Original Article

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Intralesional bleomycin and sodium tetradecyl sulphate for haemangiomas and lymphangiomas

Man Mohan Harjai, Manvendu Jha[1]

ABSTRACT

Background: To compare the efficacy of intralesional bleomycin and sodium tetradecyl sulphate in treatment of haemangiomas and lymphangiomas. **Patients and Methods:** Between July 2007 and May 2009, 120 patients, sixty each of peripheral haemangiomas and lymphangiomas, were administered intralesional injection of bleomycin in a dose of 0.5-1 U/kg in children less than one year of age and 1 to 15 units in children more than one year of age and 1 to 3 ml of 2% sodium tetradecyl sulphate, depending on the size of the lesion at intervals of 14 days. Patients more than 20 years of age and those with diffuse or visceral lesions were excluded from the study. **Results:** Complete resolution occurred in 16 patients (53%) of haemangiomas and 14 patients (47%) of lymphangiomas treated with bleomycin, while the results were 12 patients (40%) and 10 patients (33%), respectively, in sodium tetradecyl sulphate group. The satisfactory resolution (resolution more than 50%) occurred in eight patients (27%) of haemangiomas and lymphangiomas groups treated with bleomycin, while the results were six patients (20%) and eight patients (27%), respectively, in sodium tetradecyl sulphate group. Poor response rate was observed in six patients (20%) of haemangiomas and eight patients (27%) of lymphangiomas of bleomycin group and 12 patients (40%) of haemangiomas and lymphangiomas in sodium tetradecyl sulphate group. No pulmonary fibrosis or other serious side effects were found. **Conclusions:** Intralesional bleomycin and sodium tetradecyl sulphate are effective sclerosants in peripheral haemangiomas and lymphangiomas, but bleomycin was found to be more efficacious.

Key words: Bleomycin, haemangioma, lymphangioma, sodium tetradecyl sulphate, sclerosing agents

Senior Advisor Surgery and Paediatric Surgery, Command Hospital (Southern Command) Pune, Maharashtra, [1]Graded Specialist in Surgery, Military Hospital YOL Cantt, India

Address for correspondence:
Dr. Man Mohan Harjai,
Senior Advisor Surgery and Paediatric Surgery, Command Hospital, Southern Command, Pune - 411 040, Maharashtra, India.
E-mail: harjai101@hotmail.com

INTRODUCTION

Surgical resection of haemangiomas and lymphangiomas is one of the option, but incomplete resection, recurrences and complications as cosmetic deformity have prompted a search for a more concrete and benign approach.[1,2] Intralesional sclerotherapy has been tried as an alternative approach to surgical excision in the conservative management of haemangiomas and lymphangiomas. Sclerosing agents as bleomycin, sodium tetradecyl sulphate, OK-432 and alcohol have been tried with significant results. Our aim is to compare the efficacy of intralesional bleomycin and sodium tetradecyl sulphate in the management of peripheral haemangiomas and lymphangiomas.

PATIENTS AND METHODS

One hundred and twenty patients under the age of 20 years, sixty each of haemangiomas and lymphangiomas, were included in the study. Only patients with peripheral lesions were included in the study. Patients with visceral haemangiomas or lymphangiomas and patients who had already taken some form of therapy were excluded from the study. Bleomycin was reconstituted with 15 ml normal saline and injected intralesionally in a dose of 0.5 to 1 U/kg. A single dose of 15 U per session was never exceeded. Sodium tetradecyl sulphate was injected in a dose of 1 to 3 ml of 2% solution depending on the size of the lesion. All the sclerosant dosages were given at interval of 14 days. All the lesions were initially aspirated before instilling the sclerosant. Photographs were taken before and after the administration of drug to document any regression of the lesions. Complete data were compiled and analysed. Results were categorised as significant if the reduction in size was more than 50% associated with cosmetic improvement and reduction of pain in patients who presented with pain as one of the symptoms.

