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Efficacy of Intralesional Bleomycin in Low Flow Vascular Malformations of Head and Neck Region

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Abstract

Background: Vascular malformations arise due to abnormal development of the vascular system. They can be venous, lymphatic, capillary or mixed. Several treatment options are available such as sclerosing agents, surgical excision, laser therapy or a combination of these. This study aimed to evaluate the efficacy of intralesional bleomycin in vascular malformations of the head and neck region, not amenable to surgical excision.

Material and Methods: The inclusion criteria were patients above 1 year of age, with low flow vascular malformation (venous, lymphatic and mixed) of head and neck region, diagnosed clinically and with an ultrasound, and are not amenable to surgical resection. Capillary malformations/port-wine stains and patients with deranged liver function tests were not included in the study.

The demographic data and initial dimensions of the lesions were noted. A total of 51 patients with these lesions were included in the study. A minimum of 3 and maximum 6 injections were given at a dose of 0.5 mg/kg. The reduction in size of the lesions was noted at each visit. Complications, if any, were also noted. Treatment was terminated once complete reduction of the swelling was achieved or if there was no change in size four weeks after last injection and in case of any adverse reaction.

Result: It was noted that 8 patients showed 90% to 100% reduction in height, 16 patients had 80% to 90% reduction, 14 had 70% to 80% reduction and 13 had 60% to 70% reduction. The consistency also changed from soft/cystic to firm. There were no major complications of the procedure.

Conclusion: Bleomycin is a safe and effective drug for intralesional use in vascular malformations of the head and neck region.

Keywords: Vascular malformation; Bleomycin; Sclerotherapy

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Introduction

Vascular Malformations (VMs) result from anomalies occurring during embryological development of the vascular system [1]. They can be of lymphatic, venous, arteriovenous, capillary, or combined origin [2].

The International Society of Study of Vascular Anomalies (ISSVA) classification identified these benign lesions as separate from hemangiomas and further divided vascular malformation into different groups, each having distinctive clinical behaviors and cellular features [3,4]. They can be further divided into low flow and high flow according to the flow characteristics and anatomical structure. Low Flow Vascular Malformations (LFVMs) can be venous, capillary, lymphatic, and mixed malformations.

Venous malformations present as soft, ill-defined swellings that blanch readily with compression, giving it commonly known "bag of worms" feel. Overlying skin has a purple-blue discoloration due to large and irregular blood-filled channels in the deep dermis and subcutaneous tissue. They are asymptomatic and there is no palpable thrill or audible bruit. The lesion may increase in size and darken during exertion or in dependent position; they may also enlarge with compression of the ipsilateral jugular vein and valsalva manoeuvre. Venous malformations are congenital though they may not clinically present at that time. They tend to grow with age and may expand rapidly during puberty, pregnancy and hormonal change. They are common in skin, lips, oral mucosa, masseter and mandible [5].

Lymphatic malformations consist of multiple dilated lymphatic cysts that are distinct from normal lymphatic channels. They are lined by a single endothelial layer and contain a thin, tan,

proteinaceous fluid. More than 75% of these malformations occur in the head and neck region. They can be classified radiologically as macrocystic (cysts >2 cm^3), microcystic (cysts <2 cm^3) or mixed [6].

Capillary malformations are known commonly as port-wine stain. They are common in the head and neck region. Majority is in the distribution of the trigeminal nerve, most commonly in V1 and V2 [6].

Various treatment options are available for treatment of these lesions but no single modality has been found to be ideal [7]. Conservative measures are observation and compression garments [8]. These are usually of benefit in small lesions that are not creating any functional or cosmetic problem. Role of these measures is further reduced in malformations of the head and neck region. Surgical management of large lesions is based on de-bulking procedure, except for localized ones, where complete excision can be done [7]. Complete surgical excision, is rarely performed in head and neck lesions due to high risk of nerve injury and difficult dissection [9]. Hence, now it has been grossly replaced by sclerotherapy agents or combination treatment [10], although the ideal agent and overall management are yet to be ascertained.

Sclerosing agents commonly used are absolute ethanol, 5% ethanolamine oleate, 3% polidocanol, OK-432, pingyangmycin and bleomycin. New preparations and formulations of sclerotic agents are continuously evolving, such as foam preparations (sodiumtetradecyl sulphate and polidocanol) [11-13].

