Original Research

Role of Intralesional Bleomycin Injection in Management of Low Flow Vascular Malformations in Children

Dr. Vishwanath Tripathi

Assistant Professor, General Surgery, T.S. Misra Medical College & Hospital, Amausi, Lucknow, India

Corresponding Author
Dr. Shubhshree Misra
Associate Professor, Dermatology V & L, T.S. Misra Medical College & Hospital, Amausi, Lucknow
Email - shubhshree.misra@gmail.com

Received date: 25 February, 2024 Acceptance date: 1 March, 2024

ABSTRACT
Background:Vascular lesions encompass a wide range of pathologies and are comparatively common in infancy and youth.
Material and Methods: This is an observational cohort study conducted in Department of General Surgery, Sarojini Naidu Medical College and Hospital, Agra among all 25 children with radiologically confirmed low flow vascular malformations during the period of one year (January 2018 to December 2019). Multiple sessions of sclerotherapy (Intralesional Bleomycin Injections IBI) were performed.
Results: A total of 25 patients were treated with serial intralesionalbleomycin percutaneous injection. Overall, a >50% improvement was seen in 80% of this cohort of patients; 24% 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.
Conclusion: Intralesional bleomycinsclero the rapy is a great treatment choice for low-flow VMs. In paediatric patients with symptomatic or disfiguring low flowvascular malformations, serial in tralesional bleomycin in jectionshaveproven to beasafeandeffectivetreatmentoption.

INTRODUCTION

Vascular lesions are relatively common in infancy and childhood and cover an array of pathologies. Mulliken and Glowacki[1] classification of vascular anomalies provided the cornerstone for characterization for the proper identification, investigation, and management of vascular birthmarks. This classification identified two broad categories: haemangiomas and vascular malformations, as accepted by the International Society of Study of Vascular Anomalies (ISSVA), and each group has distinctive clinical behaviours and cellular characteristics [2]. Vascular malformations can be further sub-divided according to the characteristics of their flow (high or low) or on the basis and structure of their anomalous channels [3]. Low flow vascular malformations (LFVMs) includes primary venous, capillary, lymphatic, and mixed malformations. The classification of vascular anomalies continues to expand as new knowledge evolves, including genetic studies, and new lesions have also been characterized [2]. Venous malformations consist of small and large venous channels with variable amounts of hamartomatous stroma[3] and these malformations are commonly associated with pain, venous stasis, and microthrombi in the lesion [4]. Lymphatic malformations are abnormalities of the lymphatic channels, which are endothelium-lined, chyle-filled cysts. They most commonly present in early childhood, with the majority involving the head and neck [5].Management of LFVMs can be challenging, especially when involving the head and neck. Scler othe rapy agents or combination treatments have replaced traditional surgical excision and/or broad de-bulking, albeit there is much disagreement over the best agent to use and overall management techniques. Although the use of sclerotherapy has been extensively documented for lymphatic malformations or cystic hygromas in the head and neck, the body of evidence for LFVMs,

particularly in children, is more limited, and management is controversial [6].Bleomycin was developed as a cytotoxic anti-tumor agent in 1966 [7]. It was initially shown in small studies to be successful in the treatment of lymphatic malformations and cystic hygromas when given intralesionallyand has recently been shown to be an effective treatment of vascular lesions, including haemangiomas and vascular malformations [8].Intralesionalbleomycin injection has been successfully used in thetreatment of vascular malformations, with a complete resolution in 32% of cases andsignificant improvement in 52% of cases of venous malformations[9].These preliminary studies suggest that bleomycin is effective; howeverrandomized controlled trials would be required to confirm these effects.

Objective: To study the role of intralesionalbleomycin injection in management of low flow vascular malformations in children

MATERIAL AND METHODS

This is an observational cohort study conducted in Department of General Surgery, Sarojini Naidu Medical College and Hospital, Agra among all 25 children with radiologically confirmed low flow vascular malformations during the period of one year (January 2018 to December 2019).

INCLUSION CRITERIA

- Radiologically confirmed low flow vascular malformations in children.
- Treatment indications included pain, functional impairment, cosmetic deformity, or asymmetry.
- Able and willing to give informed consent of parent/ guardian of children under 18 years of age.

