RESEARCH ARTICLE

Assessment of outcomes after intralesional bleomycin sclerotherapy of lymphatic malformations in children

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Abstract

Objective: To evaluate the efficacy of bleomycin in the treatment of lymphatic malformations, and the concordance between photographic and radiological assessments of the outcome.

Method: The retrospective study was conducted at the Vascular Anomalies Centre of Indus Hospital, Karachi, and comprised data of patients enrolled with diagnosis of macrocystic or mixed lymphatic malformations from January 2017 to November 2019. All patients had been treated with injection bleomycin 0.6-1mg/kg/session. Size and location of lesions, ultrasonographic findings, photographic documentation and post-procedure complications were reviewed. Photographic and radiographical assessment outcomes were categorised as excellent, good or poor, and compared for concordance. Data was analysed using Stata 14.

Results: Of the 31 children, 22(68.8%) were boys. Mean age at presentation was 54.2±44 months (range: 2 months to 15.7 years). There were 32 lymphatic malformations; 29(90.6) macrocystic and 3(9.4%) mixed. Head and neck region was mostly involved 19(59.4%). Most lesions 23(71.9%) presented during the first year of life, and 29(90.6%) lesions were purely macrocystic. Excellent, good and poor response was seen in 16(50%), 15(46.9%) and 1(3.1%) lesions on photographic assessment, and 21(65.6%), 11(34.4%) and 0(0.0%) lesions on radiological assessment, respectively. Concordance in photographic and radiological outcomes was 22(69%). No complications were seen and no statistically significant difference was observed for photographic and radiographic assessment with respect to gender, malformation type, region involved, and number of sessions (p>0.05).

Conclusion: Intralesional bleomycin sclerotherapy was found to be effective in the treatment of lymphatic malformations. Clinical observation was reliable in assessing progress on routine follow-up, with additional radiology done when management decisions needed to be reviewed.

Keywords: Bleomycin, Intralesional injection, Lymphatic malformations, Sclerotherapy. (JPMA 73: 290; 2023)

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Introduction

Lymphatic malformations (LMs), previously called lymphangiomas, are benign vascular lesions that are formed in utero as a result of developmental embryological deformities of lymphatic vessels.[1] The incidence of LMs is reported to be 1.2 to 2.8 per 1000 births[2,3] with no gender predilection.[3] Up to 65% LMs are detected at birth and more than 90% of cases present for clinical evaluation before the end of second year of life.[2,4,5] LMs are categorised into three varieties based on the size of cysts within the lesion; macrocystic (cysts >1cm in size), microcystic (cysts <1cm), and mixed variety.[6-8] LMs can occur in any anatomic region, but the lymphatic-rich head and neck region is involved in 70-80% cases, followed by axilla, mediastinum, groin and retroperitoneum.[2,9] An asymptomatic, visible, skin-coloured swelling is the most common presenting symptom,[2,10,11] with cosmetic disfigurement being the sole reason for seeking clinical consultation.[4] In contrast, significant symptoms including airway obstruction, swallowing difficulties, pain and secondary infection are frequently reported.[2,11] The diagnosis of LM is usually clinical and can be confirmed by ultrasonography. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are used to define the extent of disease and involvement of adjacent/internal organs.[2,12]

Historically, surgical excision was the mainstay of treatment, the goal of which was to excise the lesion without sacrificing vital structures, but excision was often limited due to extensive and infiltrative disease with reported recurrence rates of 15 to 40%.[3,9,13] The inoperable nature of LM lesions in majority of cases led to evolution of

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various non-surgical treatment modalities like diathermy, cryotherapy, intralesional sclerotherapy, radiotherapy, and fibrin glue for the management of LMs. All these modalities have been tried, studied and reported in literature.[1,12]

Table-1: Response categories following sclerotherapy.

Categories	Photographic	Radiological outcome
Excellent response (>90% to 100%)	>90% to 100% reduction in size	Cyst <1cm not amenable to ILBS (tiny cystic component) OR No cyst found (Complete resolution)
Good response (>50% to 90%)	>50% to 90% reduction in size of lesion	Cyst >1cm not amenable to ILBS (sclerosed cyst) OR Cyst >1cm responding to ILBS
Poor response (0% to 50%)	0% to 50% response	No response

