

## Evaluation of Bleomycin Injection in Treatment of Infantile Haemangiomas

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**Abstract: Background:** to assess the efficacy of bleomycin injection as a one of different modalities in treatment of infantile haemangiomas. **Design:** Prospective study. **Patients and methods:** This study was done on 40 patients (26 females, 14 males) with infantile haemangiomas, recruited prospectively from the pediatric surgery outpatient clinic at Al-Azhar university hospital (New Damietta) during the period from July 2016 till December 2016 and all patients were observed for six months. **Results:** After a minimum follow-up of 6 months, 6 patients (30%) showed complete resolution of their lesions after 2-3 injections with marked colour fading and great parental satisfaction. The remaining 14 patients (70%) need more injections (4-6 injections) to be completely improved. **Conclusion:** Intraregional injection of bleomycin is an easy, safe, and effective therapeutic modality in cutaneous haemangiomas. [Mohamed Ahmed Abd El-Maaboud Abo omar; Sayed Ahmed El-hady Abd El-Monem and Ayman Ameen Mohy El-Din. **Evaluation of Bleomycin Injection in Treatment of Infantile Haemangiomas.** *Nat Sci* 2017;15(7):90-94]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). <http://www.sciencepub.net/nature>. 12. doi:[10.7537/marsnsj150717.12](https://doi.org/10.7537/marsnsj150717.12).

**Keywords:** haemangiomas, complications, intralesional bleomycin injection.

### Introduction:

Infantile haemangiomas, the most common tumors of infancy, are benign Vascular proliferations composed of densely packed capillaries, with endothelial cells and pericytes expanding in a lobular pattern. In contrast to vascular malformations, infantile haemangiomas are usually absent or inconspicuous at birth, and are instead characterized by a remarkably rapid postnatal proliferation and a slow spontaneous involution. Despite their ability to involute, it is difficult to assess the prognosis of some lesions. Even small haemangiomas can, at certain sites, have major esthetic consequences. Larger lesions can lead to complications such as bleeding, ulceration, and obstruction. For these reasons, some clinicians advise early intervention in infantile haemangiomas [1,2,3]. Conservative therapies include pharmacotherapy, laser therapy, and regular consultation with the treating physician. Bleomycin (BLM, also known as Blenoxane) was first isolated as a Cu<sup>2+</sup>-containing glycooligopeptide antibiotic from the culture medium of *Streptomyces verticillus*. It was soon found to be an anticancer agent, acting in the S phase of the cell cycle to cleave DNA strands and thereby obstruct cell proliferation, and has since become one of the most widely used cancer drugs [4,5,6]. Recently, bleomycin A5 was found to be effective in treating haemangiomas [1,2,3]. Pienaar et al. used, as the sole agent, a locally injected dose of 0.2–0.6 mg/kg bleomycin. In 73% of patients, the haemangioma responded with a greater than 75% reduction in size. Other investigators have achieved similar results, suggesting that bleomycin A5 might be

a viable new treatment for this disease. In fact, we have used bleomycin A5 as a sclerosing agent to treat infantile hemangioma over long time. Bleomycin has many side effects as anti-cancer drugs. These side effects include local reaction and general reactions in treating haemangiomas. How to use it for a better results is an important question. In some cases, depending on the patient's age and the size of the lesion.

### 2. Patients and methods:

This study was done on 40 patients (26 females, 14 males) with infantile hemangioma, recruited prospectively from the pediatric surgery outpatient clinic at Al-Azhar university hospital (New Damietta) during the period from July 2016 till December 2016 and all patients were observed for six months.

#### A- Inclusion criteria:

1. Age: from 3 months.
2. Sex: both.
3. site: anywhere of the body.

#### B- Exclusion criteria:

1. Age: less than 3 months.
2. Port wine hemangiomas.
3. Vascular tumors other than infantile hemangioma.
4. Vascular malformations.
5. Hemangiomas with intracranial extension.
6. Hypersensitivity to bleomycin.
7. any other associated congenital anomaly.
8. infant who receive previous treatment for the haemangioma.
9. Any infant who has a major medical problem

(such as cardiac pathology or airway obstruction) or syndromic cases.

**All patients were subjected to:**

1. Complete history taken from the parents.
2. Confirmation of the diagnosis (by US or MRI if needed).
3. Photographic documentation.
4. A soft tape measure was draped over the hemangioma, and the longest diameter and a measurement perpendicular to it were noted, giving a measurement in cm.
5. Whole blood count, prothrombin time, activated partial thromboplastin time.
6. The size and blood flow of hemangioma were evaluated using color ultrasonography every 3 months.
7. Abdominal US to identify co-existing congenital malformations, and intra-abdominal hemangiomas.