EXCLUSION CRITERIA

- Children above 18 years of age
- Hypersensitivity to bleomycin injection intra-lesionally
- Pulmonary Fibrosispresent on radiological imaging.
- Pulmonary Tuberculosis patients
- Pulmonary hypertension patients
- Myocardial infarction patients
- Deranged blood counts

Informed consent was taken from patients before the start of the study. Patients were diagnosed with a LFVM following clinical assessment by a Consultant Pediatric Surgeon and confirmed by a senior radiologist through imaging with magnetic resonance imaging (MRI), or ultrasound (US) for more superficial lesions. Multiple sessions of sclerotherapy(IntralesionalBleomycin Injections) were performed and response to treatment was assessed clinically and formal reporting from repeat radiological imaging, which guided whether to proceed with further treatment.Radiological imaging was used to characterize the extent and size of the lesion, estimation of volume, examine the soft tissue involvement, and to help target treatment.

RESULTS

A total of 25 patients were treated with serial intralesionalbleomycin percutaneous injection. All patients were under 18 years of age with a median age of 7.64 years (range = 8 months–16 years). 16(64%) of the LFVMs arose from the head and neck, 6 (24%) on the extremities, and the remainder involved the trunk. Table 1 shows the gender wise distribution of patients.

Table 1: Gender wise distribution of patients

	Lymphatic		Mixed		Venous		Total	
	No.	%	No.	%	No.	%	No.	%
Male	1	50.00	11	61.11	2	40.00	14	56.00
Female	1	50.00	7	38.89	3	60.00	11	44.00
	2	100.00	18	100.00	5	100.00	25	100.00

The LFVMs were subdivided: 23 venous or mixed capillary venous, and 2 lymphatic (LM) as shown in Table 2. Mean follow-up was 6 months (range = 4 weeks to 12 months). Response to treatment is summarized in Table 3. The rate of radiological response did not always concur with the rate of response in clinical evaluation, however it was not found that a radiological response from a reduction in size occurred with a worsening of clinical response, or vice versa. Treatment was stopped if fibrosis was present on radiological imaging, if it was not possible to insert a needle to administer intralesionalbleomycin due to fibrosis, or if there was no malformation seen. Overall, a >50% improvement was seen in 80% of this cohort of patients; 24% 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. The average number of treatments required in all patients groups was four (range = 2–8), with larger lesions and lymphatic malformations requiring greater serial treatments.

Table 2: Site of vascular malformation

	Lymphatic		Mixed		Venous	
	No.	%	No.	%	No.	%
Chin	1	50.00	2	11.11		
Forehead			3	16.67		
Left foream flexor	1	50.00			1	20.00
Left foream flexor aspect			1	5.56	1	20.00
Left malar prominence			4	22.22	1	20.00
Lip			2	11.11	1	20.00
Right angle of mandible			2	11.11		
Right flank			2	11.11	1	20.00
Right thigh lateral aspect			2	11.11		
Total	2	100.00	18	100.00	5	100.00

Table 3: A summary of response to intralesionalbleomycin injections (IBI) for low flow vascular

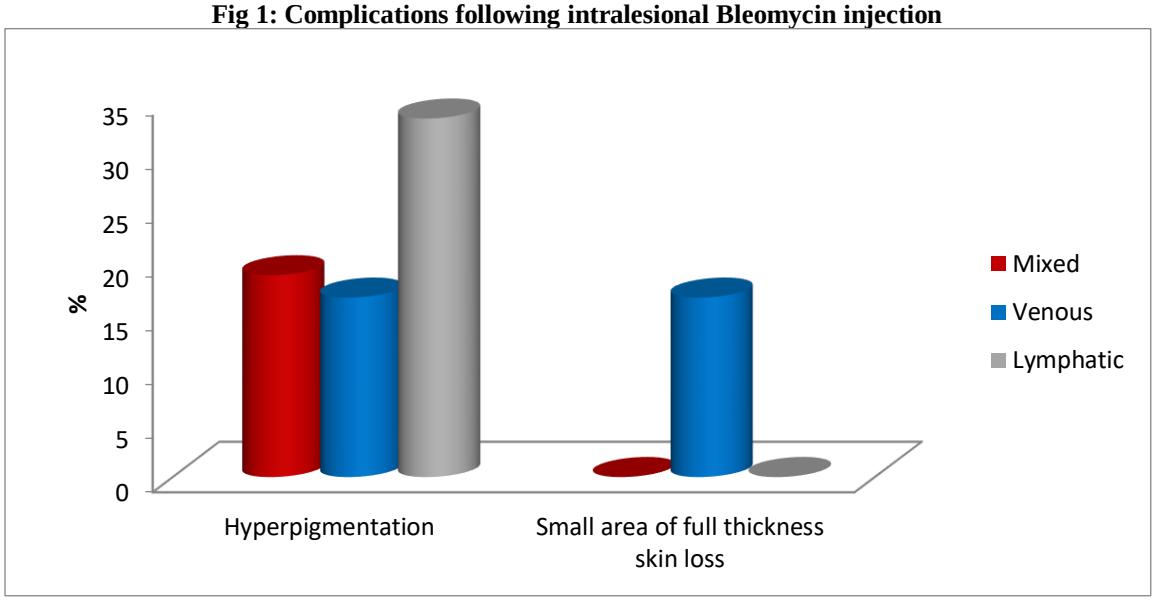
	Mixed	Venous	Lymphatic
Total, n	16	6	3
Complete response, % (n)	4 (25.00)	2 (33.33)	-
Average no. of treatments	3.5	2.0	
Major improvement >75%, % (n)	10 (62.50)	1 (16.67)	-
Average no. of treatments	3.6	6.0	
Good improvement 50–75%, % (n)	1 (6.25)	2 (33.33)	
Average no. of treatments	2.0	2.5	
Fair improvement <50%, % (n)	-	1 (16.67)	1 (33.33)
Average no. of treatments		4.0	4.0
No response, % (n)	1 (6.25)	-	2 (66.67)
Average no. of treatments	8.0		8.0

