MJMR, Vol. 34, No. 4, 2023, pages (280-292)

Open Access
ISSN:2682-4558

Research Article

Ultrasound and Fluoroscopy Guided Intralesional Bleomycin Injection (Ibi) for Treatment of Superficial Hemangiomas and Vascular Malformation

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DOI: 10.21608/MJMR.2023.192754.1342

Abstract

Hemangiomas and vascular malformations are benign lesions that can occur at any organ. Currently various medical and surgical options are available for the treatment of hemangiomas including intra lesional bleomycin, laser therapy, cryotherapy, corticosteroids and surgical excision. Recently bleomycin injections are commonly used as a sclerosing agent for the treatment of vascular malformations, compared to the surgery, intra lesional bleomycin injection is a simple, practical noninvasive method of treatment. **Aim of the work:** To evaluate the role of ultrasound and fluoroscopy guided intralesional bleomycin injection (IBI) for treatment of superficial hemangiomas and vascular malformations. This study will be conducted in the interventional radiology unit, department of Radiology, Faculty of Medicine, Minia University. **This study is including thirty** patients presented with superficial hemangiomas and vascular malformation. There was statistically significant difference in the study regards Relation between response with demographic data, Relation between response and site of lesion, Relation between response with Doppler findings and Relation between response with number of sessions. There was no statistically significant relation between response and size of lesion. Bleomycin appears to be safe, effective and has some antitumor activity and also bleomycin has local sclerosing effect on endothelial cells of hemangiomas and vascular malformation.

Keywords: Ultrasound and fluoroscopy, intralesional bleomycin injection (IBI), superficial hemangiomas and vascular malformation.

Introduction

Hemangiomas and vascular malformations are benign lesions that can occur at any organ. Hemangiomas are vasoproliferative neoplasms that arise from the endothelial cells surrounding the blood filled cavites, they have a slightly higher female predilection. Hemangiomas divided into infantile and congenital types depending upon the age. Infantile hemangiomas are either absent or present as a precursor lesion at birth while congenital hemangiomas occur fully grown at birth. Congenital hemangiomas can either involute rapidly over a very brief period in infancy (rapidly involuting congenital hemangioma (RICH) or never involute (non – involuting congenital hemangioma (NICH) [(1)].

Vascular malformations usually present at birth, most of them are seen at the head and neck regions, which are divided into slow flow (combination of capillary, venous, and lymphatic) and fast flow(has an arterial

component). Most of vascular malformations are self-limited as the child grows elder, but some of them may become larger with age [2].
Currently various medical and surgical options are available for the treatment of hemangiomas including intra lesional bleomycin, laser therapy, cryotherapy, corticosteroids and surgical excision [3,4].

Recently bleomycin injections have been used to manage hemangiomas, it is a primarily cytotoxic anti-tumor antibiotic drug which is also known as blenoxane used in the management of various types of cancer including lymphoma and squamous cell carcinoma [4,5]. However, it can also cause sclerosis by endothelial mesenchymal transition, where endothelial cells change into fibroblast–like cells, so it is commonly used as a sclerosing agent for the treatment of vascular malformations. Compared to the surgery, intra lesional bleomycin injection is a simple, practical noninvasive method of treatment [6]

Patients and Methods

This study was conducted in the interventional radiology unit, department of Radiology, Faculty of Medicine, Minia University starting from January 2022. Thirty patients presented with superficial heman-giomas and vascular malformation were referred from department of vascular surgery, at Minia University Hospital to be recruited in the study.

Inclusion criteria: Patients with superficial low flow hemangiomas and vascular malformation with no major vessel connection, No age limit.
Exclusion criteria: Deep inaccessible hemangiomas and vascular malformation, Fast (high) flow lesions with major vessel connection, Patient refusing injection, Patient with hemophilia or any blood disorder prevent the injection.

Method:
Injection of the superficial hemangioma and vascular malformation with bleomycin, the dose of bleomycin is 0.3-0.6 mg/kg per injection not exceeding 15 units per cycle. Injection is administered under local or general anesthesia by ultrasound guidance. During injection, the needle is introduced through normal skin and under ultrasound and fluoroscopy guidance advanced into the lesion and then the bleomycin is injected. Needle is then withdrawn and the lesion is being compressed for about two minutes. Follow up of the patients is done by US and in some cases by MRI.

