



Study of intralesional Bleomycin sclerotherapy in hemangiomas

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Abstract

Introduction: Hemangiomas are the most common tumors in infancy and are also the most common tumors of the head and neck in infancy. The incidence of Hemangiomas in the first 3 days of life is 1.1% to 2.6% and increases to 8.7% to 12.7% between the ages of 1 month and 1 year of life. We used Bleomycin sclerosent in the treatment of Hemangiomas and effect of intralesional Bleomycin sclerotherapy in Hemangiomas was studied.

Methods: For Intralesional Bleomycin Sclerotherapy, the lesion was confirmed by Doppler guided ultrasonography so as to know exact location, size of the lesion. The suitable puncture pathway was also to be determined through multiple scanning. A puncture needle was pricked into lesions under ultrasound guidance. After multiple scanning and the aspiration of the blood confirmed its intralesional position, the injection of bleomycin A5 prepared with 5 ml of lignocaine 2%, filled in the externally connected syringe, was carried out through the inspection of ultrasonography. A multi-point injection was used so as to uniformly distribute bleomycin A5 in the lesion area.

Results: 50 patients with peripheral hemangiomas were studied. Nearly all the patients of Hemangiomas who underwent sclerotherapy responded to treatment and response of therapy was assessed clinically and on basis of USG color Doppler according to the Weidong Shou standards into cured, basically cured, improved and ineffective. The result was, 42 patients with Hemangiomas were cured (84%), 6 patients basically cured (12%), 2 patients improved (4%) and none ineffective.

Conclusion: 50 patients with Hemangiomas underwent sclerotherapy by intralesional Bleomycin with a cured response in 84%.

Keywords: Bleomycin, Hemangioms, Sclerotherapy, Doppler USG.

Introduction

Hemangiomas and vascular malformations are quite common but over looked entity. Not much

attention has really been paid regarding the role of imaging modalities, in the detection and management of vascular malformations and the

importance of sclerotherapy by Bleomycin in the management of Hemangiomas. Literature is scarce regarding this topic in Indian subcontinent. Almost all congenital vascular malformations affect the skin and are evident from birth or become so during the first few weeks of life. Up to almost 12% of newborns are thought to have a Hemangioma although most of these disappear during the first year of life. Hemangiomas appear during the first week of life, whereas vascular malformations are always present from birth though they might not be apparent. Hemangiomas usually regress spontaneously over time whereas vascular malformations never disappear and often grow during a person's lifetime.

Hemangiomas are the most common tumors of infancy and are also the most common tumors of the head and neck in infancy. The incidence of Hemangiomas in the first 3 days of life is 1.1% to 2.6% and increases to 8.7% to 12.7% between the ages of 1 month and 1 year of life. Hemangiomas are more frequent in girls than boys, ranging from a 3:1 to 5:1 ratio. They are thought to be more common in white patients than in blacks. They are found to be more common in the head and neck region, followed by the trunk and then the extremities.

Multiple imaging modalities should be used to evaluate the characteristics of the lesion, such as size, flow velocity, flow direction, relation to the surrounding structures (vessels, muscles, nerve, bone, skin), and lesion contents. Doppler ultrasonography is considered to be the most cost-effective imaging technique for the evaluation of Hemangiomas.

Besides sclerotherapy and surgery, a broad variety of techniques are described in the literature: irradiation, electrocoagulation, cryotherapy, intra-vascular magnesium or copper needles, laser and compression. Historically, surgical treatment was often proposed. However, especially in the therapy of diffuse or large lesions, surgery is of limited success.

Material and Method

This study was carried out in Department of General Surgery, university hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi in collaboration with Department of Immunology and Pathology and Department of Radiodiagnosis IMS, BHU.

Total 50 patients were selected from Department of General Surgery included both inpatients and outpatients. The period of study was from October 2014 to July 2017. It was a prospective Non – Randomised Case Control study.

Inclusion criteria were all male/ non-pregnant females with peripheral hemangiomas size <10 cm, confirmed by any either imaging modality irrespective of age. Patients with known lung disease, hypertension, kidney disease, vascular malformations other than Hemangioma, size >10 cm, any including bleomycin known drug allergy and pregnant females were excluded from study.

