Research Article

Efficacy and Safety of Intralesional Bleomycin for Treatment of Lymphangioma: Report from a Tertiary Care Hospital of Bihar

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ABSTRACT

Background: Lymphangioma is a benign tumor of lymphatic vessels, with 75% cases occurring in head and neck. Surgical excision is the traditional management. Intralesional sclerotherapy has become a method of treatment for lymphangiomas in children. A retrospective clinical trial was conducted to evaluate the efficacy of intralesional bleomycin sclerotherapy (IBS) in the treatment of lymphangiomas in children.

Methodology: A prospective study was conducted by the Department of General Surgery of MGM Medical College, Kishanganj, Bihar. Study was commenced after getting the ethical approval from the Institutional ethical committee. The period of data collection was 2 years that is from October 2019 to September 2021. The response of IBS was assessed clinically and on the basis of color Doppler USG.

Results: 36 patients of lymphangioma were included in the study. 63.9% patients were seen before 1 year of age. Of all, 75% of the cases that is 27 patients had cystic hygroma, 3 were cavernous, and 6 were of mixed type. The neck region was the most common site with 25 (69.4%) patients. 19.4% required single dose. 11 patients developed side effects.

Conclusion: Complications can also occur postoperatively or following sclerotherapy. Bleomycin injection (intralesional) is a safe and effective sclerosant for Lymphangioma Circumscriptum.

Keywords: Intralesional bleomycin, lymphangioma, treatment.

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INTRODUCTION

Lymphangioma is a benign tumor of lymphatic vessels and consists of cystic spaces of varying size. It is a slow growing tumor. It may arise in any organ or soft tissue. This tumor is mainly confined to the pediatric age group, but occurrences have been reported in adults. The most frequent occurrence is in the head and neck, accounting for 75% of all cases[1]. It is typically detected at birth in up to 65% and presents by the age of two years in 90% of cases[1]. The incidence of lymphangioma is reported to be from 1.5-2.8 per 1000 with no predilection for either sex. Swelling and cosmetic deformity are the most common symptoms. A large lesion in the neck can compress vital structures, cause respiratory obstruction, dysphagia and symptoms of nerve compression.

Surgical excision is the traditional management, the goal of which is the removal of the involved tissue without sacrificing vital structures, but this may not be achieved in most cases. Intralesional sclerotherapy has become an acceptable method of treatment for lymphangiomas in children. It involves the use of a sclerosing agent that causes irritation of the endothelial lining of the lymphangioma, which leads to inflammation, fibrosis and involution[2]. Other modes of treatment such as surgical resection, incision and drainage, and radiation therapy have produced unsatisfactory results. Surgical resection for complete removal in many cases is impossible due to the nature of the lesion, which has a propensity to infiltrate tissue planes and encircle important neurovascular structures. Tumor recurrences and nerve injuries are common complications following surgery.

Previously reserved for treatment of unresectable lymphangiomas or in cases of tumor recurrence following surgery, intralesional sclerotherapy has gained popularity over recent years. Several studies using bleomycin and a newer agent OK-432 as sclerosants, have shown that this method of treatment produces favorable results compared to surgery.

Due to the nature of the lesion, which has a propensity to infiltrate tissue planes and encircle important neurovascular structures, complete excision is frequently impossible[3]. Multiple nonsurgical therapies have been proposed, including diathermy, cryotherapy, radiotherapy, fibrin glue, and percutaneous sclerotherapy. Intralesional

sclerotherapy has become a method of treatment for lymphangiomas in children. Various sclerosing agents have been used in the treatment of childhood lymphangiomas.

A retrospective clinical trial was conducted to evaluate the efficacy of intralesional bleomycin sclerotherapy (IBS) in the treatment of lymphangiomas in children and to determine the incidence of complications during the treatment.

METHODOLOGY

A prospective study was conducted by the Department of General Surgery of Mata Gujri Memorial Medical College & Lions Seva Kendra Hospital, Kishanganj, Bihar. Study was commenced after getting the ethical approval from the Institutional ethical committee. The period of data collection was 2 years that is from October 2019 to September 2021. The parents were informed about the study and a written consent was taken from them.