The LM group all required greater than 4 treatments (mean = 6.6, range = 4–8), which produced a modest response rate overall. Table 4 demonstrates responses to serial IntralesionalBleomycinInjection according to anatomical distribution. Thirteen of 16 head and neck lesions had a good-to-excellent improvement, with 62.5% (n = 10) with a greater than 75% reduction. Among the lesions within the extremities, 4/6 demonstrated a greater than 50% reduction, with 66.6% demonstrating greater than 75% reduction. Nineteen patients (76%) did not experience any complications from the procedure or the bleomycin. There were no cases of systemic side-effects. Five patients experienced hyperpigmentation of the skin following injection. One patient with a vascular malformation on her arm experienced a small area of full-thickness skin loss, which was treated conservatively with dressings, leaving a small scar, but there was a complete response to treatment (Fig.1).

Table 4: Responses to serial Intralesional Bleomycin Injection according to anatomical distribution

	Head and Neck	Extremities	Trunk
Total, n	16	6	3
Complete response, % (n)	3 (18.75)	-	3 (100.00)
Average no. of treatments	4.00		2.00
Major improvement >75%, % (n)	7 (43.75)	4 (66.67)	
Average no. of treatments	2.86	5.50	
Good improvement 50–75%, % (n)	3 (18.75)	-	
Average no. of treatments	2.33		
Fair improvement <50%, % (n)	-	2 (33.33)	
Average no. of treatments		4.00	
No response, % (n)	3 (18.75)		
Average no. of treatments	8.00		

Fig 1: Complications following intralesional Bleomycin injection



DISCUSSION

No single modality has been favored in the treatment of VMs. Non-operative measures include observation, compression garments, and modification with medication [10].These are usually only beneficial in small lesions with no functional or cosmetic compromise. In large VMs, compression garments can be used to improve associated discomfort, swelling, and protect the overlying skin, but are of little value in the head and neck. Bleomycin has recently been shown to be an effective treatment of vascular lesions, including haemangiomas and vascular malformations [11]. Its sclerosant impact on the vascular endothelium, apoptotic effect on quickly proliferating immature cells that induce DNA destruction, and low toxicity as a chemotherapeutic drug are its main characteristics. Patients receiving intravascular therapy for cancer have reported experiencing nausea and vomiting as side effects. Toxic doses have also been linked to hypertension and pulmonary fibrosis. There has been one reported case of pulmonary toxicity following IBI in a lymphatic malformation in over 2600 patients in the literature [12]. According to published studies, this unit administers a dose of 0.5 mg/kg to the majority of patients. Despite the low incidence of pulmonary side-effects, it is essential to monitor for pulmonary manifestations following treatment to minimize adverse effects. There have been no cases of pulmonary fibrosis in this study. There are a limited number of studies reporting the use of IBI sclerotherapy for vascular malformations. These studies have predominantly looked at the successful use and clinical response of lymphatic malformations and cystic hygromas[13]. In more recent years, a handful of studies have published results on the efficacy of IBI in venous malformations, AVMs, and mixed lesions [4]. Response rate to treatment ranged from 16–100%, with lymphatic malformation response rates between 80–100% and venous malformations responses between 84–100% [14].This study reports a 24% complete response rate, with 80% of all patients having a good-to-excellent response, which is comparable to the results in the literature. This study demonstrated a88% response rate of all venous malformations. In the 3 cases of lymphatic malformations, 1 patient had clinically fair results with satisfied patient outcomes and 1 patient had hyperpigmentation. One patient with a large LFVM of the lateral thigh only had a fair improvement following IBI treatment as the patient had missed appointments during the proposed treatment course. There were no systemic side-effects of repeated IBI treatment experienced, and local complications included 5hyperpigmentation and one cases of small area of full thickness skin loss. There were no recurrences in this study. The course of treatment is guided by the response to repeat treatments based on the radiology report and clinical response. It is uncertain why some lesions require 1–2 treatments and others require a longer course of treatment, but it may be related to structural differences in the vascular lesions, although histological analysis would be required to demonstrate this. Good response to treatment is reported to be achieved after one or two treatments with ethanol, but the average number of bleomycin treatments are around three-to-five [15]. This is comparable to present study, with an average of four injections.