RESULTS

Total numbers of patients included in the study were

120; sixty each of haemangiomas and lymphangiomas. All patients included in the study were less than 20 years of age. Of all the patients, 44.6% (53) were under five years of age [Table 1]. Overall, 70% (84) of patients were under the age of 10 years which included 35.8% (43) patients of haemangiomas and 34.16% (41) patients of lymphangiomas [Figure 1]. Sixty seven percent (80) of patients were females and 33% (40) patients were males [Table 2]. In haemangiomas, 42 patients were females and 18 were males [Figure 2]. The most common sites of involvement in decreasing order of frequency were chest wall and abdomen (40%, 24), neck (20%, 12), upper limb (20%, 12), cheek and mouth (16.6%, 10) and axilla (3.33%, 2) [Figure 3]. However, in case of lymphangiomas, 15% (18) of patients were below one year of age at initiation of treatment [Table 1], while total patients under the age of 10 years of age were 34% (41). Twenty two patients were males and 38 were females [Figure 2]. Ninety percent (54) of patients had lesions confined to the head and neck region, followed by 8.3% (5) in axilla and 1.6% (1) on the trunk. None of the patients had lesions on the limbs [Figure 3]. The minimum and maximum doses of bleomycin given for lymphangiomas were 25 U and 210 U, respectively, the mean dose being 119 U, while the minimum and maximum doses for haemangiomas were 30 U and 195 U, respectively, (mean dose 121 U) divided over a maximum of 15 doses. The total numbers of injections performed were 769 with a highest accumulative dose of 210 U in case of lymphangiomas and 195 U in case of haemangiomas. A single dose of 15 U per session was never exceeded. Reduction in the size of mass was usually seen by 2 weeks to 6 months of treatment in case of lymphangiomas using bleomycin; however, the duration was much less in case of haemangiomas (2 weeks to 3 months). The duration was 4 weeks to 6 months in cases of lymphangiomas and 3 weeks to 7 weeks in haemangiomas when sodium tetradecyl sulphate was used. Sodium tetradecyl sulphate was injected in volume of 1 to 3 ml of 2% solution depending on the size of the lesion. Complete resolution or significant improvement occurred in 80% (24) of haemangiomas [Table 3] and 73.3% (22) of lymphangiomas [Table 4] treated with bleomycin. The results were 60% (18) both for haemangiomas and lymphangiomas who underwent sclerotherapy using sodium tetradecyl sulphate. Poor response rate was observed in 20% (6) of haemangiomas and 26.6% (8) in lymphangiomas of bleomycin group and 40% (8) of haemangiomas and lymphangiomas in sodium tetradecyl sulphate group [Figures 4 and 5]. Greater than 50% resolution was seen in eight patients of bleomycin group and six patients of sodium tetradecyl sulphate group in haemangiomas and chances of more than 50% resolution of haemangioma were 2.67 times odds than that with sodium tetradecyl sulphate. The chance of more than 50% resolution in lymphangiomas with bleomycin was 1.5 times odds than that with sodium tetradecyl sulphate. The patients in the good response category are on follow up as the patients have opted for non-surgical treatment and are satisfied with the cosmetic outcome. None of the patients have reported recurrence of any lesion till date. The maximum number of injections required for complete resolution were 10 and 15 in cases of haemangiomas and lymphangiomas, respectively, using bleomycin, while it were 15 in all cases of lymphangiomas and 13 in haemangiomas when sodium tetradecyl sulphate was used. Minimum number of injections required was 7 when bleomycin was used in haemangiomas and 10 for lymphangiomas. The same figure was 10 and 12 for sodium tetradecyl sulphate. The complications of bleomycin were all minor; fever in 15, transient increase in size of swelling in 7, leucocytosis in 10, anaemia in 4 and skin discolouration in 4 children [Table 5]. Complications when sodium tetradecyl sulphate was used were also minor and included 7 children with fever, skin discolouration in 36, transient increase in swelling in 10 and leucocytosis in 20 children [Table 6]. Significant discolouration was seen in patients when sodium tetradecyl sulphate was used in 21 patients of lymphangiomas [Tables 7-8] and 15 patients of haemangiomas had skin discolouration using sodium tetradecyl sulphate. None of the patients in any group showed any evidence of any serious hypersensitivity reaction to any of the drugs used. The complications resolved on symptomatic treatment and none of the patients required hospitalisation. None of the patients had any evidence of pulmonary toxicity using bleomycin.