Successful treatment of these lesions consists of multidisciplinary approaches such as surgical procedures, embolization *via* interventional radiology (for high flow VMs), sclerosing therapy, laser therapy etc.

Material and Methods

This is a prospective study conducted at a tertiary care hospital over a 5 year period from 2015 to 2020. Informed written consent was taken for all patients. Due consent was also taken for use of clinical photographs for publication and academic purposes.

The inclusion criteria were as follows, patients above 1 year of age, with low flow vascular malformation (venous, lymphatic and mixed) of head and neck region, diagnosed clinically and with an ultrasound, and are not amenable to surgical resection. Capillary malformations/ port-wine stains and patients with deranged liver function tests were not included in the study.

Injection bleomycin at a dose of 0.5 mg/kg was given intralesionally over 2 min to 3 min. Dilution with normal saline was done according to the size of the lesion, and ranged from 1 ml to 10 ml. The lesion was first emptied, then intralesional, intravascular injection was given under sedation in adults and under general anesthesia in children. Pressure was given for 48 h with elastic tape, following which dressing was removed. Patients were admitted for 24 h for observation during which injectable pain killers were given. No steroid was used in the study.

Patients were called after 3 days and then at 4 weeks for review with a fresh liver function test report at both visits. At 4 weeks, lesion was assessed for length, breadth and height. Change in consistency from cystic/soft to firm was also noted. Local reactions (inflammation, necrosis, and ulceration), and any adverse reaction were observed and recorded. If required next dose was administered.

Treatment was terminated once complete reduction of the swelling was achieved or if there was no change in size four weeks after last injection and incase of any adverse reaction. If there was deranged liver function, injection was administered after the liver functions became normal. Results were divided into four groups, Group 1, 90% to 100% reduction, Group 2, 80% to 90% reduction, Group 3, 70% to 80% reduction and Group 4, 60% to 70% reduction.

Results

Fifty one patients with low flow vascular malformations of head and neck region were included in the study. There were 28 males and 23 females. Age of the patients ranged from 5 to 45 years, average age was 21.5 years. There 14 venous, 13 lymphatic and 24 mixed vascular malformations. Number of doses ranged from three to six. Forty two patients received 5 doses, 7 received 6 doses and 2 received 3 doses. Two patients with intraoral lesions developed ulceration and necrosis, and finally had complete clinical resolution after three doses. Three patients reported hyperpigmentation of the chest, following which therapy was discontinued. Spontaneous resolution of this complication occurred over a period of 3 months.

There was increase in alkaline phosphatase levels (200 IU/l to 500 IU/l) of all patients at the 3rd day visit (normal range: 54 IU/l to 144 IU/l). Serum bilirubin, alanine transaminase and aspartame transaminase levels remained normal. The deranged alkaline phosphatase levels became normal by the 4th week visit of the patient, so therapy was continued. No pulmonary complications were noted in any of the patients Length, breadth and height of the lesion were noted at each visit. Since change in height was the most significant, percentage change in height at first and last visit was noted. Change in consistency from cystic/soft to firm was noted in all patients. Bleomycin causes sclerosis of the endothelium of the involved vasculature causing the lesion to become firm.

Results were divided into four groups, 90% to 100% reduction was seen in 8 patients (Group 1), 80% to 90% reduction in 16 patients (Group 2), 70% to 80% reduction in 14 (Group 3) and 60% to 70% reduction was seen in 13 patients (Group 4), as given in Table 1. Better response was seen in smaller lesions, complete resolution was seen in 4 cases, lesions were less than 5 cm. This can be attributed to higher concentration of the drug being injected as the dilution volume used was less.

Follow up period ranged from 6 months to 4.5 years. Patients were asked to attend OPD on a 3 monthly basis thereafter; no increase in size was noted in any of the patients in the follow up visits.

Discussion

Bleomycin, sodium tetradecyl sulfate, polidocanol, and pure ethanol are the various agents used for intralesional sclerotherapy in low-flow VMs.

Bleomycin interrupts cell proliferation by snipping the Deoxyribonucleic Acid (DNA) chain during S stage of cell cycle. Bleomycin was discovered in 1966 as an antineoplastic antibiotic.

Table 1:

Group	Percentage change in height	Number of patients
Group 1	90-100	8
Group 2	80-90	16
Group 3	70-80	14
Group 4	60-70	13

This drug acts by inhibiting DNA synthesis and also by sclerosing the vascular endothelium [13].