Statistical analysis:
The collected data was tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1

Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) and minimum & maximum of the range and for numerical non parametric data as median and 1st& 3rd inter-quartile range, while they were done for categorical data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whitney U in cases of two independent groups with non- parametric data. Receiver operating characteristic (ROC curve) analysis was used to find out the overall productivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.

Inferential analyses were done for qualitative data using Chi square test for independent groups. The level of significance was taken at P value <0.05 is significant, otherwise is non-significant.

Results

Table (1): Demographic characteristics of the studied patients.

Parameters		Studied patients (n= 30)	
		N	%
Gender	Male	12	40.0%
	Female	18	60.0%
Age groups	2-10 years	18	60.0%
	11-18 years	3	10.0%
	19-30 years	6	20.0%
	>30 years	3	10.0%
Age (years)	Mean± SD	12.9± 11.66	
	Median	7.5	
	Range	2.0 – 35.0	

SD= standard deviation, n: number, %: percentage,

Table (2): Relation between response with demographic data.

		No response		Mild response		Moderate response		Complete response		Test value	P-value
		No.	%	No.	%	No.	%	No.	%		
Gender	Male	1	33.4%	4	66%	6	66.7%	0	0.0%	X^2= 21.67	<0.001
	Female	2	66.6%	2	34%	3	33.3%	12	100%		
Age (years)	Mean± SD	8± 0.01		4.5± 1.64		14.67± 11.79		17.0± 13.8		Z MWU=5.57	0.135
	Median	8.0		4.5		10.0		15.5			
	Range	7.0 - 8.0		3.0 - 6.0		4.0 - 30.0		2.0 - 35.0			

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Chi- Square test and Mann-Whitney U test

This table shows relation between response and demographic data. Complete response was significantly higher in female patients (p<0.001) while there was no statistically significant relation between response and age (p>0.05).

Table (3): Relation between response and site of lesion.

		No response		Mild response		Moderate response		Complete response		Test value	P-value
		No.	%	No.	%	No.	%	No.	%		
Site of lesion	Neck	0	0.0%	0	0.0%	0	0.0%	3	25.0%	X^2= 45.8	<0.001
	Foot	0	0.0%	0	0.0%	3	33.3%	0	0.0%		
	Chest wall	0	0.0%	0	0.0%	0	0.0%	3	25.0%		
	Hand	0	0.0%	3	50.0%	3	33.3%	0	0.0%		
	Face	3	100.0%	0	0.0%	3	33.3%	3	25.0%		
	Nape	0	0.0%	3	50.0%	0	0.0%	0	0.0%		
	Forearm	0	0.0%	0	0.0%	0	0.0%	3	25.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Chi- Square test

This table shows relation between response with site of lesion. There was statistically significant relation between response with site of lesion (p<0.001) as Complete response was significantly higher in patients with hemangioma in neck, chest walland forearm while no response was found higher in cases with lesions in face.