Table 1: Age distribution

	Haemangiomas	Lymphangiomas	Total
0-5	25	28	53
6-10	18	13	31
11-15	12	12	24
16-20	05	07	12
Total	60	60	120

Table 2: Sex distribution

Sex	Haemangiomas	Lymphangiomas	Total
Males	18	22	40
Females	42	38	80
Total	60	60	120

DISCUSSION

Vascular anomalies are a new, rapidly evolving multidisciplinary field that combines surgical and various other medical specialities. Intralesional injections of sclerosants now form the backbone of conservative management of haemangiomas and lymphangiomas. The simplicity of the procedure with minimal complications makes it a well-accepted mode of management. Various studies by Piennar *et al*.[3], Muir *et al*.[4] and Kullendorf[5] have proved beyond doubt the efficacy of intralesional bleomycin in management of haemangiomas. Similarly, since the inception of intralesional bleomycin for lymphangiomas by Yura *et al*.,[6] various authors as Okada *et al*.[7] and Tanaka *et al*.[8] have reported successful treatment of lymphangiomas with intralesional bleomycin. Sodium tetradecyl sulphate has been classically used as a sclerosant for venous malformations. Woods[9] used sodium tetradecyl sulphate in 18 patients of haemangiomas not amenable to surgery with good results. Similar success was reported by Kane *et al*.[10] and Tan *et al*.[11] In our study, we compared the efficacy of intralesional bleomycin and sodium tetradecyl