In a study by Mohan et al. [14] intralesional bleomycin was used in management of low flow vascular malformations in children [14]. More than 50% improvement was seen in 91% of patients; 28% of the total cohort demonstrated a complete response. One patient in the venous malformation group only demonstrated a fair response following four treatments, having missed several outpatient appointments and follow-up during the treatment course. Our study showed comparable results with all patients having more than 60% response and 8 patients showing nearly complete resolution with more than 90% reduction.

Muir et al. [4] reported complete resolution or significant improvement in 80% of all patients treated. Two of their 95 patients also reported superficial ulceration [4]. These findings were similar to ours, two of our patients who had intraoral lesions developed necrosis and ulceration. These local reactions subsided within 4 weeks and next dose was given. Complete clinical resolution of the lesion was seen in these two patients after 3 doses of bleomycin. This could be because these lesions were more superficial, intramucosal as compared to others which were intramuscular.

In a meta-analysis by Horbach et al. [15] good to excellent size reduction was reported in 84 percent of lymphatic and 87 percent of venous malformations [15]. This was at least 50% reduction in most studies included in the analysis. These results were also in accordance with our study.

Sainsbury et al. [16] report 0.8% incidence of hyperpigmentation on the chest. They noticed that this pigmentation eventually faded over 3 to 4 months in all cases [16]. Three of our patients reported this complication which resolved on its own, it was noticed after four doses. The cause of this hyperpigmentation is because of post-inflammatory pigmentary incontinence, reduced epidermal turnover increasing the keratinocyte and melanocyte contact period, melanocytic arrest in the pigment synthesis phase and fixed drug eruption due to direct keratinocytic damage by bleomycin [15].

Other sclerotherapy agents include sodium tetradecyl sulfate, polidocanol, and pure ethanol [10]. Sodium Tetradecyl Sulfate (STS) and polidocanol cause endothelial damage leading to thrombosis and fibrosis of the malformation by interfering with cell surface lipids. There is possibility of recurrence due to revascularization of treated lesions. Complications like blindness and anaphylactic shock have also been reported in treatment of extensive lesions with STS. Intralesional ethanol administration causes denaturing of proteins, vessel wall necrosis resulting in again thrombosis and fibrosis of the vascular malformation. Use of ethanol has been associated with local side effects like trophic cutaneous scars, superficial skin necrosis, skin blisters, bleeding from puncture site. Systemic complications such as cardiac arrhythmia, respiratory depression, hypoglycemia, and rhabdomyolysis have also been reported. Bleomycin reports lesser local and systemic complications when used intralesionally. As it has been found to be non traceable in the bloodstream 10 h to 24 h after injection. In our study also it has been found safe to use in low flow vascular malformations.

Conclusion

Intralesional bleomycin is an effective sclerosing agent for low flow vascular malformations. There are no major adverse reactions associated with it. It can be safely used as a treatment modality for these lesions.

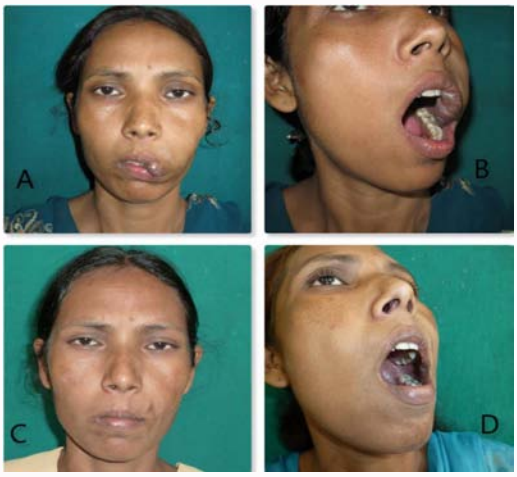

Figure 1: A 35 year old, female patient with vascular malformation of left upper lip with intraoral extension, size 6 cm × 5 cm × 6 cm. A) Front view, B) intraoral view, after 3 doses there was complete resolution. A) Front view, B) intraoral view (Group 1: 100% reduction).

Case 1

A 35 year old, female patient presented to the old with low flow vascular malformation involving left upper lip extending intraorally, of size 6 cm × 5 cm × 6 cm. She was given three doses 30 IU (weight 60 kg) of intralesional bleomycin diluted in 5 ml of normal saline. She developed necrosis of the lesion following third injection which healed with conservative line of treatment in two weeks. She was called after another two weeks and by that time as there was complete resolution of lesion; no further injection was given to patient (Figure 1).

