International Journal of Contemporary Pediatrics
Rashi et al. Int J Contemp Pediatr. 2019 Jul;6(4):1652-1657
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20192771

Original Research Article

Outcome and clinical efficacy of bleomycin and doxycycline percutaneous sclerotherapy for treatment of paediatric lymphatic malformations in a limited resource setting

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Received: 13 April 2019
Revised: 15 May 2019
Accepted: 30 May 2019

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ABSTRACT

Background: The aim was to study the role of bleomycin and doxycycline as a cheap and readily available sclero-therapeutic agent in the treatment of lymphatic malformations in paediatric populations of poor resource setting.
Methods: It was a longitudinal study. A total of 23 paediatric cases with distinct types of lymphatic malformations were treated with injection sclerotherapy. Bleomycin and doxycycline used for microcystic and macrocystic lesion type respectively. The patient was followed up to complete remission. The level of evidence was Level II and type of evidence was prognosis study.
Results: Commonest site of lesion was neck (78.3%), followed by cheek (8.7%), chest, shoulder and suprapubic region. Only 21.7% of patients had good reduction (50-89%) in their lesion volume on first follow up. Overall 43.4% of patients showed a reasonable reduction in lesion volume during the follow-up period. Almost 3/4th of patients improved symptomatically on the first follow up visit. Macrocystic lesion showed an excellent response to treatment (50-89% volume reduction) in 33.3% of cases while only 16.7% of microcystic ad 12.5% of the mixed lesion showed a similar response to treatment.
Conclusions: Doxycycline sclerotherapy can be a primary treatment modality in macrocystic and mixed macrocystic lesions. It is inexpensive and widely available and has minimal side effects. In contrast, bleomycine as a sclero-therapeutic agent showed an inadequate response in size reduction of microcystic lesions.

Keywords: Bleomycin, Doxycycline, Lymphatic Malformations, Sclerotherapy

INTRODUCTION

Lymphatic malformations (LMs) are congenital lesions of the lymphatic system which consist of lymphatic channels and cystic spaces of varying sizes[1]. The lesions may be classified as macrocystic, microcystic, or combined. Traditionally, the primary treatment of these lesions has been complete resection[2]. It was later observed that infection led to the resolution of some LMs. This generated a hypothesis that induction of inflammation in LMs can cause its resolution. A variety of inflammatory inducing agents (Sclerotherapy) undergoing clinical trials after that[3]. During the past 30 years, sclerotherapy has emerged as a promising

alternative to the surgical management for LMs in children.[1,4,5] It can be given repeatedly, produce minimum scar, morbidity, mortality and cost of therapy is much less. Several different sclerosing agents and injection protocols have been documented in the literature each with varying amounts of success. Different studies had published variable results with several different sclerosing agents. This led to the heterogeneity of the treatment protocol used. There appears to be no clear consensus as to when sclerotherapy is indicated, what agent offer most benefit and how an agent should be administered for optimal results.[6] Review the literature of 44 studies showed that most of them were retrospective study or case report. Few studies were prospective. Most commonly studied sclerotherapy agent was OK-432 followed by bleomycin and alcoholic solution. Doxycycline as sclerotherapy agent was used in the fewer study only.[2,7,8] OK-432 is very effective and used widely, but it is unavailable in authors setting.[9] Doxycycline and bleomycin are readily available and cheap alternative. In this context, author planned this study to test the outcome and efficacy of using injection bleomycin and injection doxycycline in treating lymphatic malformation in a different group of patients.

METHODS

This was a longitudinal study. The study was carried over 18 months, from July 2015 to December 2016. All the children are having distinct types of lymphatic malformations under the hospital catchment area where the study population. All the children, either new cases or follow up cases, presented with lymphatic malformation during the defined time will constitute the sample size. The children presented with lymphatic malformations and grouped as microcystic or macrocystic type after thorough clinical examination and necessary laboratory investigation (complete hemogram, renal function test, prothrombin time) and imaging studies.

Colour Doppler USG was done to differentiated between lymphatic and vascular malformations and to categorize patients. Patients with a variegated appearance on USG were advised for MRI. The exclusion criteria was haemorrhage in the cyst and the infection in the cyst.