CONCLUSION

For low-flow VMs, intralesionalbleomycinsclerotherapy is an excellent treatment option. For the successful care

of symptomatic or disfiguring low flow vascular malformations in a pediatric population, serial intralesionalbleomycin injections have been shown to be both safe and efficacious.

REFERENCES

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. PlastReconstr Surg. 1982 Mar;69(3):412-22.
2. Kunimoto K, Yamamoto Y, Jinnin M. ISSVA Classification of Vascular Anomalies and Molecular Biology. Int J Mol Sci. 2022 Feb 21;23(4):2358.
3. Lane F. Donnelly, Denise M. Adams, and George S. Bisset. Vascular Malformations and Hemangiomas. American Journal of Roentgenology 2000 174:3, 597-608.
4. Behravesh S, Yakes W, Gupta N, Naidu S, Chong BW, Khademhosseini A, Oklu R. Venous malformations: clinical diagnosis and treatment. CardiovascDiagnTher. 2016 Dec;6(6):557-569.
5. Ramashankar, Prabhakar C, Shah NK, Giraddi G. Lymphatic malformations: A dilemma in diagnosis and management. ContempClin Dent. 2014 Jan;5(1):119-22.
6. De Maria L, De Sanctis P, Balakrishnan K, Tollefson M, Brinjikji W. Sclerotherapy for Venous Malformations of Head and Neck: Systematic Review and Meta-Analysis. Neurointervention. 2020 Mar;15(1):4-17.
7. John S. Lazo. Bleomycin. Encyclopedia of Cancer (Second Edition)2002, Pages 223-227
8. Nabi A, Ferdous KMN, Khan NA et al. Intralesional doxycycline and bleomycin hydrochloride in the treatment of cystic hygroma. Ann PediatrSurg 18, 22 (2022).
9. Muir T et al. Intralesionalbleomycin injection (IBI) treatment for haemangiomas and vascular malformations. Pediatric surgery international 2004/02/01: 19(12):766-73
10. Richter GT, Friedman AB. Hemangiomas and vascular malformations: current theory and management. Int J Pediatr. 2012;2012:645678.
11. Abdelaty MH, Badran AI, Aborahma AM, Elheniedy MA, Kamhawy AH. Intralesional injection of bleomycin in the management of low flow vascular malformations: Results and factors affecting the outcome. Journal of Vascular Surgery: Venous and Lymphatic Disorders;2023;12:1-9.
12. Dhamija E, Meena P, Ramalingam V, Sahoo R, Rastogi S, Thulkar S. Chemotherapy-induced pulmonary complications in cancer: Significance of clinicoradiological correlation. Indian J Radiol Imaging. 2020 Jan-Mar;30(1):20-26.
13. Anita T. Mohan, Saleigh Adams, Kevin Adams & Donald A Hudson (2015) Intralesionalbleomycin injection in management of low flow vascular malformations in children, Journal of Plastic Surgery and Hand Surgery, 49:2, 116-120.
14. Zhang YT, Zhang C, Wang Y, Chang J. Efficacy and safety of ultrasound-guided bleomycin combined with dexamethasone in the treatment of pediatric lymphangiomas. Front Pediatr. 2022 Jul 19;10:935470..
15. Soni P, Khandelwal K, Aara N, Ghiya BC, Mehta RD, Bumb RA. Efficacy of IntralesionalBleomycin in Palmo-plantar and Periungual Warts. J CutanAesthet Surg. 2011 Sep;4(3):188-91.