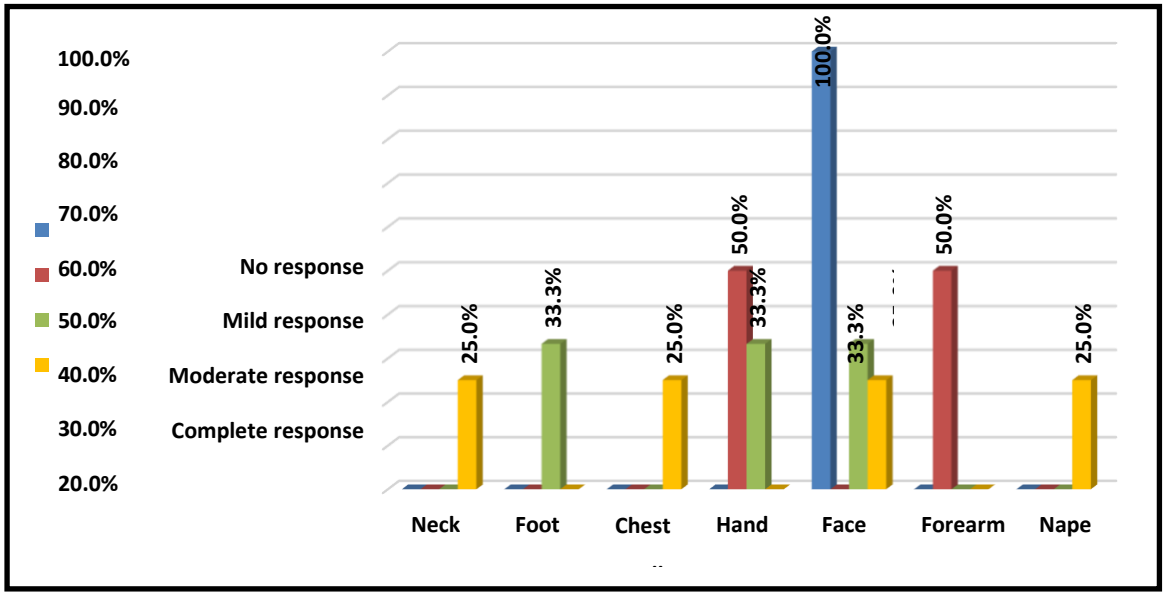

Figure (1): Relation between response and site of lesion

Table (4): Relation between response with size of lesion.

		No response	Mild response	Moderate response	Complete response	Test value	P-value
Size of lesion	Mean	2.70	4.60	3.60	4.88	z_{MWU}=7.41	0.060
	± SD	0.00	0.44	1.83	0.83		
	Median	2.70	4.60	2.80	4.90		
	Range	2.70	4.20	2.00	3.90		
		2.70	5.00	6.00	5.80		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statisticallysignificant, SD= standard deviation, * Chi- Square test and Mann-Whitney U test

This table shows relation between response and size of lesion. There was nostatistically significant relation between response and size of lesion (p>0.05).

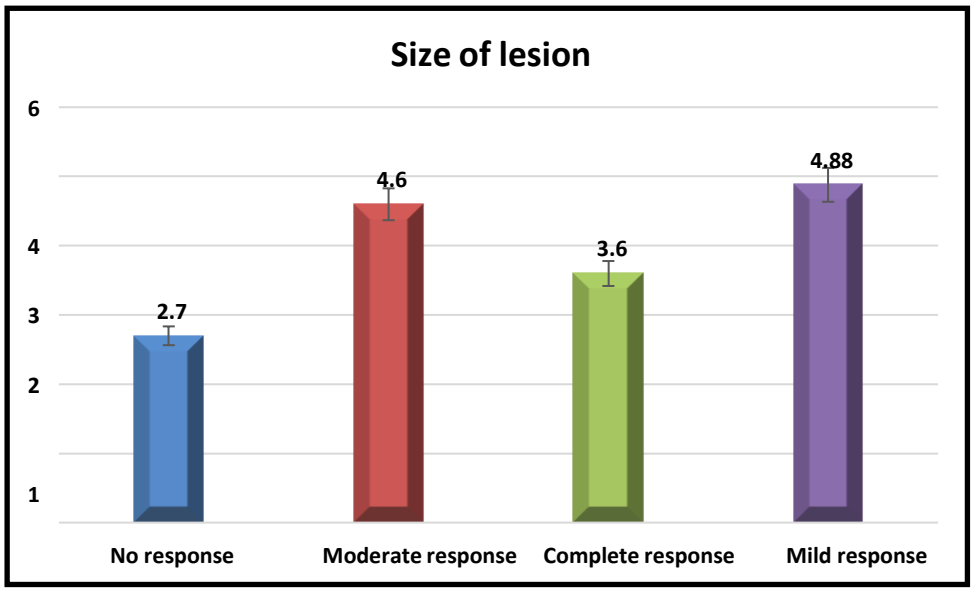

Figure (2): Relation between response with size of lesion.

Table (5): Relation between response with Doppler findings.

		No response		Mild response		Moderate response		Complete response		Test value	P-value
		No.	%	No.	%	No.	%	No.	%		
Doppler findings	**Medium flow**	3	100.0%	3	50.0%	0	0.0%	0	0.0%	**X^2= 20.6**	**<0.001**
	Low flow	0	0.0%	3	50.0%	9	100.0%	12	100.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Chi- Square test

This table shows relation between response with Doppler findings. There was statistically significant relation between response with Doppler findings (p<0.001) as complete and moderate response was significantly higher in patients with low flow in Doppler.