Technique of study

- Step-1: Selection of the new patient from the outpatient department (OPD)
- Step-2: Thorough clinical examination and the necessary investigation and imaging done
- Step-3: Patients grouped as macrocystic type, microcystic type or mixed type
- Step-4: Informed and written consent taken. Patient sent to operation theatre (OT) for injection Sclerotherapy. It was done under local anaesthesia. The injection was given at the most cystic site of the lesion.
- Step-5: Injection Bleomycin was given to the microcystic group and injection Doxycycline to the macrocystic group. For mixed type, the patient will be categorized as predominant microcystic and predominant macrocystic type and treated accordingly.
- Step-6: Immediate post-operative observation for any complication. Patient discharged on the same day, on antibiotics and analgesics.
- Step-7: Regular follow up was done every three weeks. The patient was examined for regression of the lesion and any complications. Based upon the response, either sclerotherapy was repeated with follow up or only follow up continued.

Definitions

The cyst was classified into three groups, macrocystic, microcystic and mixed. The adverse events reported by the attendant were categorized into either complications or side effects. A clinically significant adverse event like an infection, which required additional treatment after Sclerotherapy labelled as a complication. A minor adverse event such as pain which required little or no additional intervention and resolved quickly was labelled as side effects.[6]

Procedure

The protocol for the procedures included a comprehensive discussion with the patient and family regarding the risks and benefits of the procedure as well as alternative treatments, and informed consent was obtained. All outpatient Sclerotherapy procedures were performed as a day care procedure. Cyst fluid (Straw coloured serous fluid) first aspirated with proper aseptic precautions. After aspiration, the needle kept in place, and the desired sclerotic agent was injected into the cystic cavity.

Doxycycline was used for macrocystic and predominantly macrocystic lesion while Bleomycin was used for microcystic and predominantly microcystic lesions. Doxycycline was diluted in normal saline solution to a concentration of 10 mg/ml. The solution was then infused into the cavity in a 1:1 ratio of the fluid removed. The dose of doxycycline injected per session ranged from 100 mg to 1000 mg and was determined by the capacity of the LM, with a maximum dose of 1000 mg or 20 mg/kg.

Bleomycin is available as a lyophilized powder for intramuscular, intravenous or subcutaneous injection. Each vial contains the sterile Bleomycin sulfate equivalent to 15 units or 30 units. There were no immediate complications of the procedures. Patients were either discharged home the day of the procedure or kept for 24-hour observation. Post-injection analgesics and antipyretics gave at the time of discharge and patients reviewed after 3 weeks in OPD.

Treatment response

Response to treatment classified arbitrarily into four categories based on a percentage reduction in lesion volume. A serial radiographic result was used to assess it objectively. If not available, the parent's subjective assessment was considered - (Excellent >90% reduction, Good -50-89% reduction, Fair- 20-49% reduction, Poor <20% reduction).

Data obtained was entered in Microsoft excel 2016. Descriptive statistics was calculated as percentages, mean with standard deviation. Chi square test applied to test the significance difference in categorical data while t test applied for continuous data. Ethical clearance for the present study will be taken from the institutional ethical committee. Informed and written consent will be taken from the natural guardians of the children, after discussing in his/her language.

RESULTS

A total of 23 patients was followed up during the study period. Most of the patients were the age of either less than a year (39.1%) or more than three years (43.5%). The proportion of male patients (56.5%) were higher than female patients (43.5%). Mothers of most children were either illiterate (39.1%) or educated up to primary only 47.8%). Most patients were from the Muslim community (73.9%). 69.6% of patients belong to a rural area. (Table1).

Table 1: Distribution of cases according to their sociodemographic profile (n=23).

Variable	Category	Number	Percentage
Age group	< 1 year	09	39.1
	1-3 years	04	17.4
	> 3 years	10	43.5
Gender	Male	13	56.5
	Female	10	43.5
Mother's education	Illiterate	09	39.1
	Up to Middle	11	47.8
	High Secondary+	03	13.0
Religion	Hindu	06	26.1
	Muslim	17	73.9
Residence	Urban	07	30.4
	Rural	16	69.6

The commonest site of the lesion was neck (78.3%), followed by cheek (8.7%), chest, shoulder and suprapubic region, 4.3% each. The majority (87%) of cases reported their lesion at birth.

The lesion was slowly progressive in 87% of cases. Involution sometimes occurred in 21.7% lesion. The painful episode was reported in 30% of lesions. Almost half of the lesion (52.2) showed episodic enlargement (Table 2).