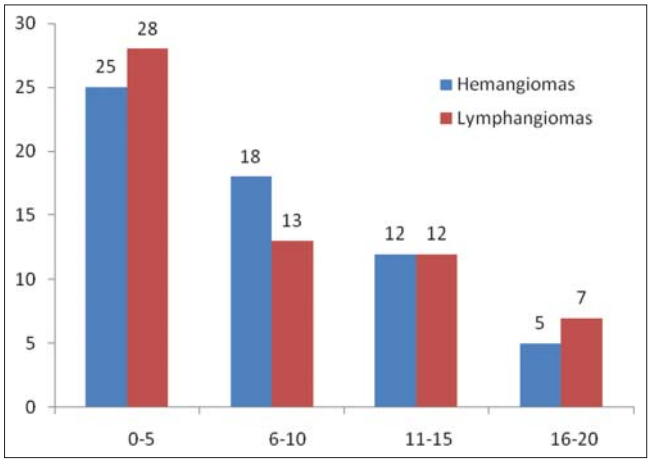


Figure 1: Age distribution

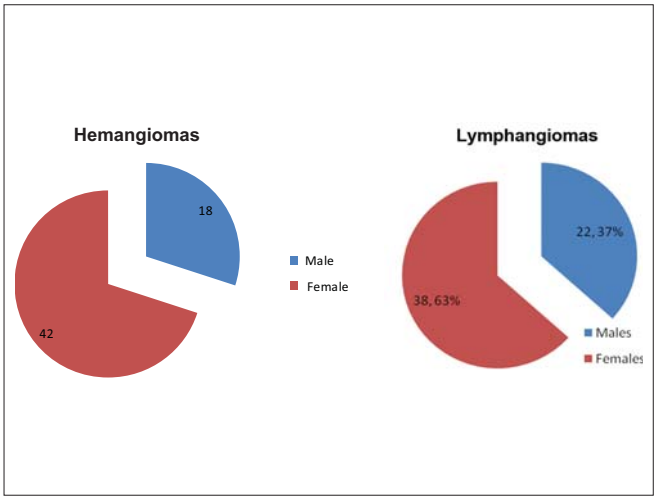


Figure 2: Sex distribution

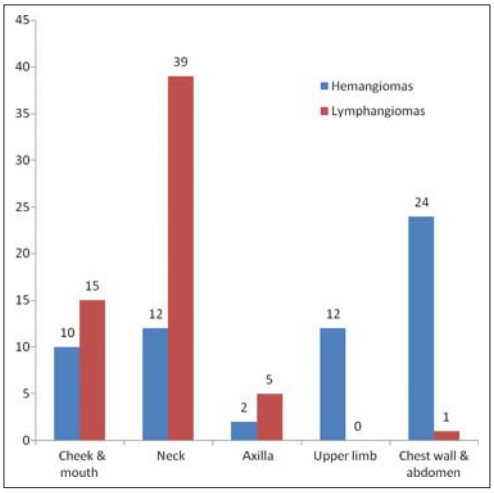


Figure 3: Sites of involvement. The association between site of occurrence and incidence of haemangioma and lymphangioma have been found to be highly significant (*P*<0.01), Yates corrected

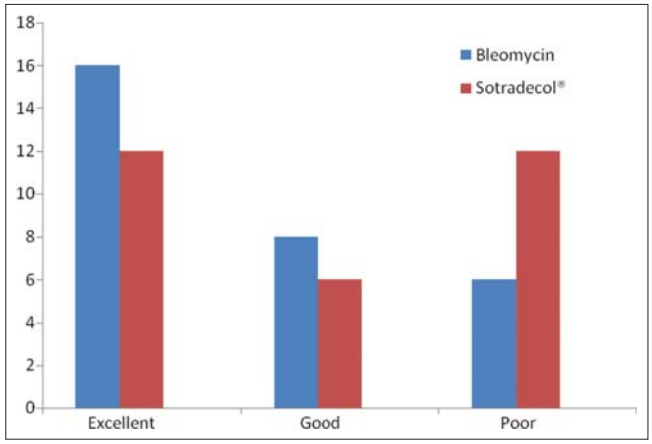


Figure 4: Results - Haemangioma group

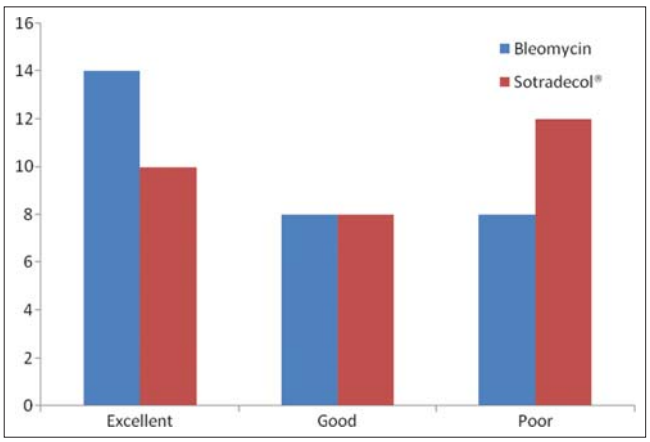


Figure 5: Results - Lymphangioma group

Table 3: Results - Haemangioma group

Haemangioma	Bleomycin	Sotradecol(R)	Statistical analysis
Complete resolution	16	12	Odds Ratio=1.71 (0.55<OR<5.44), i.e. chance of complete resolution of haemangioma with bleomycin is 1.71 times odds than that with Sotradecol(R) P=0.43 (Yates Corrected)
>50%	8	6	OR=2.67 (0.51<OR<14.77) P=0.98
<50%	6	12	(Yates Corrected)

Table 4: Results - Lymphangioma group

Lymphangiomas	Bleomycin	Sotradecol(R)	Statistical analysis
Complete resolution	14	10	OR=1.75 (0.54<OR<5.69) P=0.63 (Yates Corrected)
>50%	8	8	OR=1.5 (<0.33OR<7.01)
<50%	8	12	P=0.07 (Yates Corrected)

