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COMPARISON OF INTRALESIONAL SCLEROTHRERAPY WITH BLEOMYCIN VS SODIUM TETRA DECYL SULPHATE IN LYMPHANGIOMA

Surgery

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ABSTRACT

The purpose of this study is to compare between the efficacy of Bleomycin and Sodium tetra decyl sulphate as intralesional sclerotherapy for lymphangioma.

Materials And Methods-This prospective study was done between Jan 2018 to Jan 2020. Total of 30 patients with lymphatic malformations at head neck, axilla, chest wall and lower limb were included. Group I was given intralesional injection of bleomycin and Group II was injected with STS. All the cases were evaluated for a minimum period of one and a maximum of 2 years.

Result-Efficacy of bleomycin was found to be superior to STS, when used as intralesional sclerotherapic agent. Most of the vascular lesions of group I resolved after first dose giving excellent response in 60% as compared to 40% in STS group.

Conclusion-Intralesional bleomycin and sodium tetradecyl sulphate are safe and effective sclerosing agents in lymphangiomas of children, but bleomycin is more effective in reducing the size of the lesions.

KEYWORDS

bleomycin lymphatic malformation STS microcystic macrocystic mixed

INTRODUCTION

In 1982 Mulliken and Glowacki published the classification of vascular anomalies on the basic of clinical and histopathological characteristics and this classification scheme has been adopted by International Society for the study vascular anomaly (ISSVA) [1,2]
Lymphatic malformations are congenital malformation of lympathatic system characterized by multiple communicating lymphatic channel and cystic space. Most common sites are head neck(75%), axilla(20%), inguinal region (2%), however they can occur anywhere in the body[3,4,5]

The macrocystic type are the largest cyst >2 cm in size and microcystic type are smaller in size <1cm and soft tissue engulfment. Mixed type have veno-lymphatic component. [2]

About 65% of lymphatic malformations are present at birth while the remainder become evident by the age of 2 years. [6]

Lymphatic malformations are benign lesion sudden increase in size may occur due to infection and heamorrhage which may cause compression of adjacent structures. Lymphatic malformation may cause head-neck deformities. Early treatment can prevent morbidity and aesthetic disfigurement. Treatment options for lymphatic malformations includes surgery, sclerotherapy, liposuction and laser[7]

Complete surgical excision is not always possible because they infiltrate nerves vessels and vital organs. Incomplete resection, recurrence, injury to vital structures, disfigurement due to surgical scars makes surgery less favourable options. To prevent complications due to surgery percutaneous sclerotherapy with agents including bleomycin OK-432, doxycycline, STS, alcohol has been proposed.
This is a comparative study between bleomycin and STS.

MATERIALS AND METHODS

This was the prospective study from January 2018 to January 2020 conducted in the department of Pediatric Surgery Nilratan Sircar Medical College & Hospital. Approval consent was taken from the ethical committee of hospital. The parents were informed and written consent was taken from them. All the children having lymphatic malformation macrocystic, microcystic and mixed on head neck, back and lower limb were included in the study. While lesions involving trachea, mediastinum and retroperitoneal were excluded.

All patients had detailed clinical evaluation, pre-treatment clinical photographs, digital X-ray chest PA view and USG colour Doppler to make the diagnosis and for follow up results. MRI scan were performed only in few patients.

The volume of lymphangioma was calculated by colour Doppler USG by using the following formulas:

Length* width * depth * 0.52 cc
where 0.52 is correction factor
[Length* width * depth * π/6]
= L* W * D * 0.52

Reduction in the lesion volume was estimated by substracting post treatment volume. The ratio reduction in the lesion volume was determined by dividing the amount of reduction in the lesion volume by pretreatment volume then multiplying by 100. Visual and symptomatic assessment was done by treating doctor with the help of follow-up digital photographs and parent assessment.

PROCEDURE

All the procedures were done in operation theatre under anaesthesia in aseptic way. Injection bleomycin was given at a dose of 0.5mg/kg body weight after reconstituent with normal saline. The fluid of lymphangioma was aspirated with 10ml disposable syringe as much as possible, the needle is left in-situ then the calculated dose of bleomycin with further dilution with 10ml normal saline injected intralesionally. Few patients were admitted for 24 hours. Others were kept under observation till evening. Patients were called in the OPD after 3 weeks to see response. Wherever required 2nd dose was given after 3 weeks interval. Monthly follow up was done to see response by taking digital photographs and USG colour Doppler.

The response is considered as:
Excellent >90% reduction of lesion
Good >50% reduction
Poor <20% reduction

Similarly intralesional STS was given at the dose of 1 to 2 ml of 2% solution at the interval of 4 weeks. Post operative syrup Antibiotic and analgesics given to all patients.