USG color doppler of all the patients were done and size and flow of lesion was noted. Routine investigations like Chest X-ray, Renal Profile, CBC and Coagulation Profile were also done to rule out any morbidity. CT or MR angiography was done in few patients to confirm diagnosis.

Prior to procedure, analgesia and anti-allergic is given in form of pentazocine (Inj Fortwin) and promethazine hydrochloride to prevent hypersensitivity, anti-emetic (Inj Ondem). First, the lesion was again confirmed by Doppler ultrasonography so as to know exact location, size of the lesion. After multiple scanning and the aspiration of the blood confirmed its intralesional position, the injection Bleomycin A5 prepared with 5 ml of lignocaine 2%, filled in the externally connected syringe, was infiltrated under ultrasound guidance. Dose of Bleomycin used was 0.5 unit/kg body weight not exceeding 15 units in each sitting. Patients were followed 2 weekly and lesion was assessed again both clinically and using USG color Doppler and if required another dose of freshly prepared USG guided intralesional Bleomycin injected to maximum of 3 doses at 2 weeks interval.

Response was assessed clinically and on basis of USG color doppler according to the Weidong Shou standards in-

1. **Cured**- Lesions disappear completely and color of sin and mucosa are normal without functional disturbance. No recurrence has been observed on follow up visit.
2. **Basically Cured**- Lesions disappear basically. The color of skin and mucosa are normal or pigmentary lightly without functional disturbance. The appearance is asymmetrical and patient needs observing.
3. **Improved**- The reduction of lesion is more than 50%, but the lesion did not disappear completely and needed other treatment or surgery.
4. **Invalid**- The reduction of lesion is less than 50% after 3 cycles of treatment.

Observation and Result

This study was carried out in 50 patients. In our study majority of the cases were less than 40 yrs (92%), half of them were between age group 11-20 years. Only 4 cases were above 40 years age, higher in males (58%) when compared to females (42%). Majority of patients were below 20 years in both sex i.e. 58.6% male and 47.7% female. 90% were located in head & neck region and limbs. Of 50 patients, 16 Hemangiomas were present in head and neck (32%), 18 in lower limb

(36%), 13 in upper limb (26%), 2 over chest wall (4%) and 1 in back (2%). Swelling was the presenting complaint in all the patients followed by pain in 26 patients (52%), pain was mild grade and dull aching type. Color Doppler was used as a primary modality for diagnosis and MR angiography was done in 7 out of 50 patients (14%) and Plain CT or CT angiography in 4 out of 50 patients (8%) to better delineate the lesion.

Median size of lesion before injection was 3.7150, median size after 1st dose was 2.2200 (p<0.001), median size after 2nd dose was 1.6300 (p=0.012), median size after 3rd dose was 3.000 (p=0.157).

Table 1: Median reduction in size of lesion after sclerotherapy

Size	Median	P-value
Size before Treatment	3.7150 (2.1750-5.6250)	-
Size after 1 st Dose	2.2200 (1.5600-3.6750)	<0.001
Size after 2 nd Dose	1.6300 (1.2850-3.2500)	0.012
Size after 3 rd Dose	3.000 (2.400-3.600)	0.157

26 out of 50 patients were given single dose of intralesional Bleomycin injection (52%), 16 were given two doses (32%), 6 were given 3 doses (12%) and only 2 required >3 doses (4%) but with incomplete response signifying treatment failure.

All the patients after completion of treatment were classified according to Weidong Shou standards, 42 out of 50 patients were cured (84%), 6 out of 50 patients were basically cured (12%), 2 out of 50 patients were improved (4%).