**All data were recorded including:**

-Age, sex, age of onset, number, location, size of hemangioma, age at treatment, family history, presence of other malformations.

-Presence of life-altering or life-threatening complications, response to treatment, complications associated with treatment, follow-up period and final outcome.

**Application of bleomycin:**

The dosage was calculated according to the weight of the patient and size of the lesion as follows:

- The dosage of bleomycin was calculated as 0.2 I.U/kg per injection) recommended range: 0.2 to 0.6 I.U/kg per injection).

- The volume of drug injected was determined by the amount needed to deliver the drug throughout the tumor. So, the dose in milligrams calculated above is then diluted in a volume of normal saline roughly equivalent to the volume of the lesion; for example, if the lesion measures  $1 \times 2 \times 2 \text{ cm} = 4 \text{ cm}^3$ , then the calculated dose is diluted in 4 ml normal saline.

**Technique of injection:**

- Infants were held during the injection with application of topical anesthesia.
- Sterilization of site of the lesion before injection by betadine solution.
- To minimize bleeding, the lesions were injected at multiple sites entering through normal skin and advancing into the lesion, in a radial pattern, until the surface of the tumors became a little pale.
- After injection, local pressure applied for 10 min.
- Analgesics were prescribed post-injection.

**3. Results:**

Forty children with IH (26 females, 14 males) were enrolled and randomized and treated with intralesional injection of bleomycin.

**1. Pre-treatment assessment:**

There were 10% of patients with history of prematurity, 20% of patients of multiparous mother and 15% of patients with history of difficult delivery. There were no visceral hemangiomas detected by abdominal U.S in all patients or intracranial extension detected by MRI in patients with scalp hemangiomas.

**2. Age:**

- The age of patients ranges from 3 to 12 months at the start of the treatment. the mean age of patients was around 7months as shown in (Table 1). (So, treatment of patients in this study started during the proliferative stage).

**3. Sex:**

- Patients of both groups were predominantly female (67%), while males were (33%) with (female to male ratio, 2:1).

Table (1): mean and stander deviation of age and percentage sex.

Variable	Results
Age (month)	
Mean $\pm$ SD	7.55 $\pm$ 2.84
Range	3 - 12
Gender %	
Male	14(35%)
Female	26(65%)

**4. Site of lesions:**

- Most of the lesions (80%) were located on the head and neck (25% on the lip, 15% on the scalp and 40% on other sites of the head). The rest of lesions (20%) were located on the trunk and extremities.

Table (2): site, no. and percent of lesions.

Site	No	percent
Back	4	10%
Face	8	20%
Chest	4	10%
Lip	16	40%
post auricular	4	10%
Scalp	4	10%
Total	40	100%

**5. Size of lesions:**

The pre-treatment size of lesions ranged from (4 cm<sup>2</sup> to 80 cm<sup>2</sup>) with a mean size of (19  $\pm$  18.48).

Table (3): mean of size.

Size	(cm <sup>2</sup> )
Mean $\pm$ SD	19 $\pm$ 18.48
Range	4 – 80

**6. Number of injections:**

- Number of injections ranged from 2 to 6 injections with a mean number ( $4.18 \pm 1.39$ ).

Table (4): mean and range of no. of injection

	No. of injection
Mean $\pm$ SD	$4.18 \pm 1.39$
Range	2 – 6

**7. Effect of treatment:**

- Each patient in both groups received from 2 to 6 injections according to clinical improvement with 2

Table (5): Difference between pre and after treatment size of lesions with statistically significant difference at all times of post treatment follow up (after 2, 4 and 6 injections).

(size (cm <sup>2</sup> ))			Paired Diff.		Paired Sample t-test	
	Mean	$\pm$ SD	Mean	$\pm$ SD	T	p-value
Pre-treatment	16.35	22.99				
After 2 injections	6.50	6.74	-9.85	5.42	2.655	0.033
After 4 injections	5.40	5.51	-10.95	6.02	2.839	0.026
After 6 injections	3.17	2.21	-13.18	7.25	3.122	0.016

**8. Doppler U.S:**

Blood flow through the lesions markedly decreased after the second injections in the both groups (during follow up by U.S) as shown in (Figure 1).