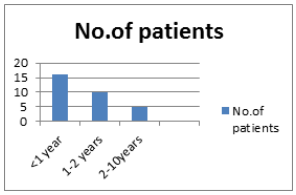
The patients were followed for period of 1-2 years after the last responding intralesional injection.

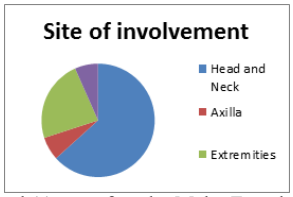
Both the groups were compared with the respect to clinical presentation, efficacy and side effects of sclerosants used.

RESULTS

We have studied 30 patients of macrocystic, microcystic and mixed type. Out of 30 patients, 15 patients were treated with intralesional bleomycin Group I and rest 15 patients with intralesional STS Group II.

The age range was from 2 month to 10 years. Out of which 16 patients presented before 1 year of age, 10 presented between 1-2 years and 5 patients presented between 2-10 years of age.





Out of 30 children 19 were male and 11 were female. Male: Female ratio is 1.7:1.

Most common site of lymphangioma head and neck n=19 (%), followed by axilla 2, extremities 7, trunk 2

There were 14 macrocystic lesions, 7 microcystic lesions and 9 mixed type lesions.

In group I, 50% cases bleomycin was used while other 50%, group II STS was used.

Response To Therapy:

In Group I, total no of patients were 15, where 7 were mixed type lesion, 1 was microcystic and 7 were macrocystic lesion. The response was 9 cases had excellent response, 4 cases were good and 2 cases had shown poor response.

Only 5 patients developed fever, 3 patients had transient increase in swelling, 2 patients developed intralesional bleed while 3 patients developed blister on palm and fingers. No systematic toxicity was noted in this period. All patients responded well with oral antibiotics and analgesic.

In Group II, rest 15 patients, where 7 were mixed type lesion, 6 was microcystic and 2 were macrocystic lesion. The response was 7 cases had excellent response, 4 cases were good and 5 cases had shown poor response.

Complications observed were 4 patients had fever, 1 had skin ulceration, 2 patients had intralesional bleed and 4 patients had transient increase in swelling. All responded well with oral antibiotics and analgesic.

In both the groups, macrocystic and mixed variety had excellent and good response. Poor response was seen in microcystic lesions. Bleomycin has better results then STS.

Follow-up- all patients in both the group were followed up in OPD at the interval of 2-3 months after giving last responding dose for a period of 1-2 years.

Patients having excellent response in both groups had no recurrence. Patients having good response had a fibrous tissue left as residue which also decreased and subsided by itself gradually. Patients having poor response underwent surgical intervention in the satisfactory results.

Table 2: Response To Therapy In Both The Groups

	EXCELLENT	GOOD	POOR
GROUP I (BLEOMYCIN)	9(60%)	4(26.67%)	2(13.33%)
GROUP II (STS)	6(40%)	4(26.67%)	5(33.33%)

Table 3: Complications Following Intralesional Injections In Both The Groups

COMPLICATIONS	GROUP I	GROUP II
Fever	5	4
Transient increase in lesion size	3	4
Intralesional bleed	3	2
Skin ulceration/ blister	3	1
Systematic toxicity	Nil	Nil

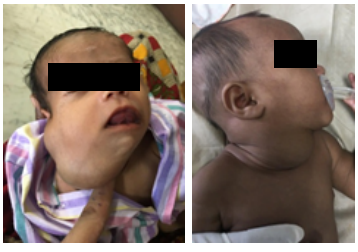


Fig1. Pre And 10months Post Op Image With Patient Treated With Intralesional Bleomycin

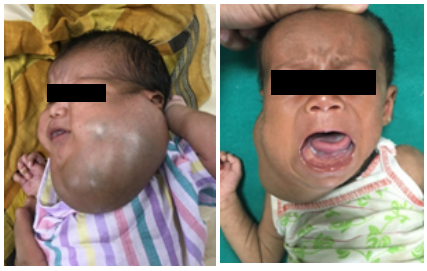


Fig2. Pre And 13 Months Post Op Image With Patient Treated With Intralesional Sts

DISCUSSION

Lymphatic malformations(LM) are abnormalities of lymphatic vessel morphogenesis, which presents mostly at birth and prevalence ranges from 1 in 1000 to 16,000 live births[7,8]The most common site for LM head and neck, followed by extremities and trunk. [2]The current literature suggest 75% occurrence of LM are of head and neck. Nearly 50% of LM are detected at the time of birth and 80-90% appears before 2 years.[9,10,11] which is similar to the findings of this study.

