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EFFECTIVENESS OF DOXYCYCLINE SCLEROTHERAPY IN PEDIATRIC HEAD AND NECK LYMPHANGIOMAS

ABSTRACT:

Objective:

To assess the effectiveness of intralesional Doxycyline sclerotherapy in pediatric head and neck lymphangioma.

Materials & Methods:

It was a retrospective chart review of the children who underwent Doxycycline sclerotherapy of lymphangioma of head and neck region over a period of 2 years between August 2017 to July 2019 at the Department of ENT & HNS, Tribhuvan University Teaching Hospital, Kathmandu Nepal.Medical records were reviewed and evaluated for following variables like age, sex, history, examination findings including site of lesion, ultrasonographic findings, number of injection, dose of Doxycycline and any side effectsnoted and the final outcome of sclerotherapy.

Results:

There was complete resolution of the macrocysticlesion infourcases (12.5%) after two sessions of Doxycycline sclerotherapy. The partial resolution of lymphangioma occurred in 20 cases (62.5%) with mixed type of lymphangioma whereas, in eight cases (25%), there was no response observed even after six sessions of sclerotherapy. Minor side effects like local site erythema and swelling were observed in 20 cases. Secondary infection was seen in eight cases. Eight patients developed fever after injection which was resolved within 24 hours.

Conclusion:

Doxycycline sclerotherapy is safe and effective in the treatment of head and neck lymphangioma in the pediatric population.

Keywords: Doxycycline, Lymphangioma, Pediatric, Sclerotherapy

INTRODUCTION

Lymphangiomas are the congenital malformations of the lymphatic system which are benign in nature.[1]They are classified as microcystic (capillary lymphangiomas), macrocystic (cavernous lymphangiomas) and cystic hygromas.[2] Due to their location in the head and neck, they can cause a significant functional and cosmetic morbidity.In children, these lesions may present with asymptomatic neck swelling with cosmetic deformity, recurrent infections, dysphagia, sleep disordered breathing, respiratory distress, etc.

Lymphangiomas can be treated surgically or with a non surgical approach such as sclerotherapy. Numerous sclerosing agents have been described in the literaturesuch as OK-432 (Picibanil), Bleomycin, Dextrose, ethanol, alcoholic solution of zein (Ethibloc), fibrin sealant (Tissucol), acetic acid and Doxycycline.[3-8] Doxycycline is a broad-spectrum antibiotic which is widely available and relatively inexpensive. Initial study by Molitch et al. demonstrated Doxycycline to be very efficient in decreasing the size of lymphangioma.[6] Doxycycline has been shown to be effective with macrocystic and mixed lymphatic malformations of the head and neck in children. The exact mechanism of action of Doxycycline is unknown but it is speculated that an inflammatory process causes fibrosis and involution of cysts.[9]Itis thought to inhibit matrix metalloproteinases and the vascular endothelial growth factor induced angiogenesis and lymphangiogenesis.[10,11]

This study aims to review theeffectivenessand side effects associated with Doxycycline as sclerotherapyin pediatric head and neck lymphangiomas.

MATERIALS AND METHODS

This was a retrospective review of chart of allchildren who underwent Doxycycline sclerotherapy for lymphangiomas of head and neck region in twoyears duration betweenAugust 2017 to July 2019 at the Department of ENT & HNS, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Patients who underwent sclerotherapy with other sclerosants were excluded from this study. The medical records were reviewed and data were evaluated for thevariableslike; age, sex, history, examination findings including site of lesion, ultrasonographic findings, number of injections, dose of Doxycycline, side effects, and outcome of procedure. The lymphangiomas were classified admacrocystic lesions (cystic spaces ≥2 cm^3), microcystic lesions (cystic spaces <2 cm^3), and mixed (both macrocystic and microcystic components).[6] The children had basic hematological investigation to rule out any bleeding and coagulopathy disorders. Doxycycline solution at a concentration of 10 mg/ml was prepared by mixing 100 mg of Doxycycline powder with 10 ml of sterile distilled water. Under aseptic condition, intralesional Doxycycline 10mg /ml was injected at multiple sites after aspiration of lymphangioma fluid. We used a dose of 100 mg–800mg per session, depending on the age and weight of the child and the size of lesion. Doxycycline was injected under intravenous anaesthesia for children less than five years and under local anaesthesia for older children. Post procedure, the children were given analgesics for pain and observedfor 24 hours in the hospital for any adverse reactionsrelated to the procedure. The children were reassessed aftersixweeks and ultrasonography was repeated to assess the size of the lesion. The data were recorded in Microsoft Excel program. The outcome was measured in terms of complete,partial and non resolution of swelling.