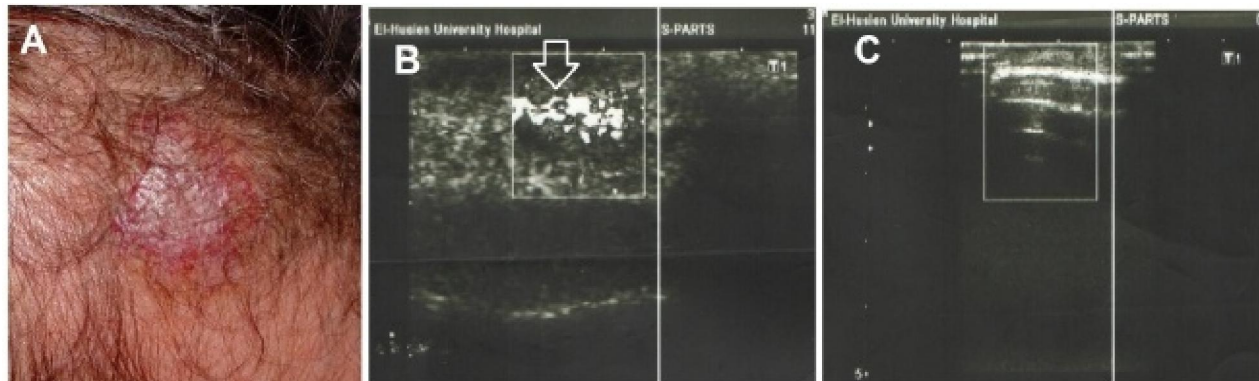


Figure (1): (A) IH located on the scalp of female child 12 months old (B) U.S of lesion pre-treatment with intralesional bleomycin showing marked blood flow (arrow) (C) U.S of same lesion after 2 injections showing marked decrease in blood flow.

**9. Complications of injection:**

Table (6): complication of the study.

Complication	Count	Percent
Ulceration	16	40%
Fibrosis	8	20%
Other complication	2	5%
No complication	14	35%
Total	40	100%

- 26 patients (65%) developed complications. The main complication was ulceration (40% of

weeks interval. All patients (100%) showed considerable decrease in size of lesions after the first injection. 6 patients (30%) showed complete resolution of their lesions after 2-3 injections with marked colour fading and great parental satisfaction. The remaining 14 patients (70%) need more injections (4-6 injections) to be completely improved.

- There was statistically significant decrease in size of lesions between pre and after treatment in all times of follow up (after 2, 4 and 6 injections) as shown in (Table 5).

patients) (Figure 60) then fibrosis (20% of patients) Ulceration of all injected IHs completely healed after topical care (local antibiotic and emollient).

**10. Final outcome of treatment:**

- 24 patients (60%) showed marked regression in size of their lesions more than 75 %. (Grade (Ib) response).

- 16 patients (40%) showed total regression in size of their lesions with no residual masses. (Grade (Ia) response).

- The Final outcome was very good as all patients showed first grade response 40% of patients with grade Ia, 60% of patients with grade Ib.

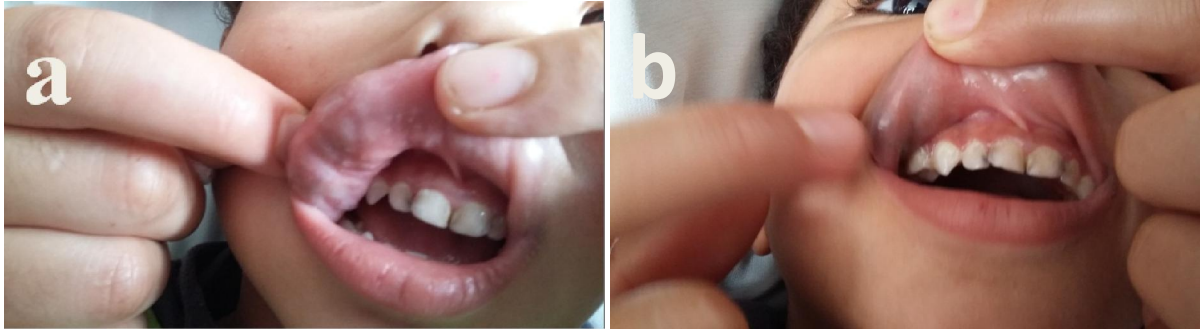


Figure (2): IH of male child 11 months old (a) before treatment (b) after two times of injection of bleomycin showing complete resolution of the lesion.

#### 4. Discussion:

IHs are the most common tumors of childhood. They are benign lesions however; they possess potential for permanent local tissue damage, ulceration, infection, bleeding, functional impact, and pain (Arkan Hadi et al., 2012) reported that many children may experience a complete or near complete involution without significant sequelae. So Classical management strategy in IH is observation with regular follow-up and education of the family. However, the duration of the spontaneous regression cannot be estimated and this may result in psychosocial stress for parents.

