

# Intralesional bleomycin versus sodium tetradecyl sulphate in the management of peripheral lymphangiomas in children: a prospective comparative study

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## Abstract

**Introduction:** Surgical resection in lymphangiomas is associated with high rate of complications, recurrences and total excision is not possible in every case. Therefore, sclerotherapy have emerged as alternative mode of management. It is essential to know the efficacy of the sclerosants and the merits and demerits of the agents. However, a prospective study comparing the efficacies of the sclerosing agents exclusively on lymphangioma is lacking. **Methods:** A prospective, comparative clinical trial was conducted in a tertiary health care pediatric institute among lymphangioma patients. Patients were divided into two groups by randomisation; Group A: patients in whom intralesional bleomycin injection was administered, Group B: patients in whom intralesional sodium tetradecyl sulphate was administered. Both the groups were compared with respect to clinical presentation, efficacy of the drugs and side effects/complications. **Result:** Out of 36 patients included in this study, 18 patients were treated with intralesional bleomycin and 18 patients with intralesional sodium tetradecyl sulphate. Most common site of lymphangioma was neck (44.5%) followed by axilla in 27.7% of cases. Reduction in size was noted in 15 (83.3%) patients in group A, 9 (50%) had excellent response, while 6 (33%) had good response. Reduction in size was noted in 12 (66%) patients in group B, 5 (27%) had excellent response while 7 (38%) had good response. **Conclusion:** Intralesional bleomycin and sodium tetradecyl sulphate are safe and effective sclerosing agents in peripheral lymphangiomas of children, but bleomycin is more effective in reducing the size of the lesions.

**Key words:** Bleomycin, Lymphatic malformations, Sclerosing agents, Sodium tetradecyl sulphate

## Introduction

Lymphangioma is a developmental malformation of lymphatic system. The reported incidence of the lesion is 1.5 to 2.8 per 1000 and there is no specific sex or race predilection [1]. It is usually seen in pediatric age group and constitutes 6% of benign tumors in this age group [2]. In about 50% of patients, the disease is found at birth and 80 to 90% of cases present before 2 years of age [3]. Head and neck area is the commonest site affected by lymphangioma [1,4]. Sites other than head and neck include axilla, mediastinum, thigh, chest and

abdominal wall [5]. Landing and Ferber classified lymphatic malformations into 3 types (i) Lymphangioma simplex: consisting of thin lymphatic channels of capillary size, (ii) Cavernous lymphangioma: composed of dilated lymphatic channels, (iii) Cystic lymphangioma: consists of cysts having diameter of few millimeters to centimeters [6,7]. Combination of these groups are frequently detected in the same lesion.

Management of lymphatic malformations are complicated and challenging. Surgical resection is the traditional modality of management but is associated with high rate of complications and total

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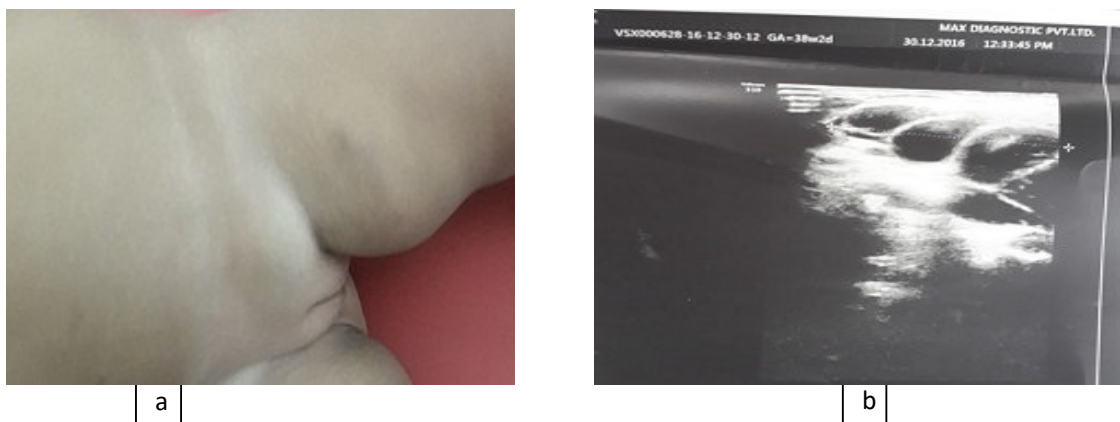
excision is not possible in every case. The reported recurrence rate after resection of lymphangioma varies from 15 to 53% [7,8]. Therefore, nonsurgical methods such as sclerotherapy have emerged as alternative mode of management. Sclerosants act by destroying the epithelial lining of the cysts followed by collapse and scarring [7,9]. Sclerosing agents such as Ethanol and Sodium tetradecyl sulphate (STS) became popular initially and are commonly used [8,9]. However, in the recent years OK-432 and Bleomycin are favoured by many surgeons due to encouraging results. But, OK-432 is not easily available and is costly [6,7]. Bleomycin was first discovered as a cytotoxic antitumor antibiotic and later on used as a sclerosing agent in lymphangiomas [10,11]. It has specific effect on