All patients coming to the department were included in the study. The exclusion criteria were lesions infiltrating the mediastinum, lesions around trachea, frank infection, and deep retroperitoneal lesions. All patients had a detailed clinical evaluation. Color Doppler ultrasonography (USG) of all patients was performed. The volume of lymphangiomas was calculated by the following formula- Length × breadth × depth × 0.52 cc 0.52 is (correction factor)

Based on color Doppler USG report, the lesions were classified as:

1. Lymphangioma simplex (composed of capillary sized thin-walled lymphatic channels)
2. Cystic lymphangioma or cystic hygroma
3. Cavernous lymphangioma (dilated lymphatic channel with a fibrous adventitial covering) (mixed forms also exist).

Procedure- 1 unit of Bleomycin is equivalent to 1 mg. The required dose was calculated as 0.5 mg/kg body weight, not exceeding 10 units at a time. The patient was then taken in O.T. and sedated either by oral chloral hydrate or intravenous (IV) diazepam[4]. The fluid of the lymphangioma was aspirated as much as possible with a 10 ml disposable syringe. After that, bleomycin was injected intra-lesionally in a ratio of 5:1 (aspirated volume: bleomycin volume). The patient was kept under observation till evening. If fever occurred, oral paracetamol was prescribed. Patients were called after 4 weeks for evaluation of the response in the proforma and clinical photograph. If needed, repeat color Doppler USG was performed for estimation of its volume and comparison with the previous USG. If regression was not complete, another dose of freshly reconstituted bleomycin was injected in the same manner. Bleomycin was stopped when the swelling disappeared clinically, on the basis of color Doppler USG, or there was no response or the swelling became stationary. The patients were subjected to surgery when there was no response or the swelling became stationary even after three to four injections.

The response was assessed clinically and on the basis of color Doppler USG as: excellent - complete regression without induration, or good - >50% regression, and poor - <50% regression.

RESULTS

During the study period of 2 years, 36 patients of lymphangioma were included in the study. 63.9% patients were seen before 1 year of age. Among the rest 13 patients, 7 patients presented between 1 to 2 years of age and 6 patients presented after 2 years. Of all, 75% of the cases that is 27 patients had cystic hygroma, 3 were cavernous, and 6 were of mixed type.

The neck region was the most common site with 25 (69.4%) patients, followed by face with 6 patients, 3 in axilla, 1 had in chest wall, and 1 in buttock and thigh.

Out of the 36 patients included in the study, 7 (19.4%) required single dose, 24 (66.7%) required two doses, 2 (5.6%) required three doses, 2 (5.6%) required four doses, and 1 (2.8%) required five doses of intralesional bleomycin. Lesions that could be aspirated completely required a smaller number of total doses because more bleomycin per unit surface area was available for action.

Table 1: Distribution of patients according to their type of lymphangioma and their response to intralesional bleomycin sclerotherapy

Type of lesion	Type of response		
	Excellent	Good	Poor
Cystic hygroma (N = 27)	3 (11.1%)	23 (85.2%)	1 (3.7%)
Cavernous (N = 3)	-	1 (33.3%)	2 (66.7%)
Mixed type (N = 6)	-	5 (83.3%)	1 (16.7%)
Overall (N = 36)	3 (8.3%)	29 (80.6%)	4 (11.1%)

Out of the 36 patients, 11 patients developed side effects [Figure 1].

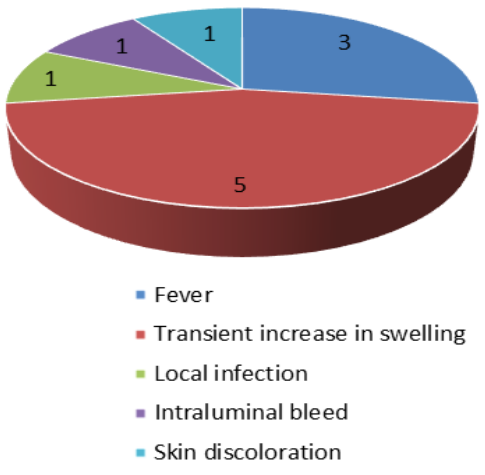

Figure 1: Pie diagram showing distribution of cases who showed side effects of the therapy

Out of the 29 patients in the good response group, 5 required surgery after completion of sclerotherapy for cosmetic purpose and all four patients of the poor response group underwent surgery.