Case 2

A 38 year old, male patient presented to the OPD with vascular malformation left cheek and lips of size 9 cm × 6 cm × 6 cm. He was given 4 doses of intralesional bleomycin at a dose of 32.5 IU (weight 65 kg) diluted in 10 ml of normal saline. After 3 doses size reduced to 9 cm × 5 cm × 1 cm. After 4 weeks, one more injection was given

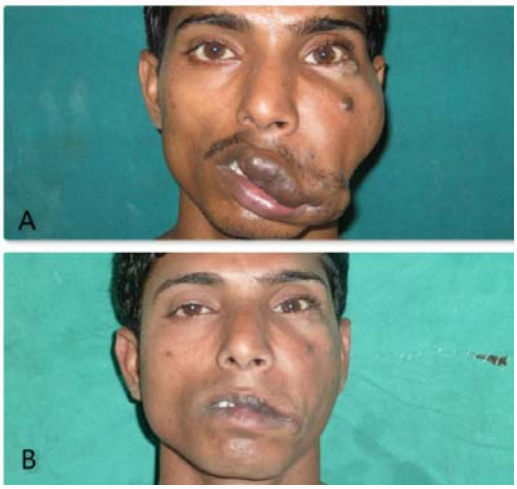

Figure 2: A 38 year old, male patient with vascular malformation left cheek and lips of size 9 cm × 6 cm × 6 cm, after 4 doses size reduced to 9 cm × 5 cm × 1 cm. A) At 1st visit B) after 4 doses (Group 2: 83.3% reduction).

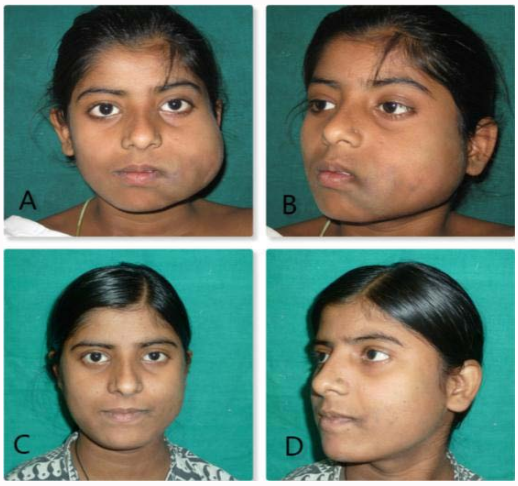

Figure 3: A 23 year old, female patient with vascular malformation left cheek of size 8 cm × 7 cm × 8 cm at 1st visit A) Front view, B) side view. After 5 doses size reduced to 8 cm × 7 cm × 1 cm, C) Front view, D) side view (Group 2: 87.5% reduction).

but there was no change in size at 4 weeks following injection so no further injections were given to the patient (Figure 2).

Case 3

A 23 year old, female patient presented to the OPD with low flow vascular malformation of the left cheek of size 8 cm × 7 cm × 8 cm. She was given five doses of intralesional bleomycin, 25 IU (weight 50 kg) diluted in 8 ml normal saline at four weekly intervals. After 5 doses size reduced to 8 cm × 7 cm × 1 cm (Figure 3).

Case 4

A 20 year female, presented to the OPD with vascular malformation right cheek of size 12 cm × 8 cm × 8 cm. Calculated dose of bleomycin was 22.5 IU (weight 45 kg) diluted in 10 ml of normal saline. Patient received 5 doses after which size reduced to 12 cm × 8 cm × 2 cm (Figure 4).

Case 5

A 7 year old, female patient presented to the OPD with vascular malformation left cheek of size 10 cm × 8 cm × 8 cm. She received

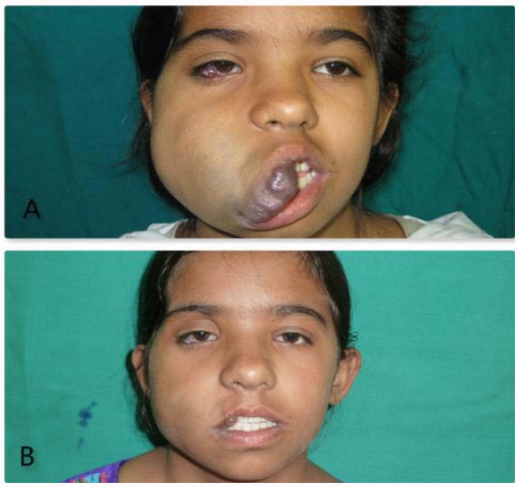

Figure 4: A 20 year female, patient with vascular malformation right cheek of size 12 cm × 8 cm × 8 cm, after 5 doses size reduced to 12 cm × 8 cm × 2 cm. A) At 1st visit, B) after 5 doses (group 3:75% reduction).