vascular endothelium and inflammation is the mechanism of action. We were using bleomycin and STS, as both are readily available in our locality and are economical. It is essential to know efficacy of the sclerosants and the merits and demerits of both the agents. However, a prospective study comparing the efficacies of the two sclerosing agents exclusively on lymphangioma is not available.

On this background the present study was conducted in our tertiary health care Pediatric Surgical Institute as a prospective, controlled and comparative clinical trial. The aim of the study was to evaluate, assess and to compare the efficacy of two common sclerosants; bleomycin and STS in the management of lymphangiomas in children.

## Methods

The study was carried out in the department of pediatric surgery at SVP Postgraduate Institute of Pediatrics, SCB Medical College, Cuttack, Odisha, India from November 2014 to October 2016 and follow up till October 2017. This was a prospective, comparative, controlled clinical trial. Lymphangioma patients attending the OPD of this tertiary health care hospital were examined and assessed. Children only with peripheral lymphangiomas were included in the study. Patients having intra-abdominal or visceral lymphangioma and postoperative recurrent lymphangiomas were excluded. The detailed history and physical examination of all patients were recorded. The diagnosis was based on clinical examination and ultrasound scan [Figure-1].



**Figure-1:** (a) A 2-year-old female child with swelling on anteromedial aspect of left thigh, (b) Ultrasonography showing soft tissue lesion with cystic spaces; no vascularity could be appreciated on colour Doppler within the lesion, underlying muscles of thigh normal. She was successfully treated by intralesional sclerotherapy with two injections of STS at 4-week interval.

Routine hemogram and X-ray were performed. Patients were divided into two groups by randomization; Group A: patients in whom intralesional bleomycin injection was administered, Group B: patients in whom intralesional STS was administered. Each group had equal number of patients according to age and the site of lymphangioma so as to assess the efficacy of drugs accurately. Written informed consent was taken from the parents after counseling regarding the mode of treatment, merits and demerits of the procedure.

Normal saline (15 ml) was added to 15 mg bleomycin powder in the vial to prepare a strength of 1 mg/ml. The dose of bleomycin was calculated as 0.5mg/kg body weight and was taken from the reconstituted solution. It was again

diluted in 10 ml normal saline. Cyst content was aspirated with a 10cc disposable syringe with 20-24 gauge needle. The needle was placed in situ and bleomycin solution was injected slowly. Patients were kept on observation for at least 24 hours. Fever, pain and swelling at the injection site were specially looked for and managed accordingly. On discharge, parents were advised for follow up at 4 weeks. The size of the lesion was recorded and injection was repeated at four-weeks intervals with same dosage, with a maximum of four injections. Each patient had clinical assessment and ultrasound scan on each visit, to assess the size reduction of the lesion. Similarly, intralesional STS was given at the dose of 1 to 3 ml of 2% solution depending on the size of the lesion at an interval of 4 weeks. The patients were followed for 1 year to 2 years (mean follow up 11/2 year). The response was measured clinically (size of lesion) and radiologically (ultrasonography) and graded as follows;

1. Excellent (regression of lesion size > 90%),
2. Good (regression of size 50-90%) and
3. Poor (less than 10% or no response).