As it is evident from the table, swallowing difficulty was reported in 17.4% of cases, while breathing difficulty was in 13.0% of cases. 34.0% of cases were presented with the infected lesion. Majority 82.2% of cases had some kind of visible cosmetic disfigurement (Table 3).

Table 2: Distribution of cases according to their lesion characteristics (n=23).

Variable	Category	Number	%
Site of lesion	Neck	18	78.3
	Cheek	02	8.7
	Chest	01	4.3
	Shoulder	01	4.3
	Suprapubic region	01	4.3
Lesion noticed	At birth	20	87.0
	After birth	03	13.0
Progression of lesion	Slow	20	87.0
	Rapid	01	4.3
	Static	02	8.7
Involution of lesion	Never occurred	18	78.3
	Sometimes occurred	05	21.7
Pain in lesion	No pain	16	69.6
	Mild pain	06	26.1
	Moderate pain	01	4.3
Episodic enlargement	Occurred	12	52.2
	Not occurred	11	47.8

Table 3: Distribution of lesion symptomatology and complications (n=23).

Variable	Number	%
Swallowing difficulty	04	17.4
Breathing difficulty	03	13.0
Infection	08	34.8
Cosmetic disfigurement	19	82.2
Involvement of deep structure	08	34.8
Any associated condition	01	4.3

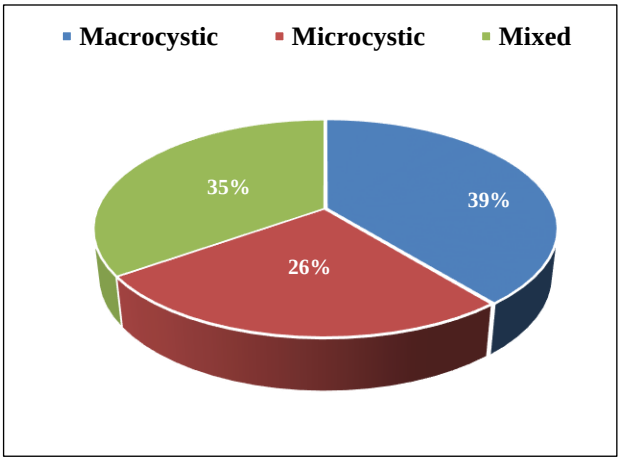

Figure 1: Distribution of lesion types in lymphatic malformations (n=23).

The macrocytic type was slightly more common (39.1%) than mixed (34.8%) and microcystic type (26.1%) (Figure 1). As evident from the Table 4, only 21.7% of patients had good reduction (50-89%) in their lesion volume on first follow up. Overall, 43.4% of patients showed a good reduction in lesion volume during the follow-up period.

Almost 3/4th of patients improved symptomatically at first follow up visit. On third follow up visit symptoms relieved in all patients (Table 5). Female child had a good treatment response in 30% of cases in comparison to the male which was only 15.3%. However, the difference was not statistically significant. Response to treatment was similar across various age groups.

Table 4: Treatment success over time (n=23).

Variable	Category	1st follow up (n=23)	2nd follow up (n=17)	3rd follow up (n=09)
Reduction in size	Good	05 (21.7)	03 (17.6)	02 (22.2)
	Fair	10 (43.5)	11 (64.7)	06 (66.7)
	Poor	08 (34.8)	03 (17.6)	01 (11.1)
Symptomatic relief	No	06 (26.1)	04 (23.6)	00 (00)
	Yes	17 (73.9)	13 (76.4)	09 (100)

Table 5: Treatment response across gender, age and type of lesion (n=23).

	Treatment response			
	Good	**Fair**	**Poor**	**Test of significance "Fischer exact"**
Types of lesion				
Macrocystic	03 (33.3)	06 (66.7)	-	Exact Value (8.53), p (0.048)
Microcystic	01 (16.7)	02 (33.3)	03 (50.0)	
Mixed	01 (12.5)	02 (25.0)	05 (62.5)	
Gender				Exact Value (1.84), p (0.49)
Male	02 (15.3)	05 (38.4)	06 (46.3)	
Female	03 (30.0)	05 (50.0)	02 (20.0)	
Age groups				Exact Value (1.28), p (0.96)
<1 year	02 (22.2)	04 (44.4)	03 (33.4)	
1-3 years	02 (20.0)	05 (50.0)	03 (30.0)	
>3 years	01 (25.0)	01 (25.0)	02 (25.0)	

Macrocystic lesion showed an excellent response to treatment (50-89% volume reduction) in 33.3% of cases, while only 16.7% of microcystic ad 12.5% of the mixed lesion showed a similar response to treatment. The difference in treatment response was found to be statistically significant.