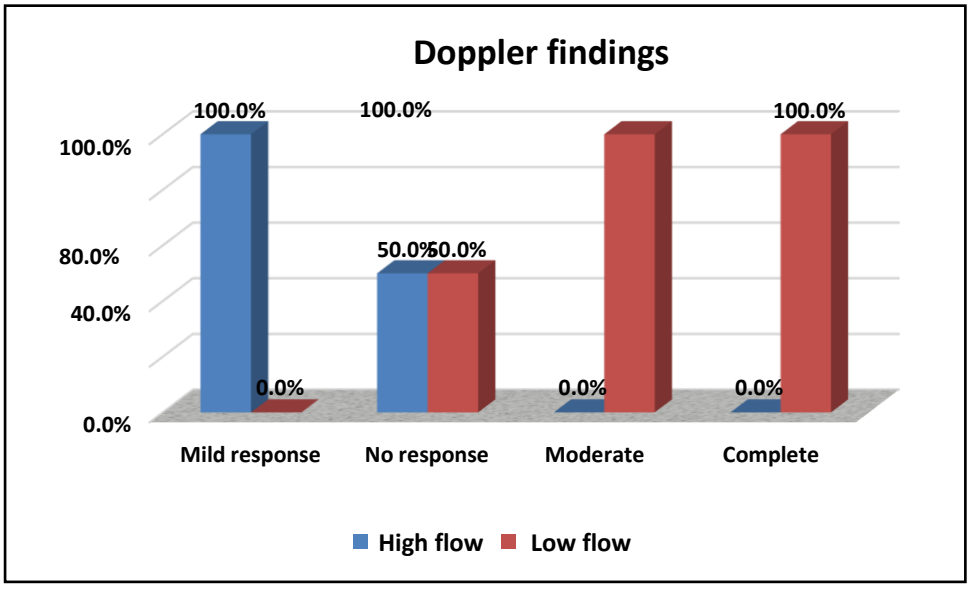

Figure (3): Relation between response and Doppler findings.

Table (6): Relation between response with number of sessions.

		No response		Mild response		Moderate response		Complete response		Test value	P-value
		No.	%	No.	%	No.	%	No.	%		
Number of sessions	One session	0	0.0%	3	50.0%	9	100.0%	9	75.0%	X^2=35.9	<0.001
	Two sessions	0	0.0%	3	50.0%	0	0.0%	3	25.0%		
	Three sessions	1	100.0%	2	0.0%	0	0.0%	0	0.0%		

p≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, * Chi- Square test

This table shows relation between response with number of sessions. There was statistically significant relation between response with number of sessions (p<0.001) as complete and moderate response was significantly higher in patients received one session.

