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Review Articles

Doxycycline sclerotherapy in children with head and neck lymphatic malformations☆

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ABSTRACT

Objective: This is a systematic review of the literature describing doxycycline sclerotherapy (DS) to treat pediatric head and neck lymphatic malformations and examine patient factors associated with treatment success.
Data sources: PubMed, EMBASE, and Ovid.
Review methods: A query of PubMed, EMBASE, and Ovid search engines (1995–2014) for studies examining outcomes for doxycycline sclerotherapy (DS) as primary treatment strategy for children with head and neck lymphatic malformations was undertaken. Successful outcome was defined as clinical resolution of symptoms or greater than 50% reduction in radiographic involvement.
Results: Five studies met the inclusion criteria for review. All were retrospective case series reports with high risk of bias. The dose of doxycycline used in all but one of the studies was 10 mg/mL, and the highest concentration administered was 20 mg/mL. Thirty-eight children met the inclusion criteria for analysis. Thirty-two (84.2%) children were successfully treated with DS, with 23 (60.5%) utilizing only one treatment session. Average follow-up was 9.7 months. Age, gender, de Serres stage 1, and type of lymphatic malformation were not related to successful treatment outcome ($p = 0.23$, 1, 1, and 0.13, respectively).
Conclusions: DS is very effective for treatment of macrocystic and mixed head and neck lymphatic malformations in children. Overall success with DS treatment in children with lymphatic malformation of the head and neck was 84.2%. DS has distinct advantages over other sclerotherapy agents including that it is inexpensive and widely available, and has minimal side effects. No associated patient characteristics were found to predict improved success.
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Lymphatic malformations of the head and neck may present in a pediatric patient with various symptoms including asymptomatic neck swelling, cosmetic deformity, recurrent infection, dysphagia, sleep disordered breathing, or respiratory distress. These lesions often are infiltrative and do not respect and span multiple tissue planes, and are often intimately involved with critical neurovascular structures. They arise from signaling errors that are not fully understood during embryogenesis of the lymphatic system [1]. Optimal treatment and management strategies for lymphatic malformations in children involving the head and neck have not yet been well elucidated with options including expectant management, sclerotherapy, or surgical resection.

Multiple sclerotherapy agents have been described including doxycycline, OK-432 (Picibanil), ethanol, sodium tetradecyl sulfate (STS), bleomycin, and others [2–7]. Adams et al. [8] systematically reviewed head and neck lymphatic malformations and reported that both surgery and sclerotherapy may be effective for treatment without any clear evidence as to which modality is superior. However, in most major pediatric vascular anomaly centers, the primary treatment of choice in most patients with head and neck lymphatic malformations patients is sclerotherapy. Surgery is typically reserved for refractory cases after sclerotherapy is no longer improving symptoms or cosmesis or for microcystic lesions which are not amenable to sclerotherapy or medical management. Unfortunately, at this time, there is no widely accepted management paradigm to guide decision making or standardized reporting guidelines for treatment outcomes, which makes generalizable statements difficult. As doxycycline is widely available for clinical use for sclerotherapy for head and neck lymphatic malformations in children and has been reported to be quite successful, an examination of overall effectiveness and patient factors that may be associated with improved success was performed.

1. Methods

A query of PubMed, EMBASE, and Ovid search engines (1995–2014) for studies specifically examining outcomes for doxycycline sclerotherapy as primary treatment strategy for children with head and neck lymphatic malformations was undertaken. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist were utilized [9]. The search for the term "doxycycline sclerotherapy," along

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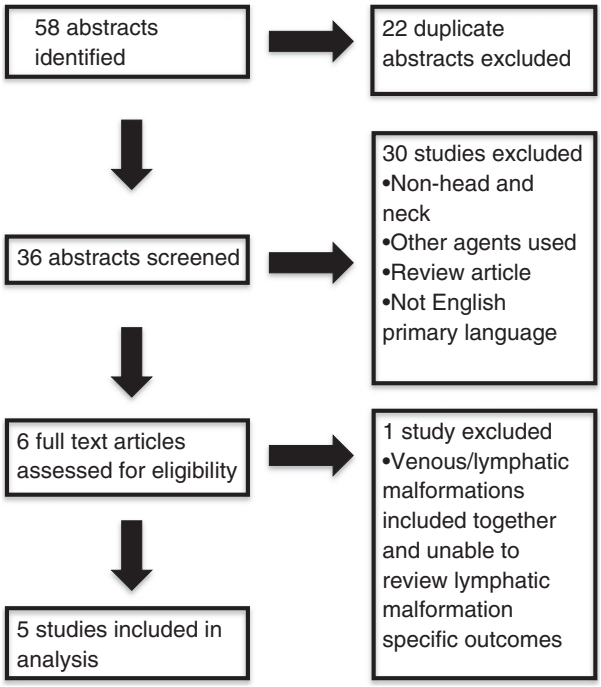

Fig. 1. Flow diagram for study inclusion.

with individual searches for "lymphatic malformation" and "cystic hygroma" or "lymphangioma" was performed. Abstracts were reviewed for appropriate inclusion criteria including: 1) original study reporting individual or aggregated patient outcomes; 2) children who underwent sclerotherapy with doxycycline; and 3) treatment location in the head and neck.