The data was recorded for the frequency and percentage of patients and analysis was done. Both the groups were compared with respect to clinical presentation, efficacy of the drugs and side effects/complications.

## Results

Out of 36 patients included in this study, 18 patients were treated with intralesional bleomycin (group A) and 18 patients (group B) with intralesional STS. The age range was from 18 days to 7 years with 17 patients below one year of age. Fifteen patients were between 1 to 2 year of age and 4 children above 2 years of age. Both the groups contained 11 (61.1%) male children and 7 (38.9%) female children; the male to female ratio being 1.57:1. Most common site of lymphangioma was neck in 44.5% cases [Figure-2] followed by axilla in 27.7% of cases [Table-1].



**Figure-2:** A 3-year-old male child with lymphangioma of left cervical region. He was found to have cystic variety of lymphangioma and treated with two injections of intralesional bleomycin (0.5 mg/kg body weight) at 4 week interval.

**Table-1: Site of the lesions treated with sclerotherapy.**

Site of lesion	Intralesional bleomycin	Intralesional STS
Neck	8	8
Axilla	5	5
Parotid	2	2
Back	1	1
Limbs	2	2

Cervical area is the most common site of lymphangioma (44.5%) followed by axillary area (27.7%).

We found simplex type of lymphangioma in 12 patients, cystic lymphangioma in 18 patients and the rest 6 patients were having cavernous type of lymphangioma. 50% of the lesions in each category were administered with intralesional bleomycin and the rest 50% were administered with intralesional STS.

### Response to intralesional sclerotherapy

**Intralesional bleomycin sclerotherapy:** Reduction in size was noted in 15 (83.3%) patients in group A, 9(50%) had excellent response, while 6(33.3%) had good response [Table-2].

**Table-2: Clinical response to intralesional sclerotherapy**

	(Gr A) Intralesional bleomycin(n=18)	(Gr B) Intralesional STS (n =18)
Reduction in size	15 (83.3%)	12 (66.7 %)
Excellent response	9 (50%)	5 (27.8 %)
Good response	6 (33.3 %)	7 (38.9 %)
Poor response	3 (16.7 %)	6 (33.3 %)

Intralesional bleomycin is more effective in reducing the size of the lesions than intralesional STS.

Three patients (16.7%) had poor response. Out of nine patients with excellent response on bleomycin therapy, 6 cases were lymphangioma simplex type, and they had regression of lesion with one injection of bleomycin. Rest 3 cases were cystic type and required two injections of bleomycin. All the 6 patients having good response were cystic variety and they needed 4 injections of bleomycin at 4 week intervals. Three patients with poor response were cavernous types. Fever was found in 3 patients, which was subsided within two days with oral paracetamol. Cellulitis as observed by pain, redness and swelling of the lesion was assessed in three more patients. These children were treated with antibiotics and analgesics. There was no serious side effect or systemic toxicity.

**Intralesional STS sclerotherapy:** Reduction in size was noted in 12 (66.7%) patients in group B, 5 (27.8%) had excellent response while 7(38.9%) had good response [Table-2]. All 5 patients with excellent response were lymphangioma simplex. Two had regression of lesion with one injection of STS and three with two injections. Among the 7 patients having good response to STS, one was simplex type and 6 were cystic variety lymphangiomas. All had 4 number of injection at 4 week intervals. Six patients (33.3%) had poor response and three of them were multiloculated cystic type and rest three were cavernous types. Cellulitis and transient increase in size was assessed in three and two patients respectively and were treated conservatively with antibiotics and analgesics. Systemic side effect or toxicity was not detected.