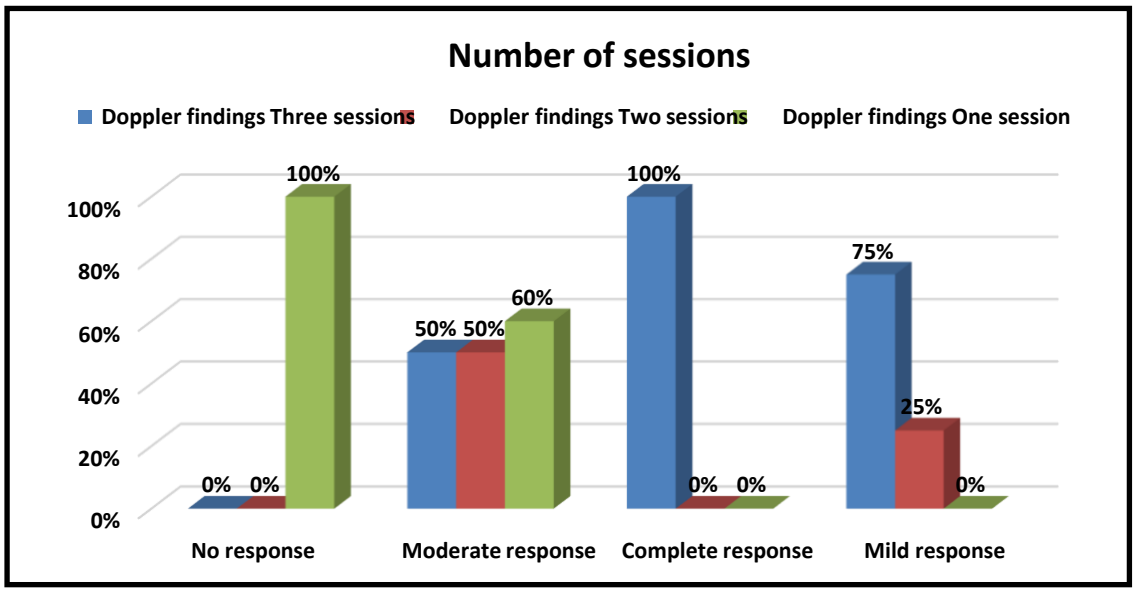

Figure (4): Relation between response and number of sessions.

Case descriptions:

Case 1: 6 year-old female patient presented with lower lip hemangioma (fig 4) measuring 2.5x2 cm on ultrasound presenting as low flow on color Doppler (fig 4a), with no prior treatment received. Intralesional bleomycin was administered in doses of 10 mg per session (Fig 4b)

In Figure 5a/5b: Same patient after two treatment sessions of intralesional bleomycin showing moderate response was observed clinically and >70% reduction on ultrasound after two sessions of U/S guided IBI (moderate response) (Fig. 6).

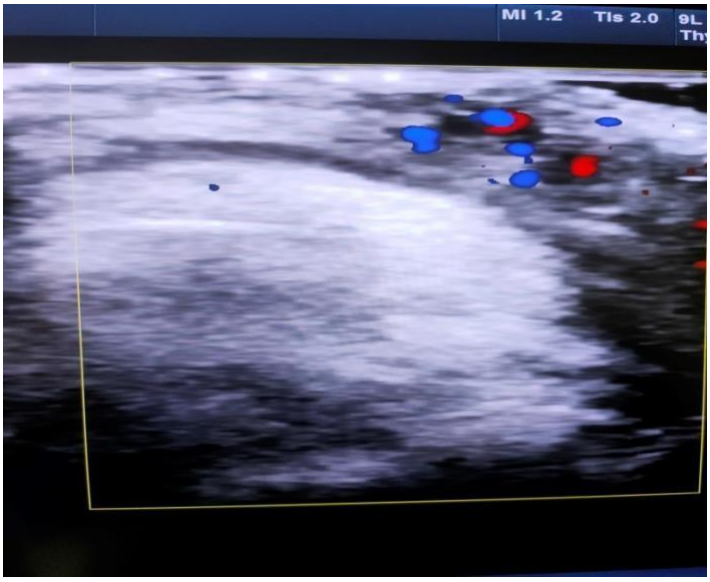

Figure 4a. Doppler US image showing low flow hemangioma in lower lip

Figure 6. fluoroscopic image of the same patient as in fig 4 during IBI under

Figure 5a. U/S image showing moderate response (reduction more than 70%) after two sessions of IBI

Figure 5 b. The same patient as in figure 4 after two sessions of IBI

Case 2: 2.5 year-old female presented with chest wall hemangioma (fig.7) measuring 3.5x4 cm presenting as medium flow on color Doppler, with no prior treatment received (fig. 7a). Intralesional bleomycin was administered in doses of 5 mg per session (Fig. 7 b)
In Figure 8a/8b: Same patient after two treatment sessions of intralesional bleomycin showing complete resolution with no cystic spaces and only residual fibrotic tissue is noted
The patient was followed up for one year at three monthly intervals, and shows no recurrence

Figure7. 2.5 year old female presenting with chest wall hemangioma

Figure7b. fluoroscopic image of the same patient during IBI under fluoroscopy guidance

Figure 8a: The same patient as in fig. 7. after two sessions of IBI

Figure 8b. U/S image showing complete reduction in size of the lesion on ultrasound after two sessions of US guided IBI

Discussion

Hemangiomas and vascular malformations are benign lesions that can occur at any organ. Intra-lesional Bleomycin injection (IBI) is an effective treatment in haemangiomas and vascular malformation lesions, avoiding the need for invasive primary surgery or systemic treatment regimens in 80% of cases, and allowing for limited need of secondary surgical or adjunctive procedures in cases with a moderate result [7]

In our study, demographic characteristics of the studied patients showed that the age of patients ranged from two years to 35 years with mean age ±SD was 12.9± 11.66 years. There were 18 (60%) females and 12 (40%) males with male to female ratio was .0.67:1Regmi et al., 3 underwent a study aimed to determine the efficacy and safety of intralesional Bleomycin sclerotherapy for head and neck haemangioma and slow flow vascular malformation including thirty-six patients ([12)]

males and 24 females) with their ages ranged from five years to 54 years with a mean age of 25 years .

