tempero RM et al (2010) Lymphatic malformations: review of current treatment. Otolaryngol Head Neck Surg 142:795–803
10. De Serres LM, Sie KC, Richardson MA (1995) Lymphatic malformations of the head and neck. A proposal for staging. Arch Otolaryngol Head Neck Surg 121(5):577–582
11. Molitch HI, Unger EC, Witte CL et al (1995) Percutaneous sclerotherapy of lymphangiomas. Radiology 194:343–347
12. Dubois J, Garel L, Abela A, Laberge L et al (1997) Lymphangiomas in children: percutaneous sclerotherapy with an alcoholic solution of zein. Radiology 204:651–654
13. Gigue CM, Bauman NM, Sato Y et al (2002) Treatment of lymphangiomas with OK-342 (Picibinal) Sclerotherapy: a prospective multi-institutional trial. Arch Otolaryngol Head Neck Surg 128:1137–1144
14. Waner M (2018) Multidisciplinary approach to the management of lymphatic malformations of the head and neck. Otolaryngol Clin North Am 51(1):159–172
15. Balakrishnan K, Edwards TC, Perkins JA (2012) Functional and symptom impacts of pediatric head and neck lymphatic malformations: developing a patient-derived instrument. Otolaryngol Head Neck Surg 147:925–931
16. Cheng J, Liu B, Farjat AE et al (2017) The public health burden of lymphatic malformations in children: national estimates in the United States, 2000–2009. Lymphat Res Biol 15(3):241–245
17. Meara JG, Leather AJ, Hagander L et al (2015) Global surgery 2030: evidence and solutions for achieving health, welfare, and economic development: the Lancet Commission on Global Surgery. Lancet 386:569–624
18. Poldervaart MT, Breugem CC, Speleman L et al (2009) Treatment of lymphatic malformations with OK-342 (Picibanil): review of the literature. J Craniofac Surg 20:1159–1162
19. Shiels WE 2nd, Kang DR, Murakami JW, Hogan MJ, Wiet GJ (2009) Percutaneous treatment of lymphatic malformations. Otolaryngol Head Neck Surg 141(2):219–224. https://doi.org/10.1016/j.otohns.2009.04.001
20. Peters DA, Courtemanche DJ, Heran MK et al (2006) Treatment of cystic lymphatic vascular malformations with OK-435 sclerotherapy. Plast Reconstr Surg 118:1441–1446
21. WHO (World Health Organization) (2012) "Congenital Anomalies." Fact Sheet No. 370. WHO, Geneva
22. Hurewitz AN, Lidonicci K, Wu CL et al (1994) Histologic changes of doxycycline pleurodesis in rabbits. Effect of concentration and pH. Chest 106(4):1241–1245
23. Alomari AI, Karian VE, Lord DJ (2006) Percutaneous sclerotherapy for lymphatic malformations: a retrospective analysis of patient-evaluated improvement. J Vasc Interv Radiol 17(10):1639–1648
24. Bloom DC, Perkins JA, Manning SC (2004) Management of lymphatic malformations. Curr Opin Otolaryngol Head Neck Surg 12(6):500–504
25. Bagrodia N, Defnet AM, Kandel JJ (2015) Management of lymphatic malformations in children. Curr Opin Pediatr 27(3):356–363
26. Jamal N, Ahmed S, Miller T et al (2012) Doxycycline sclerotherapy for pediatric head and neckmacrocystic lymphatic-malformations: a case series and review of the literature. Int J Pediatr Otorhinolaryngol 76(8):1127–1131
27. Cahill AM, Nijs E, Ballah D et al (2011) Percutaneous sclerotherapy in neonatal and infant head and neck lymphatic malformations: a single center experience. J Pediatr Surg 46(11):2083–2095
28. Burrows PE, Mitri RK, Alomari A et al (2008) Percutaneous sclerotherapy of lymphatic malformations with doxycycline. Lymphat Res Biol 6(3–4):209–216
29. Krishnaswami S, Nwomeh BC, Ameh EA (2016) The pediatric surgery workforce in low- and middle-income countries: problems and priorities. Semin Pediatr Surg 25(1):32–42
30. Butler EK, Tran TM, Nagarajan N et al. (2017) Epidemiology of pediatric surgical needs in low-income countries. PLoS One 3: 12(3)
31. Ozgediz D, Riviello R (2008) The 'other' neglected diseases in global public health: surgical conditions in sub-Saharan Africa. PLoS Med 5:6
32. Cheng J (2015) Doxycycline sclerotherapy in children with head and neck lymphatic malformations. J Pediatr Surg 50(12):2143–2146