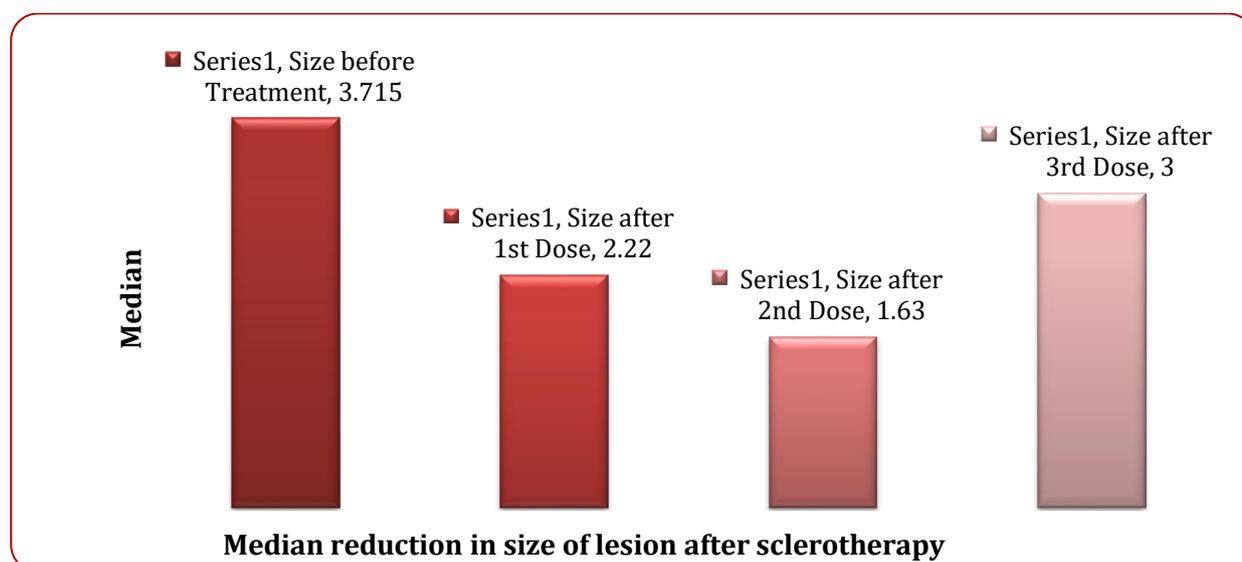


Table 2: Classification of patients according to response to treatment

Response	No. of Patients	Percentage
Cured	42	84.0
Basically cured	6	12.0
Improved	2	4.0
Total	50	100.0

The study found that the smaller and superficial lesions responded well to therapy and required

less number of doses as compared to larger and deeper seated lesions.

Table 3: Comparison of size of lesion with response to treatment

	Size (Median, IQR)				p-value		
	Before treatment	1 st dose	2 nd dose	3 rd dose	Before treatment vs 1 st dose	Before treatment vs 2 nd dose	Before treatment vs 3 rd dose
Cured	3.25 (2.00-4.77)	1.92 (0.93-2.23)	0.98 (0.98-0.98)	-	<0.001	<0.001	-
Basically Cured	6.25 (5.32-7.87)	3.65 (3.25-4.20)	1.60 (1.35-1.93)	-	0.028	0.043	-
Improved	9.40 (8.80-10.00)	5.50 (4.80-6.20)	4.00 (3.60-4.40)	3.00 (2.400-3.60)	0.180	0.180	0.157

Table 4: Classification of patients according to response to treatment

Response	No. of Patients	Percentage
Cured	42	84.0
Basically cured	6	12.0
Improved	2	4.0
Total	50	100.0

Table 5: Comparison of size of lesion with response to treatment

	Size (Median, IQR)				p-value		
	Pre treatment	1 st dose	2 nd dose	3 rd dose	Pre treatment vs 1 st dose	Pre treatment vs 2 nd dose	Pre treatment vs 3 rd dose
Cured	3.25 (2.00-4.77)	1.92 (0.93-2.23)	0.98 (0.98-0.98)	-	<0.001	<0.001	-
Basically Cured	6.25 (5.32-7.87)	3.65 (3.25-4.20)	1.60 (1.35-1.93)	-	0.028	0.043	-
Improved	9.40 (8.80-10.00)	5.50 (4.80-6.20)	4.00 (3.60-4.40)	3.00 (2.400-3.60)	0.180	0.180	0.157

Table 6: Complications observed during intralesional Bleomycin sclerotherapy

Complication	No. of Patients (N=50)	Percentage
Local swelling	46	92.0
Hyperpigmentation/Erythema	36	72.0
Momentary Dizziness	2	4.0
Tenderness	3	6.0
Ulceration	1	2.0
Cellulitis	1	2.0