Table 5: Complications with bleomycin

Bleomycin	Haemangioma	Lymphangioma
Fever	8	7
Increase in size	1	6
Haemorrhage	0	1
Leucocytosis	6	4
Anaemia	3	1
Skin discolouration	2	2
Hypersensitivity	None	None
Pain	35	23

Table 6: Complications with Sotradecol(R)

Sotradecol(R)	Haemangioma	Lymphangioma
Fever	4	3
Increase in size	6	4
Skin discolouration	15	21
Rashes	5	8
Leucocytosis	9	11
Hypersensitivity	None	None
Pain	25	17

Table 7: Complications in Haemangioma group

Haemangioma	Bleomycin	Sotradecol(R)	Chi square
Fever	8	4	P=0.9 (Yates Corrected)
Increase in size	1	6	P=0.9 (Yates Corrected)
Skin discolouration	2	15	P=0.001 (Yates Corrected)
Pain	35	25	P=0.629 (Yates corrected)

Table 8: Complications in Lymphangioma group

Lymphangioma	Bleomycin	Sotradecol(R)	Chi square
Fever	7	3	P=0.5 (Fishers Exact)
Increase in size	6	4	P=0.1 (Fishers Exact)
Skin discolouration	2	21	P<0.001 (Fishers Exact)
Pain	23	17	P=0.9 (Yates Corrected)

sulphate in non-surgical management of peripheral haemangiomas and lymphangiomas. The total follow-up period ranged from 6 months to 2 years. Complete resolution or significant improvement was seen in 80% of cases of haemangiomas treated with bleomycin as compared to 60% in sodium tetradecyl sulphate group. The results were comparable to studies conducted by various authors. Similarly, efficacies of bleomycin and sodium tetradecyl sulphate in lymphangiomas were 73.3% and 60%, respectively. The odds ratio was 2.67 in favour of bleomycin in haemangiomas and 1.83 in favour of bleomycin in lymphangiomas. All the patients were satisfied with the cosmetic outcome of treatment; even those who were in the poor response group. The summated dose with bleomycin for lymphangiomas has been described to be 5 mg/kg and minimum dose per injection as 1 mg/kg. No such dose range has been described for sodium tetradecyl sulphate. The most important area where we differed from all other studies was the number of injections. In quite a few patients, we required complete 15 sittings for the same amount of resolution. This however can be explained by the fact that quite a few of our patients had diffuse and large lesions. Intralesional therapy was given by targeting a specific area at a time, which might have resulted in increased number of injections. However, in none of our patients, we exceeded the permissible safe limit of the drug doses recommended in literature. We believe that the use of minimum per kg dose of bleomycin as described in the literature is not mandatory for the sclerosing effect of bleomycin to occur. The desired effect of sclerosis depends on the local action of the drug which in turn depends on the concentration of the drug available per unit area of the lesion. Hence, the dose injected should depend on the size of the lesion rather than weight of the patient and sclerosis can be induced by a much smaller dose than the weight of the patient would warrant. Another factor that would influence the dose to be injected is the completeness of aspiration of the lesion before injecting the drug. As seen in our study, the numbers of injections required for significant improvement in the lesions were also dependent on the size of the lesion. Large cystic hygromas and multifocal haemangiomas required more injections of bleomycin or sodium tetradecyl sulphate for similar effect as compared to small lesions. If the cystic hygroma or haemangioma could be aspirated

completely, the concentration of the drug required per unit area would be much less. The drug gets diluted in the fluid, thus providing less drug per unit surface area for the sclerosing effect. The exact dosage requirement per unit volume of the lesion has not been worked out and it will probably require further trial with lower doses. None of our patients reported back with recurrence of symptoms. In our study although both the drugs were found to be effective for sclerotherapy of haemangiomas and lymphangiomas but given the various criteria used to assess the efficacy, bleomycin was found to be more effective than sodium tetradecyl sulphate.

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