Intralesional injection of sclerosing agents causes irritation of the endothelial lining of LM, leading to inflammation, fibrosis and involution.[14] The first case of LM treated with injection sclerotherapy with sodium morrhuate was reported in 1933; complete regression was noted within 6 weeks.[15] This treatment method has become increasingly popular in the last few decades, with successful outcomes reported using different sclerosing agents and protocols. These sclerosing agents include picibanil (OK-432), bleomycin, doxycycline, sodium tetradecyl sulphate 3%, alcoholic solution of zein, ethanolamine oleate, and absolute ethanol.[1] Bleomycin was discovered as an antineoplastic agent in 1965.[3] The use of bleomycin for managing cystic hygromas was initially reported with good results.[13] This was subsequently confirmed by other investigators and led bleomycin to become the most commonly used agent for sclerotherapy of LMs .[1,4,10,11] Multiple sessions are required, involving repeated clinic visits and radiological assessments. While these interventions have been used successfully for the management of macrocystic LMs, microcystic lesions do not respond to this treatment method.[1,3]

The current study was planned to evaluate the effectiveness of intralesional bleomycin sclerotherapy (ILBS) in the management of macrocystic and mixed LMs and to assess the concordance between photographic and radiological assessment of ILBS treatment outcome on routine follow-up.

Materials and Methods

The retrospective, longitudinal study was conducted at the Vascular Anomalies Centre of Indus Hospital, Karachi, and comprised data of patients enrolled with diagnosis of macrocystic or mixed LMs from January 2017 to November 2019. Data of children who had either completed treatment or were under treatment with a minimum follow-up period of 3 months was included. Data of children with purely microcystic lesions or those with associated syndromic malformations was excluded.

After approval from the institutional ethics review board, a predefined questionnaire was used to collect demographic and clinical data, including age, gender, time of presentation, location of lesion (cervicofacial, truncal or extremity), duration and type of symptoms, and prior interventions. Photographic documentation had been routinely performed for each child enrolled after informed written consent from the parents. Photographs at baseline and at the final or most recent follow-up visit were reviewed. Patient identity was masked and study numbers were assigned. Photographs taken at the corresponding clinic visit were reviewed, and the percentage decrease in the size of the lesion was estimated and categorised. Imaging ultrasounds were reviewed to determine the type, size and extent of lesions and cysts, at baseline and following the final or most recent sclerotherapy session. Both clinical and radiological outcomes were categorised into excellent, good and poor (Table 1).

ILBS was performed as a day-care procedure under local or general anaesthesia depending on the patient's ability to tolerate the procedure. Under ultrasound guidance, cyst contents were aspirated, keeping the tip of the aspiration needle within the cyst lumen after which bleomycin aqueous solution (1mg/ml) up to a maximum dose of 0.6-1mg/kg body weight was injected.[17] Subsequent sessions were scheduled after an 8-12 weeks interval based on the size of lesion and clinical response. Follow-up visits were scheduled at least 6 weeks after each ILBS session.

Data was kep on Microsoft Excel and analysed using Stata 14. Mean±standard deviation (SD) values were calculated for continuous variables. Frequencies and percentages were reported for categorical variables. Concordance between radiological and photographic outcome assessment was checked. To study the association of radiological and photographic assessment outcomes with the independent variables, the outcome variable was cross-tabulated with independent variables. On tabulation, the expected counts were found to be <5, therefore, *p*-values of two-sided Fisher's exact test were reported. Independent sample T test was used to assess the difference in mean number of sessions and mean number of follow-ups between patients who were on treatment and those who had completed their treatment. P<0.05 was considered statistically significant.

Table-2: Association of photographic and radiographic assessment outcomes with independent variables.

		Photographic assessment				Radiographic assessment		
	Total (n=32) n (%)	**Excellent response** (n=16) n (%)	**Good response** (n=15) n (%)	**Poor response** (n=1) n (%)	***p*-value***	**Excellent response** (n=21) n (%)	**Good R response** (n=11) n (%)	***p*-value***
Age at initial symptoms								
At Birth or <1 year	23 (71.9)	9 (39.1)	13 (56.5)	1 (4.4)	0.14	14 (60.9)	9 (39.1)	0.44
>1 year	9 (28.1)	7 (77.8)	2 (22.2)	0 (0.0)		7 (77.8)	2 (22.2)	
Gender								
Male	22 (68.8)	11 (50.0)	10 (45.5)	1 (4.5)	1.00	14 (63.6)	8 (36.4)	1.00
Female	10 (31.2)	5 (50.0)	5 (50.0)	0 (0.0)		7 (70.0)	3 (30.0)	
Diagnosis								
Macrocystic	29 (90.6)	16 (55.2)	12 (41.4)	1 (3.4)	0.19	20 (69.0)	9 (31.0)	0.27
Mixed	3 (9.4)	0 (0.0)	3 (100.0)	0 (0.0)		1 (33.3)	2 (66.7)	
Areas involved								
Head & Neck	19 (59.4)	10 (52.6)	8 (42.1)	1 (5.3)	0.80	12 (63.2)	7 (36.8)	0.73
Trunk	10 (31.2)	4 (40.0)	6 (60.0)	0 (0.0)		6 (60.0)	4 (40.0)	
Extremity	3 (9.4)	2 (66.7)	1 (33.3)	0 (0.0)		3 (100.0)	0 (0.0)	
Treatment status								
Completed	24 (75.0)	15 (62.5)	9 (37.5)	0 (0.0)	0.01	21 (87.5)	3 (12.5)	<0.001
On going	8 (25.0)	1 (12.5)	6 (75.0)	1 (12.5)		0 (0.0)	8 (100.0)	
No of sessions								
1 to 2	17 (53.1)	8 (47.1)	8 (47.1)	1 (5.9)	1.00	10 (58.8)	7 (41.2)	0.47
> 2 to 7	15 (46.9)	8 (53.3)	7 (46.7)	0 (0.0)		11 (73.3)	4 (26.7)	