In our study, the clinical characteristics of studied patients showed that face was the most common site of hemangiomas that found in nine (30%) cases followed by hand in six (20%) cases then neck in three (10%) cases, foot in three (10%) cases, chest wall in three (10%) cases, nape in three (10%) cases, and forearm in three (10%) cases. the mean size of lesions was 4.22± 1.34 cm and ranged from 2 cm to 6 cm. while in a Regmi et al., 3 study, commonest site of these lesions were face, oral cavity and oropharynx in 12 (33.3%) followed by neck in five (13%), cheek in six (16%), lip in five (13%), parotid in four (11%), ear in two (5%) and nose in two (5%). In another study by Garzon et al. 8 who reported that, vascular malformations are among the most common congenital and neonatal abnormalities, head and neck is the most common site of occurrence of these lesions (60%) followed by the trunk (25%) and the extremities (%15) Redkar et al., 9 found that, sixteen children (94%) had lesions in the head, neck, and chest region and one had (6%) lesion on the hand.

In this study, radiological (US & Doppler) findings observed that, most (80%) cases revealed slow flow, while medium flow was seen in six (20%) cases .
Regmi et al., 3 found that, most of their study cases were slow flow vascular malformations (86%) and only five cases of haemangioma (14%) were high flow.

In this study, according to number of sessions we found that, 70% of cases received two sessions; six (20%) cases received one session while 10 % of cases received three sessions. While Redkar et al., 9 observed that, three patients (hemangiomas: 17%) required only one injection, two patients required (cystic hygroma: 11%) two sessions of injections, four patients (hemangiomas: 23%) required three sessions of injections, (one had 80% resolution who is under follow-up) two patients (one hemangiomas and one cystic hygroma: 11%) required five injections, and four patients (cystic hygroma: 23%) required six injections with 4 weeks gap in between each injection. Also, Regmi et al., 3 found that, mean number of injections required in 15 patients of lymphangioma (Group 1) and equal number of slow flow vascular malformation (Group 2) were 3 and 5 respectively.

In this study, complete response was observed in 15 (50%) cases, moderate response was observed in 9 (30%) cases, mild response was observed in 6 (20%) cases, and no significant response was observed in three (10%) cases. In a study by Regmi et al., 3 ten patients (28%) had complete resolution (cured), 19 had marked improvement (53%), five had mild improvement (14%) and two had no response (6%). Muir et al., 7 showed that, complete response was obtained in 40 (42%) of patients, Significant improvement of the treated lesion occurred in 38 (38%) of patients, Moderate improvement in 16 (17%) and only one (1%) had no response. There was an overall significant effect seen in a total of 80 patients (80%), 1–3 years post IBI treatment. All patients were regularly followed up at 4- to 6-month intervals, showing the same good results.

In this study, the relation between response with Doppler findings observed that, there was statistically significant relation between response with Doppler findings ($p<0.001$) as complete and moderate response was significantly higher in patients had low flow in Doppler. This was in the same [10]
response was statistically higher in line with Eivazi et al., demonstrated the significant positive correlation between response and low flow in Doppler findings.
In our study, we found that relation between response and number of sessions showed that, there was statistically significant relation between response with number of sessions ($p<0.001$) as complete and moderate response was significantly higher in patients who received one session. This in agreement with Regmi et al., 11 that found that the number of injections required ranged from 2-7 which was similar to pienaaret et al., [12] .

Conclusion

Based on our study finding and results we conclude that, intra-lesional injection of Bleomycin appears to be safe, effective treatment method for treatment of hemangiomas & vascular malformation based

on its antitumor activity and also its local sclerosing effect on endothelial cells of hemangiomas and vascular malformation. There was statistically significant relation between response with flow type of the lesions in Doppler, and number of sessions. Further research with larger sample size is necessary to evaluate the importance and efficacy of ultrasound and fluoroscopy guided bleomycin injection in treatment of superficial hemangiomas and vascular malformations.

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