Discussion

Vascular anomalies are among the most common congenital abnormalities in infants and children. Historically, the treatment of these lesions has been impeded by confusing terminology and lack of a precise classification system. The current

classification system is based on the landmark investigation by Mulliken and Glowacki published in 1982, we now recognize 2 main types of vascular anomalies: vascular tumors and vascular malformations⁽¹⁾. The management of vascular anomalies is a dynamic and rapidly developing

subspecialty, which requires interdisciplinary collaboration and multidisciplinary intervention. Majority of the patients who presented to us were less than 40 yrs of age Marler et al, (2010) reported majority of vascular tumors were between 2 yrs to 14 years & vascular malformation to be between 4 yrs & 15⁽²⁾. Juan caberra et al, (2003) stated the mean age is 26 years in venous malformations⁽³⁾. P. Redondo et al, (2009) stated the mean age was 30.5 in venous malformations⁽⁴⁾. In most of the series the patients presented at the early age but because of the majority of the Indian population belong to rural areas & because the transport facility is scarce so the patients present at the later age group.

In our study 58% of Hemangiomas were male and 42% were female. Erin et al, (2010) stated 61 % of all patients were females P. Redondo et al, (2009) stated that 54 % of venous malformations were formed by males & 46% was formed by females^(4,5). Enjolras et al, (2004) stated that no gender prevalence was noticed in their study⁽⁶⁾. Marler et al, (2010) stated a female preponderance noted in both vascular malformations & Hemangiomas⁽²⁾. Most of the series the females predominated but in our series because of the customary & the social customs females do not present in the hospital until & unless there is a significant problem.

In our study 38% of Hemangiomas were present on lower limb region, followed by head and neck region in 32%, upper limb 22%, trunk & back 6%. Erin et al, (2004) reported a predominance of head & neck lesions in both Hemangiomas & vascular malformations 31%, followed by lower limb 18%⁽⁴⁾. Enjolras et al, (2004) reported AV Malformations in cephalic presentation in 70%^(6,7). So in most of the series head & neck and lower limb formed the main bulk of the disease similar to our series.

In our study, USG guided intralesional Bleomycin sclerotherapy was used as treatment modality. All 50 patients received intralesional Bleomycin sclerotherapy. Gangopadhaya et al (2010) states that surgery is used for residual masses persisting

after medication especially for cosmetic reasons⁽⁸⁾. Excision during proliferative phase is not recommended due to excessive bleeding nature of Hemangioma. McHeik et al, (2005) reported excisional surgery is mainly utilized for removal of residual fibrofatty tissue and scar⁽⁹⁾. In a study by Hou et al (2010) evaluate the therapeutic outcome of ultrasound-guided intralesional injection of Bleomycin A5 on treatment of venous malformation (VM) in cervical-facial region in seventy-five patients (32 male, 43 female⁽¹⁰⁾. According to criteria of therapeutic outcome, their results showed cured in 42 patients (84%), basically cured in 10 patients (13.33%), improved in two patients (2.67%), and none ineffective, very similar to our result. In a prospective study conducted by Hassan et al (2013) of 75 patients received bleomycin, Complete resolution (cured) occurred in 18 (24%) patients, marked improvement in 35 (47%) patients, mild improvement in 14 (18.5%) patients, and no cure in 8 (10.5%) cases⁽¹¹⁾. In another prospective study conducted by Muir et al (2004) showed complete resolution or significant improvement in 80% of patients treated⁽¹²⁾. Zhang et al (2005) reported 84% cured, 13.33% basically cured, 2.67% improved, and none ineffective result in 1335 patients treated with usg guided bleomycin therapy⁽¹³⁾. Although their study was confined to cervico-facial Hemangiomas but the results were very similar to our study.