RESULTS

A total of 40 cases were treated with intralesionaldoxycycline in twoyears duration. Eight cases lost to follow up so only 32 cases were included in the study.Among the 32 children, 20 were male and 12 were female.The majority of cases were below five years (Figure I).

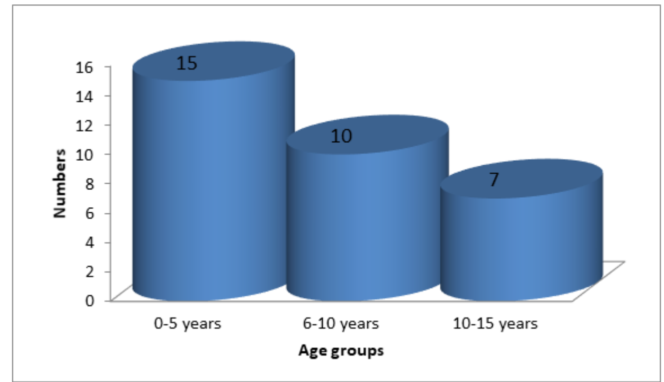

Figure I: Age distribution of the cases

The commonest site of lymphangioma wasneck followed by face (cheek), oral cavity and larynx (Table 1).

Table1. Various sites of distribution of lymphngioma in children

Sites	Number of cases
Various compartments of neck	25
Face (cheek)	4
Oral cavity	2
Larynx	1

Ultrasonography showed mixed pattern in 22cases (68.75%) whereas predominantly macrocystic pattern was seen in 6 cases (18.75%) and predominantly microcystic pattern was seen in 4 cases (12.5%) (Figure II).

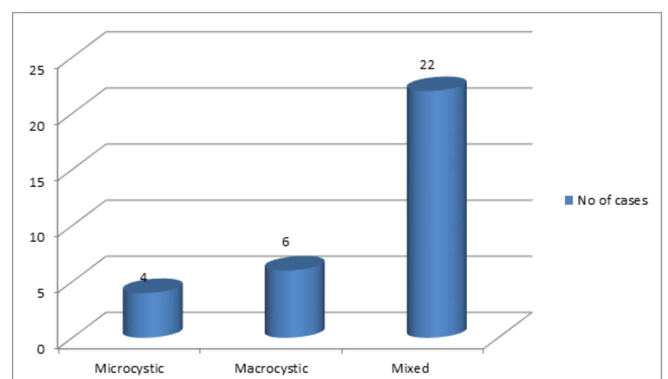

Figure II. Ultrasonographic findings of Lymphangiomas

There was complete disappearance of themacrocysticlesion infour cases after twosessions ofDoxycycline injection.Partial resolution of the swelling occurred in 20 cases with mixed type of lymphangioma.In 8 cases, there was no change in the size of swelling (Table 2).

Table 2. Outcomes of Doxycycline sclerotherapy

Outcome after doxycycline injection	No of cases
Complete resolution of swelling	4 (12.5%)
Partial resolution of swelling	20 (62.5%)
No change in size of swelling	8 (25%)

Erythema and swelling at the site of injection were observed in 20 cases which disappeared after 24-72 hours. Secondary infection was seen in eight cases which got resolved with antibiotics. In threecases, patients developed fever after injection which resolved within 24 hours (Table 3).

Table 3. Complications of Doxycycline sclerotherapy

Complications	No of cases
Erythema and swelling at the injection	20 (62.2%)
Secondary infection	8 (25%)
Fever	3 (9.3%)

DISCUSSION

Lymphangiomasare common vascular malformation in the pediatric population, and over 50% occur within the head and neck region.[12-14]Due to their location in the head and neck, lymphangiomas may cause cosmetic and functional morbidity. Traditionally, surgery was considered the standard of treatment forlymphangiomas but it is deferred now a daysowing to the numerous complications including cranial nerve injury, malocclusion, and poor cosmetic results.According to Kennedy et al.the rate of complications increased from 17% in stage I lesions to 100% in stage V lesions.[14]

A rangeof sclerosing agents are being been used to treat lymphangiomasandDoxycycline is one of them. It is considered as one of the good options for treating lymphangioma as it is widely available and relatively cheap. Considering this fact, we evaluated the efficacy of Doxycycline as a sclerosing agent for head and neck lymphangioma in the pediatric population.