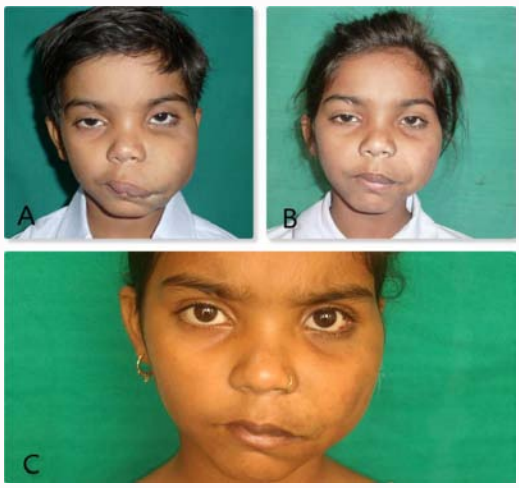

Figure 5: A 7 year old, female patient with vascular malformation left cheek of size 10 cm × 8 cm × 8 cm, after 4 doses size reduced to 10 cm × 8 cm × 3 cm A) at 1st visit. B) After 4 doses, C) at 4.5 years follow up (Group 4:62.5% reduction).

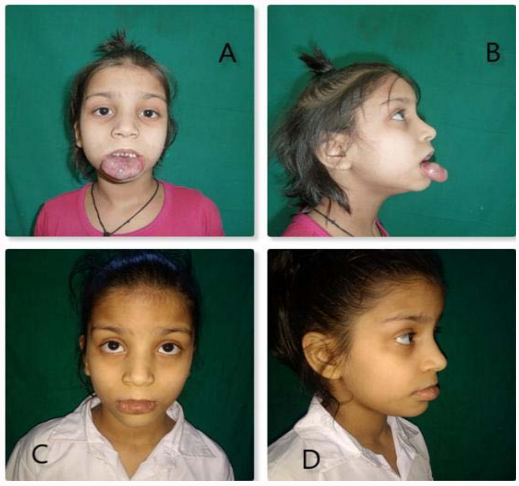

Figure 6: Eight year old, female patients with vascular malformation lower lip of size 6 cm × 5 cm × 5 cm at 1st visit A) Front view, B) Side view. After 5 doses size reduced to 4 cm × 4 cm × 2 cm, C) front view, D) side view (group 4:60% reduction).

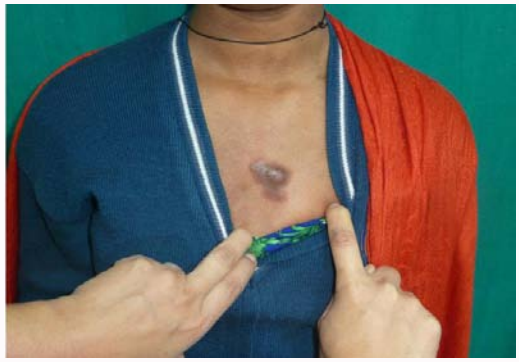

Figure 7: Hyperpigmentation on the chest in an 18 year old female patient after 4 doses of intralesional bleomycin.

intralesional bleomycin at a dose of 11 IU (weight 22 kg) diluted in 8 ml of normal saline. After 4 doses size reduced to 10 cm × 8 cm × 3 cm, A at 1st visit. B. She had the longest follow up in the study, till she

was more than 11 years of age. There was no increase in size of the lesion in subsequent years (Figure 5).

Case 6

An 8 year old, female patient with vascular malformation lower lip of size 6 cm × 5 cm × 5 cm presented to the OPD. Patient had been refused admission in schools due to fear of injury. She was planned for intralesional bleomycin at a dose of 12.5 IU (weight 25 kg) diluted in 5 ml normal saline. After 5 doses size reduced to 4 cm × 4 cm × 2 cm (Figure 6, 7).

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