In our study, complications like local swelling following the procedure was seen in 46 patients (92%), which disappeared by itself without needing any special treatment in 2-3 days, 36 patients developed hyperpigmentation at injection site (72%), which resolved by itself in 2 weeks without needing any special treatment, 2 patients had tenderness post injection at injection site (4%), which got relieved with 1-2 dose of analgesic, 2 patients had momentary dizziness after injection (4%), but felt better within 15 minutes of treatment, 1 patient developed ulceration at injection site (2%), and treated with incision and drainage and antibiotic coverage for 2

weeks, 1 patient developed cellulitis post treatment (2%), treated with course of antibiotics and sumag dressing. None patients had anaphylactic shock, GI symptoms, fever, pulmonary fibrosis or any other systemic or local complication after therapy.

Hou et al (2010) concluded that intralesional injection of Bleomycin A5 establishes a promisingly effect way for patients suffering from VM in the cervical-facial region under ultrasound guidance and has a low complication rate.

Muir et al (2004) concluded that Intralesional Bleomycin is an effective treatment in haemangiomas and vascular malformation lesions, obviating the need for invasive primary surgery or systemic treatment regimens in 80% of cases.

Hassan et al (2013) also concluded that intralesional Bleomycin injection is an effective and a safe method for treatment of Hemangiomas and vascular malformations, decreasing the need for invasive primary surgery or systemic treatment in 71% of cases and have a low complication rate.

Conclusion

In this study 50 Hemangioma patients were studied for their clinical presentation, imaging spectrum, response to USG guided sclerotherapy treatment. This procedure of minimally invasive UGG guided injection of Bleomycin resulted in precise injection of drug into lesion, which made drug concentration centralize in the lesion so as to improve the therapeutic effects and safety and reduce the complications. To conclude, this mode of treatment therefore can avoid major surgeries in many patients thus decreasing morbidity and risk associated with surgery and anesthesia with promising result.

Declarations

Competing interests: There is no competing interests.

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Ethical approval: Not required.

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References

1. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg.* 1983;18:894-900.
2. Marler JJ, Fishman SJ, Kilroy SM, Fang J, Upton J, Mulliken JB, Burrows PE, Zurakowski D, Folkman J, Moses MA. Increased expression of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. *Paediatrics* 2010; 116: 38-45.
3. Juan Cabrera, Juan Cabrera, Jr, M Antonia Garcia-Olmedo et al. Treatment of venous malformations with sclerosant in microfoam form. *Arch dermatol* 2003; 139:1409-16.
4. Erin F.D. Mathes, Anita N. Haggstrom, Christopher Dowd et al. Clinical characteristics and management of vascular anomalies. *Arch dermatol* 2010;140:979-83.
5. Pedro Redondo, Antonio Martinez-Cuesta, Emilio G. Quetglas et al. Active angiogenesis in an extensive arteriovenous vascular malformation. *Arch dermatol* 2009, 143:1043-45.
6. Enjolras O, Breviere GM, Roger G, et al. Vincristine treatment for function- and life-threatening infantile hemangioma. *Arch Pediatr.* 2004;11:99-107
7. Odile Enjolras, Rene Chapot and Jean Jacques Merland. Vascular anomalies and the growth of limbs: a review. *Journal of Pediatric Orthopaedics.* 2004; 13:349-57.
8. Gangopadhaya AN, Pandey A. Hemangiomas In: *Manual of Vascular surgery.* AK Khanna, Puneet (Eds.). Jaypee Brothers Medical Publishers (P) Ltd, 2010,342
9. McHeik JN, Renauld V, Duport G, et al. Surgical treatment of haemangioma in infants. *Br J Plast Surg.* 2005;58(8):1067-72

10. Hou et al., A clinical study of ultrasound-guided intralesional injection of bleomycin A5 on venous malformation in cervical-facial region in China. *J Vasc Surg* 2010;51:940-5.
11. Hassan et al., Noninvasive Management of Hemangioma and Vascular Malformation Using Intralesional Bleomycin Injection. *Annals of Plastic Surgery* 2013; 70: 1
12. Muir T, Kirsten M, Fourie P, Dippenaar N. Intralesional bleomycin injection (IBI) treatment for haemangiomas and congenital vascular malformations. *Pediatr Surg Int* 2004;19:766–73.
13. Zhang L, Lin X, Wang W, et al. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. *Plast Reconstr Surg*. 2005;116(1): 200-04.