LM has been classified on the basis of size as macrocystic(>2cm), microcystic(<1cm) and mixed type. Macrocystic LM are mostly located in the head neck and upper trunk and microcystic LM are mostly located in the proximal extremities and trunk[12,13,14]

The nature of surrounding tissues determines the type of LM as capillary, cavernous or cystic. Cystic hygroma are seen in loose areolar tissue, while capillary and cavernous are found in muscles.

Since LM is a benign condition it rarely requires any intervention. The most frequent problem with LM is cosmetic disfigurement. Other problems may include pain and discomfort. They may also cause functional problems like compression of trachea,oesophagus. It may also cause infection, oozing and bleeding from the surface LM. It has been reported 35% bleeding and 71% with infection.[15] the infection is treated with antibiotics[16] Spontaneous regression has been reported in 15% of LM[6]

The diagnostic modalities of LM comprises of history, clinical presentation, physical findings, imaging and histology. Characterising a true LM apart from lymphatic venous malformation(LVM) can be challenging by imaging only. USG colour Doppler shows no flow in LM whereas venous malformation shows flow in 85% of LVM. Administration of gadolinium constrast in MRI enhances LVM unlike LM. [17,18,19]

Management of LM is challenging for a surgeon, as some of the LM total resection is not possible due to anatomical location, extent, involvement of the surrounding tissues and the skill of the surgeon.[20,21]In recent management of LM, sclerotherapy has been considered as the primary treatment of choice for LM. Studies has shown that sclerotherapy compared to surgical resection have less complications post-operatively and more efficient in resolving LM. There is a high recurrence rate of 15-35% with surgical resection.[22]

Mechanism of action of sclerotherapy is permanent disappearance of the vessels due to obliretation of the luminal endothelial cells which is subsequently replaced by fibrosis[23]. Sclerotherapy has a good response in macrocystic LM and has good potentiality in improving microcystic LM as well, but some microcystic LM requires a combined approach with surgical resection.

Different sclerosing agents has been used over years such as bleomycin, OK432, doxycycline, alcoholic solution of Zein(Ethibloc) and sodium tetradecyl sulphate(STS). Bleomycin is an anti-tumour agent, produced by the fermentation of streptomyces verticillus. Bleomycin causes single and double strand DNA breaks and inhibits DNA and RNA synthesis.[24] it was ued in the treatment of malignant pleural effusion and it caused marked interstitial pneumonia and pulmonary fibrosis. This sclerosing property was used for treating LM. The common side effects of bleomycin are local oedema and inflammation, allergy, flu-like symptoms, nail bed changes, hair loss and skin pigmentation.

In this study Chest Xray was done prior to sclerotherapy ,bleomycin

provided good results in most cases. Larger cysts communicate well with one another making it favourable for sclerotherapy after aspiration of LM. A study conducted by Hellman et al [25] suggested that LM with haemorrhagic cysts appeared to have greater response to percutaneous sclerotherapy.

Intralesional bleomycin was used by Oxford et al[26] in 16 patients in cystic hygroma and excellent response was seen in 44%. Good response in more than 50% and poor or no response in 12%.While in this study excellent response to intralesional bleomycin was 60 %, good response 26% and poor response 13%.

Sodium tetradecyl sulphate(STS) another sclerosing agent which is commonly used. Sodium tetradecyl sulphate, 3 % STS (Sotradecol® [27], Fibro-Vein®) [28], has been widely used as sclerosing agent since 1946.STS causes intimal inflammation, thrombus formation and permanent obliteration. Minkow et al[29] used 0.1-0.5 ml of 3% STS in oral haemangioma and obtained satisfactory results with minimal adverse effect in their study. Our study findings were with intralesional STS 40% with excellent response, 26% with good response while 33% had poor response.

In study conducted Khandpur S and Sharma V K with 3% STS in 13 patients with VLM good response was seen in 11 cases after 4 injections and with no response in 2 cases. Complications were similar to our study like blister, local edema and scarring.

The first case of lymphangioma was treated by sclerotherapy was in 1933 using sodium morrhuate, complete tumour regression was seen within six weeks, since then many other sclerosing agents were used.

In our study we found that macrocystic and mixed type of LM responded well to the treatment after aspiration of the cyst in both the groups. While microcystic LM were difficult to treat as they left behind microscopic lymphatic channels. However, the reduction in size was cosmetically acceptable.

No serious complications were seen in both the groups. Most patients complained of local oedema, mild skin erythema and fever. In group I 5 patients suffered post-injection fever as compared to 4 patients in group II. Other complications included transient increases in size, intralesional bleed and skin ulceration the incident were comparatively similar in both the groups.Bleomycin and STS both are effective sclerosing agent in LM, but it revealed that bleomycin is more effective in children below 1 year.

CONCLUSION

To conclude our study, both the sclerosing agent bleomycin and sodium tetradecyl sulphate are equally effective in regressing the size of lymphatic malformation. The response was better observed in children below 1 year of age.

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