DISCUSSION

The reported incidence of these tumors in the literature is quite variable, ranging from 1 in 1000 to 16000 live births[5,6]. Lymphangioma are thought to arise from a combination of the following: a failure of lymphatics to connect to the venous system, abnormal budding of lymphatic tissue, and sequestered lymphatic rests that retain their embryonic growth potential. These lymphatic rests can penetrate adjacent structures or dissect along fascial planes and eventually become canalized. These spaces retain their secretions and develop cystic components because of the lack of a venous outflow tract. The nature of the surrounding tissue determines whether the lymphangioma is capillary, cavernous, or cystic.

Cystic hygroma tend to form in loose areolar tissue, whereas capillary and cavernous forms of lymphangiomas tend to form in muscle[6]. At present, complete excision remains the treatment of choice for lymphangioma. For complex lymphangioma, complete removal may require multiple operations and may not be possible without damaging adjacent vital structures[7]. The complications from the surgical excision of a lymphangioma are related to the location and structures adjacent to the mass; these include damage to a neurovascular structure (including cranial nerves), chylous fistula, chylothorax, hemorrhage, and recurrence. Most recurrences occur within the first year but have been reported to occur as long as 10 years after excision. Unlike in hemangiomas, spontaneous resolution of lymphangioma is uncommon. Recurrence is rare when all gross disease is removed. If residual tissue is left behind, the expected recurrence rate is approximately 15%[8]. Postoperative complications, including recurrence, wound seromas, infection, and nerve damage, occur in 30% or more of cases. Recurrence rates vary depending on the complexity of the lesion and the completeness of excision.

Complete surgical resection may be difficult due to the presence of multiple loculations and extensive disease. Sclerotherapy provides a treatment option in such patients, offering a viable alternative to surgery in patients with macrocystic lymphatic malformations (LM). Although the popularity of sclerotherapy in the treatment of LM is growing, there is no consensus regarding the type of sclerosant. This is largely due, in part, to a lack of understanding on sclerosant mechanism of action[9].

Umezawa first developed bleomycin as an antitumor agent in 1966 and its mechanism of action was by inhibition of DNA synthesis[10]. This drug was also known to produce a sclerosing effect due to its direct action on the endothelial cells producing non-specific inflammatory reaction. Desired effect of sclerosis is achieved by local action of bleomycin, which depends on availability of drug per unit surface area of lesion[11,12].

Side effects of Bleomycin are fever, transient increase in size of swelling, hemorrhage, leukocytosis, infection, and pulmonary fibrosis. Pulmonary fibrosis has been associated with intravenous bleomycin administration exceeding the total cumulative dose of 400 mg. Bleomycin doses used in sclerotherapy are small in comparison, typically 1% to 5% of the lowest dose associated with possible pulmonary fibrosis[13]. We used 0.5 mg/kg of dose. Others have used it in doses ranging from 0.3 to 3 mg/kg[9,14,15]. In this study, complications were noted less as compared to other studies[14]. Others have noted fewer complications as compared to this study[16,17].

Although surgical excision has been considered to be treatment of choice by most of the surgeons but it is associated with tedious dissection along with lot of morbidity in the form of disfigurement and damage to vital structures and ugly scar. Therefore, sclerotherapy of lymphangioma has gained popularity during recent years.

In this prospective study, we found the response to bleomycin was satisfactory. Rozman *et al* noted excellent and good response in 63% (15/24) of lesions and 21% (5/24) patients[16]. Niramis *et al* noted 83% of response whereas Baskin *et al* noted about 95% of response, suggesting good activity of bleomycin for the purpose[9,14]. In short term follow up no recurrence was encountered. Others have also not found recurrence to be of much concern[15,17]. Although mortality has been reported,[14] it was not seen in this series.

CONCLUSION

Complications can also occur postoperatively or following sclerotherapy. Bleomycin injection (intralesional) is a safe and effective sclerosant for Lymphangioma Circumscriptum.

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