All the patients in both the groups were followed for 1-2 years. Recurrence or increase in size was not found in excellent and good response category of children. There was no scarring or pigmentation at the site of injection in either group of patients. No other complication related to intralesional sclerotherapy was found in any of these patients. Serious side effects or pulmonary fibrosis was not detected. Patients with poor response were advised for surgical intervention in our routine operation theater. Out of total 9 children 7 patients were operated during follow up period with complete removal of the lesion in all cases. Postoperatively all the parents were satisfied regarding our treatment plan and outcome.

### Discussion

Vascular lesions are traditionally classified into two broad categories: Hemangiomas and Vascular malformations (VM). VM are further divided depending on the type of vessel involved; capillary, arterial, venous, lymphatic malformation or mixed lesions [12]. Capillary, venous and lymphatic malformations are classically categorized as 'low flow' lesions as compared to arterial or arteriovenous malformations which are 'high flow' lesions [13]. Lymphatic malformations may be subdivided into microcystic (diameter <1 cm), macrocystic or mixed lesions [9]. The pathogenesis of the anomalies is unknown, but there is an error in the morphogenesis of lymphatic vessels [14]. There is a failure of communication of lymphatic channels to venous system [8].

By rule, vascular malformations are present at birth, but may not be clinically evident in all cases. Being classified under VM, lymphatic malformations are detected at birth in about 60% of the patients and most of the lesions are

recognized before 2 years of age [3]. Lymphangiomas grow in proportionate with the growth of the child [15]. They enlarge by hypertrophy in contrast to hemangiomas which grow by hyperplasia [16]. They usually displace adjacent organs, but there may be abrupt expansion of the lesion due to infection and haemorrhage [16]. Lymphatic malformations are unique among VM in that they may enlarge during systemic illness like viral or bacterial infection [8]. Lymphangiomas usually affect both sexes equally [2,16]. In our study male to female ratio was 1.57:1. This may be due to the fact that more of the male children are referred to us from periphery or more importance being given to male babies in some areas. Head and neck is the most commonly involved site [4,16]. The commonest site of lymphangioma seen in our study was neck (44.5%) followed by axilla (27.7%). Anatomically, neck and axillary areas are associated with major lymphatic channels, so there is increased preference for lymphatic malformations [8]. We followed the classification system described by Landing and Ferber. In our study, 50% of the lesions were cystic type of lymphangioma, 33.3% simplex type and the rest 16.7% were of cavernous variety. Like other vascular malformations, lymphangiomas do not show signs of involution. This is in contrast to hemangiomas which show proliferative phase followed by slow and spontaneous involution [16]. Lymphatic malformations can cause significant morbidity due to cosmesis, compression of adjacent structures, inflammation and internal haemorrhage [6,7].

Management of lymphatic malformations is still challenging for the surgeons. Although, surgical excision can provide an effective cure for these anomalies, the outcome depends on the anatomical location, extent, involvement of adjacent tissue and expertise of the surgeon. Total resection is not possible in every case because of extensive lesion, infiltrating nature of the tumor and involvement of vital structures in some cases [2,5]. Postoperative complications like feeding difficulties, infection and airway obstruction especially in lymphangiomas of cervical areas (most common location) are of significant concern. Wound infection, nerve palsy and residual scars are also possible complications [17]. High recurrence rate reported by many surgeons, complicates the treatment plan [6,7]. The fact that 'lymphangiomas are benign tumors' should be kept in mind before considering other treatment options. Management of lymphangiomas are cosmetically important as they are commonly seen in vital areas such as head and neck. Therefore, nonsurgical methods have emerged as alternative modes of management. These include radiotherapy, argon beam ablation therapy, lasers; CO<sub>2</sub> and more effectively Nd-YAG laser and sclerotherapy [7,16]. But, sclerotherapy gained more popularity and continued to be choice of nonsurgical management in Lymphatic malformations.