Only studies published in English were considered. Successful treatment outcome was determined by either reported improvement in clinical symptoms or greater than 50% reduction in radiographic imaging burden of disease. No minimum or maximum length of follow-up was required after treatment. Exclusion criteria included: 1) single case reports; 2) case series that included adult patients (aged >18 years); 3) case series that included results using adjuvant surgical interventions; 4) case series that included use of other sclerotherapy agents in addition to doxycycline; 5) results reported in non-human subjects; and 6) anatomic sites outside of the head and neck. Also, studies that obviously did not fulfill inclusion criteria, including review articles, basic-science studies, as well as reports either not involving doxycycline sclerotherapy or only lymphatic malformations were excluded. Abstracts and unpublished reports were also excluded. The remaining articles underwent full-length review and data were extracted for individual-level analysis (Fig. 1). References were reviewed for further potentially applicable studies. No contact with the authors was performed given the retrospective nature of the reports and that available data were adequate for further analysis. Each study was assessed for risk of bias according to the Cochrane Collaboration guidelines [10].

Individual-level patient data were extracted from full review articles and analysis was performed for children with any follow-up reported. Predominantly macrocystic lesions were identified by author report and/or described as ≥2 cm in any dimension. Patients with no follow-up, along with those who received additional sclerotherapy agents in addition were excluded from further analysis. Children were defined as 18 years of age or less at the time of their initial treatment. Clinical factors were examined for association with successful treatment for both overall and single-session therapy and included: age, gender, de Serres stage and type (macrocystic or mixed). Successful outcome was defined as undergoing clinical resolution of symptoms or greater than 50% reduction in radiographic involvement.

Statistical analysis was performed using VassarStats, a statistical computation Web site (www.vassarstats.net). A paired t-test was used to examine if age was related to successful treatment outcome. Fisher's exact analysis was used to examine if gender, de Serres stage (when reported), and type of lesion (macrocystic/mixed) were associated with successful treatment outcome. *p*-Values were reported as two-tailed unless otherwise noted. Statistical significance was set at a *p*-value of ≤0.05.

2. Results

Fifty-eight abstracts and 22 duplicates were identified. Thirty-six abstracts were screened and 30 excluded based on our exclusion criteria. Six studies underwent full text review. One full text review was excluded because other vascular malformations were included and treatment outcomes specific to lymphatic malformations were unable to be determined (Fig. 1). Five studies were then included for analysis. All were retrospective case series reports and no review protocol currently exists. Each study was assessed for risk of bias according to the Cochrane Collaboration. Risk of bias involving randomization, treatment allocation, blinding, standardization of treatment and outcome, selective reporting, and completeness of data was generally high for the included studies (Table 1).

The dose of doxycycline used in all but one of the studies was 10 mg/mL, and the highest concentration administered was 20 mg/mL.

From the six studies that underwent full text review and individual-level data abstraction and analysis, five were included for further analysis (Tables 2–4). A summary of the children extracted for further interpretation can be found in Table 3. A total of 45 children underwent only DS treatment, but only 38 children met the inclusion criteria for review, as 7 (15.6%) had no follow-up reported. Twenty-three (60.5%) were female and 15 (39.5%) were male. The average age at first treatment was 32.3 months [range 2 days to 168 months]. Thirty-two (84.2%) children were successfully treated, with 23 (60.5%) utilizing only one DS treatment session. Average follow-up was 9.7 months. Macrocystic lesions represented 29 (76.3%) children with head and neck lymphatic malformations treated with DS. Age, gender, and type of lymphatic malformation (macrocystic or mixed) were not related to successful treatment outcome ($p = 0.23$, 1, and 0.13, respectively). For those studies reporting de Serres stage, de Serres stage (I–IV) was also not associated with successful treatment outcome ($p = 1$, 1, 0.56, and 0.32, respectively).

Table 1
Risk of bias in included studies.

Study	Year	Randomization	Treatment allocation	Blinding	Standardization (treatment)	Standardization (outcome)	Selective reporting	Complete data
Cahill et al. [14]	2011	High	High	High	Mid	Low	Low	Mid
Cordes et al. [2]	2007	High	Low	High	Low	Low	Low	High
Jamal et al. [13]	2012	High	Low	High	Mid	Low	Low	High
Motz et al. [16]	2014	High	Low	High	Low	Mid	Mid	Mid
Nehra et al. [15]	2008	High	Low	High	Low	Low	Low	Low

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