*Fisher's exact test

Table-3: Concordance in treatment response on radiographic and photographic assessments.

Photographic Assessment	**Treatment Response**	**Excellent response** (>90% to 100%)	**Good Response** (>50% to 90%)	**Poor response** (0% to 50%)	**Total** (n=32)
	Excellent response (>90% to 100%)	14*	2	0	16 (50.0)
	Good Response (>50% to 90%)	7	8*	0	15 (46.9)
	Poor response (0% to 50%)	0	1	0	1 (3.1)
	Total (n=32)	21 (65.6)	11 (34.4)	0 (0.0)	32 (100.0)

*Radiographic vs Photographic concordance observed in (14 + 8= 22 lesions) (69.0%)

Results

Of the 31 children, 22(68.8%) were boys. Mean age at presentation was 54.2±44 months (range: 2 months to 15.7 years). There were 32 lymphatic malformations; 29(90.6) macrocystic and 3(9.4%) mixed. Most lesions presented during first year 23(71.9%) while 9(28.1%) presented after one year of life, and 29(90.6%) lesions were purely macrocystic. The head and neck region was mostly involved 19(59.4%), followed by trunk 10(31.2%) and extremities 3(9.4%).

Excellent, good and poor response was seen in 16(50%), 15(46.9%) and 1(3.1%) lesions on photographic assessment, and 21(65.6%), 11(34.4%) and 0(0.0%) lesions on radiological assessment, respectively.

No significant difference was observed for the radiological and photographic outcomes with respect to age at first presentation, gender, type of LMs, location of lesion and number of sessions (Table 2). No short-term complications were seen during the study period.

Concordance in photographic and radiological outcomes was 22(69%) (Table 3). The mean number of ILBS sessions were 2.50±1.14 for the treatment completed group which had 24(75%) subjects compared to 3.0±1.92 for the under-treatment group having 8(25%) (p=0.37). Mean follow-up visits in former group were 7.13±2.52 compared to 7.13±3.04 in the latter group (p=1.00). No recurrence was found in the treatment-completed patients after a mean of 7.13±2.52 months.

Discussion

In the current study, 72% LMs were noted at birth, while cumulatively 87.5% presented by the second year of life. This is similar to earlier studies.[2,4] The head and neck region as the commonest site of involvement followed by trunk and extremities has been reported frequently,[2,14,16] and the same was the case in the current study.

In the current study, males were predominantly affected (68.8%), which is similar to an earlier series.[1] One study has reported equal incidence,[14] while female preponderance has also been reported.[15]

As per the present study, upon photographic evaluation the response to ILBS was excellent in 50%, good in 46.9% and poor in 3.1% patients. These results compared favourably with studies done previously.[3,4] One study[4] included all the three varieties of LMs, and revealed excellent to good response in all patients with mixed malformations, but since all purely microcystic lesions were excluded in the current, so, this might be a contributory reason for overall better outcome.

The current study compared the photographic review with the radiological assessment that showed comparable results in 69% cases. Other studies solely relied on radiological assessments.[4,11] We failed to find any prior study where photographic and radiological outcomes for all patients were monitored and compared as was done in the current study.

The photographic assessment was carried out by two researchers who were responsible for the clinical management of these patients. Because all microcystic LM cases were excluded, a very high rate of satisfactory response to ILBS was reflected in the current study compared to other studies where such an exclusion criterion was not applied.[10,18,19]

The limitations of the current study include limited sample of patients, retrospective analysis, being a single-centre study, absence of histopathological data, and lack of local studies for comparison.

Despite the limitations, because of good concordance between photographic and radiological assessments, we recommend using photographic assessment method in patients undergoing ILBS treatment. This will reduce the need for repeated radiological investigations during the course of treatment, decrease patient discomfort, and lessen health system costs.

Conclusion

ILBS was found to be effective in the treatment of macrocystic and mixed LMs. Photographic assessment was a reliable method on follow-up of patients undergoing ILBS treatment.

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