DISCUSSION

Lymphatic malformations (LMs) can be effectively treated by percutaneous intralesional injection of a variety of sclerosant drugs. This study aims to evaluate the efficacy of doxycycline and bleomycin in the treatment of LMs. In this present study, 43.5% of patients were above age of three years. This contrasted with other studies which found that 90% of LMs get diagnosed before age two years.[5,10]

Most of the patients who participated in this study belonged to the lower socioeconomic group. This may be a reason for their delayed treatment seeking. The study showed that LMs were slightly more common in male children. This was like earlier studies where the author stated that both genders were equally affected.[11,12]

In this study, the most frequent site of LMs was neck (78%) followed by another site like cheek, chest, shoulder, and suprapubic region. Various other studies also reported neck as the most frequent site for LMs in different proportion (40-60%).[12–14] This study observed a much higher percentage (78%). This could be due to the small sample size of the present study. Kennedy et al. reported that approximately 50% of LMs present at birth.[10] This study reported a much higher percentage. 87% of lesions were reported to be present at birth. Despite that medical advice was not taken for a long duration. Hassanien et al, reported the progression of the lesion in 40.8% of cases in childhood.[13] 87% of the lesion in the present study were slowly progressive, and in approximately 80% of cases, involution never occurred. A similar finding was given by Perkin J et al, where the author observed no involution of the lesion in 88% of cases.[14] The present study found that the lesion was

painful in 30% of cases and episodic enlargement occurred in 52% cases. It was evident in this study that 52% of parents delayed taking medical advice for LMs beyond six months. Even when they took it, they preferred homoeopathic modality as initial treatment.

This study reported swallowing difficulty in 17% and breathing difficulty in 13% of cases. Hassanien et al, in their study found that LMs tend to enlarge over time, causing distortion, obstruction, and functional problems.[13] Infection found in 35% of cases. Cosmetic disfigurement due to the lesion was very high among patients. Considering the various types of lesion, this study found 39% as macrocystic, 20% as microcystic and 35% as a mixed type of lesions. When the patient visited first, injection doxycycline was given in all cases of macrocysic and predominantly macrocystic lesions, and injection bleomycin given in all cases of microcystic and predominantly microcystic lesions. Post-injection pain was reported in all cases varying from mild to severe grades. 39% suffered post-injection fever while 13% got an infection at the injection site. On successive follow-up visits, post injection pain, fever and infection remained a problem in varying proportion of cases throughout the follow-up period.

Bowden et al, reported fever as the most common post-injection complication with bleomycin.[15] Similarly, Churchill et al, found pain in all participants injected with doxycycline.[6] Against this, Shergill A et al, reported no post-procedural pain, though the author reported post injection infection in 6% of cases.[16]

In the present study, overall good to excellent resolution was found in 48.7% of cases during the entire follow up period. Various other studied reported complete resolution between 25-40%.[17,18] Almost 75% of patients got asymptomatic by 2nd follow up visit. It was evident in the present study that macrocystic lesion showed good to excellent result in of cases. Shergill A et al, also found an excellent response in 87.7 % of macrocystic lesions, 77% in mixed type and 57% in the microcystic type of lesions. In another study, the macrocystic lesion showed a significantly higher resolution rate than microcystic and mixed type.[17]

Macrocystic lesion responded well to sclerotherapy treatment followed by the mixed and microcystic type. Use of injection sclerotherapy needs only minimal expertise with a basic medical facility. Response to treatment did not differ across gender and age of patients. OK-432 have excellent clinical response in lymphatic malformation patients. Its availability and cost are significant constraints in a low resource setting. Doxycycline and bleomycin sclerotherapy are given an almost similar clinical response. Easy availability and low cost are the reason for its use in a low resource setting. Limitation of the study was Image-guided pre-treatment and post-treatment lesional volume could not be obtained in all patients. An assessment of cystic volume reduction by Computed Topography scan and by clinical measurement may vary as dept assessment may not be exact in manual measure.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rashi, Basu KS, Ganguly SS, Saha K, Ahmad S. Outcome and clinical efficacy of bleomycin and doxycycline percutaneous sclerotherapy for treatment of paediatric lymphatic malformations in a limited resource setting. Int J Contemp Pediatr 2019;6:1652-7.