In this study, we observed that lymphangioma was more common in children less than FIVE years of age. Similar finding was observed by Nehra et al., where the mean age of the children was 5 months with a range from 2 days to 21 months.[13]A study by Shergill et al. showed the mean age at the first treatment session was 5.9 years.[15]

Lymphangioma can involve various parts of the body. It can involve multiple sites as reported by Nehra et al.[13]They observed that out of 11 lesions that involved the head and neck; 5 extended into the chest (mediastinum), 2 extended posteriorly to the back and 4 extended into the axilla. In our study,we observed that the most common site of involvement was neck followed by face (cheek), oral cavity and larynx. Laryngeal lymphangioma presented with hoarseness and occasional difficulty in breathing which partially resolved after 2 sessions of doxycycline injection.

Various Doxyclinesclerotherapy dose regimens are used in different studies. In our study, we used injection Doxycycline 10mg/ml and it was injected at multiple sites after aspirating the fluid. We used a dose of 100–800mg per session, depending on the age and weight of the child. Cordes et al.used Doxycycline in concentrations of 5 to 20 mg/mL which was delivered via a drainage catheter.[9] They observed the effect was obvious after 4 to 6 weeks. Serghillet al. used doxycycline solution at a concentration of 10 mg/ml. [15] An arbitrary maximum dose of 300 mg was used for children ≤12 months of age and 1,200 mg for those older than 12 years.

Lymphangiomais thought to result from regional maldevelopment of the lymphatic channels. They are generally classified into three groups;microcystic, macrocystic, and mixed forms.[4, 16]We found that mixed lesions (68.75%) were more common than macrocystic (18.75%) and microcysticlesion (12.5%). Macrocystic lesions in our study showed excellent results in which complete resolution was observed in four cases (12.5%) after two sessions of Doxycycline injection but on other hand, results were less satisfying with mixed and microcystic lesions which showed partial resolution in 62.5% and no improvement at all in 25% cases even after 6 sessions of injection. Studies have shown varied responses with Doxycycline injection. Cordes et al.demonstrated an improvement (complete resolution or marked reduction) of lymphangiomas after percutaneous injection of doxycycline in almost all followed up patients.[9]In the study by Nehra et al., all seven patients with macroscopic lesions achieved complete clinical resolution, and the four patients with mixed lesions achieved partial clinical resolution.[13] A report on 41 patients who were treated with

Doxycycline sclerotherapy was published by Burrows et al.[17] showing encouraging results, with a mean reduction in lesion size of 83%. They stated that Doxycycline seems to be more effective in treating microcysticlymphangiomas than OK-432.This result was supported by the study of Shiels et al.[12]Jamal et al. reported 50% of their patients had complete resolution of their lymphatic malformation and 33% of the patients did not experience significant clinical improvement or developed a recurrence at the endpoint of the study.[18] Cheng J got an encouraging overall success rate of 84.2% with Doxycycline sclerotherapy treatment in children with lymphatic malformation of the head and neck.[19]Various other literatures also have established 70-100% efficacy of Doxycycline sclerotherapy. [6,20,21]

In this study, we didn't notice any major complications. Local site erythema and mild swelling occured in 20 cases following injection which improved after 24–48 hours. Eight cases had secondary infection that occurred 5 to 15 days following injection and got resolved with antibiotic treatment andthree cases developed fever after Doxycycline injection which was treated with antipyretics and got resolved in 24 hours. Similar complication was observed by Cordes et al.[9] They speculated that risks associated with Doxycycline were local erythema, edema, and pain at the injection site. Other literatures had reported more serious complications, Burrows et al. reported a case of Horner syndrome after injection of doxycycline into a cervical lymphangioma.[17]

A low sample size was one of the drawbacks of our study. Also, due to the unavailability of Doxycycline in infusion form while the study was being conducted, we had to rely on powered form for sclerotherapy. In our opinion, use of sterile infusion form could have further reduced the cases with secondary infection.

CONCLUSION

In our experience, Doxycycline sclerotherapy proved to be safe and effective for the treatment of head and neck lymphangiomasin the pediatric population.

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