Sclerotherapy is preferred in many centres because of risks associated in surgical intervention, anaesthesia, postoperative complications and recurrence rate. However, the choice of an ideal sclerosing agent and the exact dosage of the intralesional drug are still controversial. Ideal sclerosing agent should produce adequate destruction of the lesion and lack systemic toxicity [18]. The agent should be safe, inexpensive and easily available. Sclerosing agents such as Ethanol, OK-432, Bleomycin and STS are tried with variable outcome. Ethanol sclerotherapy is associated with problems like skin necrosis, nerve injury and systemic effect [2,19]. Ethanol may enter vascular system causing hypotension and lethal intoxication [20]. OK-432 is a lyophilized incubation mixture of Group A *Streptococcus Pyogenes* [2]. It causes cytokine mediated endothelial permeability leading to shrinkage of cystic spaces and regression of LM. OK-432 may cause transient local inflammation in some cases and there is a risk of airway compression in cervical lesions [21]. Rozman *et al.* reported a patient, who received 3 dosages of OK-432 injection after failure with bleomycin sclerotherapy [1]. The lesion also failed to respond to OK-432 and surgical intervention was undertaken. OK-432 is not yet approved by U.S. Food and Drug Administration [2]. The cost and availability of the drug are prohibiting factors [7,17,22].

Bleomycin was first introduced into medical literature in 1966 by Umezawa *et al.* as aglycopeptide antibiotic [10]. Surprisingly it was never used as an antibiotic. It was found to have cytotoxic antitumor properties and presently established as an anticancer drug. Its effect towards sclerosing agent was first described by Yura *et al.* in 1977 [11]. It causes DNA intercalation, strand breaks and free radical formation [1]. The drug acts on the endothelial lining of lymphatic vessels [1,2,23]. Although the exact mechanism of action in lymphangioma is unknown, it is inflammatory mediated as there occurs transient increase in the size of lymphangioma after intralesional injection [24]. Bleomycin took about two decades and several trials to be popularized as an efficient sclerosant [5,23,25]. The minimum dose of intralesional bleomycin is described as 1 mg/kg body weight and the

summed dose as 5 mg/kg body weight [3,5,22]. But, the effective dose of bleomycin for sclerosis will depend upon, the availability of drug per unit surface area. Drug availability will be increased after aspiration of fluid in the lesion. Complete aspiration should be the goal to avoid dilution of the drug. Therefore, we gave more emphasis on complete aspiration of cyst and administration of minimum amount of drug to avoid local and systemic complications. The dosage of our study and schedule of administration was similar to other studies but, we have administered lowest summated dose among these studies [5,22,26].

Side effects after bleomycin therapy includes allergy, flu-like symptoms, skin pigmentation, hair loss and mucositis [2,9]. Pulmonary toxicity is a notable side effect with bleomycin, but it is dose related [6,7]. The sequel of toxicity includes diffuse alveolar damage, interstitial pneumonitis followed by progressive pulmonary fibrosis [27]. The risk for pulmonary toxicity is reported when the single dose of Bleomycin is more than 30mg/m<sup>2</sup> of body surface area or the total dose exceeds 400U [7,17,22]. Pulmonary fibrosis due to intralesional bleomycin is not yet reported even in clinical studies from Australia, Japan, Malaysia and Pakistan [1,17,28]. We have also not reported pulmonary toxicity in follow up of our patients due to a safe and low dose of administered bleomycin. A low concentration of enzyme bleomycin hydrolase may account for the susceptibility of these tissues for bleomycin toxicity [29]. The enzyme may also be deficient in patients having pulmonary and skin toxicities due to bleomycin [27]. STS is a sclerosing agent for VM, which causes obliteration of vessels followed by adventitial fibrosis and luminal collapse [14]. STS is used for sclerotherapy in lymphangiomas in some centres and authors published their encouraging results [30,31,32]. It is found to be effective and safe sclerosant.

The sclerosing effect of bleomycin solution will be higher after complete aspiration of the lesion due to increased availability of the drug per unit area. Poor response with intralesional bleomycin may occur due to partial aspiration of lesion before injecting sclerosant or mixed variety of Lymphatic malformation. Although, the dose of bleomycin used in different studies is variable, we have used 0.5 mg/kg/dose, which is much lower than the development of potential complication especially pulmonary toxicity. In our study reduction in size was noted in 83.3% cases with excellent results i.e. complete regression in 50% cases. The results are comparable with other studies [Table-3].

**Table-3: Comparison of the results in different series.**

Study	Year	Total no of patients	Significant regression (size resolution >50-100%)	Excellent response (size regression >90%)
Tanaka et al [5]	1990	47	41(87%)	20(43%)
Oxford et al [24]	1995	16	14(87.5%)	7(43.75%)
Mahajan et al [23]	2004	15	13(86.7%)	8(53.3%)
Saddal et al [18]	2007	33	29(90%)	10(30%)
Rozman et al [11]	2011	24	20(83%)	15(62.5%)
Present Study	2017	18	15(83.3%)	9(50%)

Comparison of the results in series using bleomycin, Intralesional bleomycin is effective in reducing the size of lymphangiomas in 83-90% cases with excellent response varying from 30-62.5% cases in different series.

Excellent and good response was noted in simplex and cystic varieties and poor response in cavernous types. Okada *et al.* and Rawat *et al.* reported similar findings; good response to bleomycin in cystic varieties than cavernous types [3,7]. Authors reported better effect of bleomycin in cystic variety as compared to cavernous and capillary types [5,22,23]. However, our study revealed that bleomycin is also effective in capillary varieties of lymphatic malformations.

OK-432 is effective in macrocystic lymphangioma and its effectiveness is limited in microcystic lesions [2]. So authors suggested its use in simple lymphatic cysts and macrocystic lesions. They also recommended surgical intervention after OK-432 sclerotherapy in microcystic and cavernous type of lesions [33]. However, we have noted significant response in 83.3% of our cases with bleomycin sclerotherapy alone. Studies on intralesional

aqueous solution of bleomycin in lymphangioma is limited [3,7,23]. A single study exclusively on lymphangiomas for comparison between two sclerosants with respect to their effectiveness, side effects and complications is not reported [1]. This is a prospective controlled clinical trial exclusively on lymphatic malformations comparing two established agents to find out the most effective sclerosant and the management approach in a tertiary health care paediatric institute.

**Contribution of this study towards existing knowledge-** Although, both bleomycin and STS are used as sclerosing agent in lymphangioma, this clinical trial revealed, bleomycin to be more effective in reducing the size of the lesions in children. When administered properly and in proper dose (0.5 mg/kg body weight), bleomycin is very safe without serious side effect, especially pulmonary fibrosis described in literature. Although, authors reported better effectiveness of bleomycin in cystic variety as compared to other types, we found bleomycin is also very effective in capillary variety of lymphatic malformations.

## Conclusion

Lymphangiomas in children are detected most commonly in cervical area followed by axilla, which are cosmetically important. Intralesional bleomycin and STS are effective alternatives to surgery in lymphangiomas.

Both the sclerosants are safe in children, without any serious side effects or pulmonary complications, when administered properly and in proper doses.

However, bleomycin is more effective in reducing the size of the lesions than STS.

Excellent and good response to the drugs should be expected in simplex and cystic variety of the lymphangiomas as compared to cavernous variety of the lesion.

We together with other published studies support the use of intralesional sclerotherapy as first-line of treatment for peripheral lymphangiomas in children. Surgery should be reserved for the lesions, failed to respond to sclerotherapy.

**Contribution by authors:** Nayak K: Data collection and processing, Tripathy PK (corresponding author): Data management and reporting, literature review, logical interpretation and presentation of the results construction of the whole of the manuscript, Jena PK: Reviewing the article before submission, Mohanty HK: Hypothesis for research, planning methodology

**Abbreviations:** STS- Sodium tetradecyl sulphate, VM- Vascular malformations.

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## Original Research Article

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