Arkan Hadi et al., 2012 reported that intervention may be required for lesions with potential to interfere with a vital structure or function. These include lesions in the airway, liver or gastrointestinal tract and lesions in the periorbital region. In addition, intervention may be indicated for very large rapidly growing cutaneous hemangiomas, lesions associated with other complications such as ulceration and/or bleeding, increased risk of scarring or disfigurement, these include lesions complicated by ulceration, lesions of the nose, lip, ear, large, segmental hemangiomas of the face and pedunculated hemangiomas. In this present study, the indications for intervention was required for patients with big IHs (4 cm<sup>2</sup> or more), IH complicated with pain, bleeding, ulceration or unaesthetic appearance, hemangiomas that occlude vital structures as ear causing decreased auditory conduction, tongue causing impaired ventilation and feeding or eye causing visual axis obstruction, hemangiomas associated with slow involution or scarring as parotid lesions, lip lesions, lesions on the tip of the nose or anogenital lesions. (Hassan et al., 2013) defined sclerotherapy as an injection of a sclerosing substance (as alcohol, steroids, or bleomycin) directly through the skin into a lesion and it is used for management of vascular anomalies. They reported that the simplicity of the procedure with minimal complications makes it a well-accepted mode of management. In 1997,

(Kullendorff and Sarihan et al) initially reported that intralesional bleomycin injection is an effective method in treating IH. (Kullendorff, 1997) treated five children had pain in massive, inoperable IHs with intralesional bleomycin injection. All treated children were relieved of pain, and the swelling was reduced with no complications or side effects.

Sarihan et al., 1997 also had injected fourteen patients with complicated hemangiomas with intralesional bleomycin injection. Lesions of three patients were completely reslouted after only one Injection. In the other eleven patients lesions regressed 60-100% with two to three injections. More recently, (Muir et al., 2004) evaluated the effectiveness of intralesional bleomycin injection in 37 patients. They reported complete resolution or significant improvement in 87% of the patients. (Omidvari et al., 2005) assessed the effectiveness of intralesional bleomycin injection with two weeks intervals for 4 to 6 times in treatment of 32 patients with complicated IHs. They observed the maximum of lesion regression occurred in the first three months of treatment. They had a follow-up of 6 months and reported no recurrence or systemic and local complications. They concluded that bleomycin is a good therapeutic modality for treatment of IHs especially in painful or massive lesions. In another study undertaken by (Pienaar et al., 2006), following the treatment of 30 patients with intralesional bleomycin injection, a response rate of 75 - 100% was attained in 73% of the patients and a response rate of 50 -75% was reported in the rest of the patients.

Luo and Zhao, 2011 evaluated the effectiveness of bleomycin in 82 cases of IH, and found that after treatment with intralesional bleomycin injection in appropriate quantity and concentration, injecting depth, all IHs involuted completely, with smaller lesions showing better recovery of skin color and less scar formation, and no serious side effects happened.

Recently, (Chinnadurai et al., 2016) treated 75 patients with intralesional bleomycin injection and

found complete resolution (cured) in (24%) patients marked improvement occurred in (47%) patients, mild improvement in (18.5%) patients, and no cure in (10.5%) cases. In this present study, intralesional bleomycin injection was used for treating IH at a dose of 0.2 IU /kg per dose, from 2-6 injections at 3 weeks intervals. It was found to be an effective and safe protocol. All lesions markedly regressed in size (40% of lesions completely involuted with no residual masses and 60% of lesions decreased in size more than 75%). None of the patients in this present study exhibited signs of serious systemic complications of bleomycin toxicity (e.g., pneumonitis, pulmonary fibrosis and thrombocytopenia). On the other hand, the main reported complications were local at the injection site (i.e., ulceration, fibrosis and hyper-pigmentation) affecting about 65% of study patients. (Smit and Meyer, 2012) reported that the reactions that commonly occur immediately after intralesional bleomycin injection include local erythema, swelling, and pain. Bleeding, ulceration, cellulitis, hypopigmentation, transient alopecia and flu-like symptoms may also occur. Lymphangitis, flagellate hyperpigmentation, and Raynaud's phenomenon have been reported but are rare. (Muir et al., 2004) reported flu-like symptoms, ulceration, cellulitis and partial, temporary hair loss in some patients. (Pienaar et al., 2006) noticed that the most common complications hyperpigmentation, which occurred in 40% of the lesions. Other less common complications include hypopigmentation and superficial scarring. (Smit and Meyer, 2012) reported that pulmonary fibrosis is the most important dose-dependent complication of systemic bleomycin therapy but has not been reported after intralesional bleomycin injection as the dosage used in sclerotherapy are much lower than those used in oncology. Finally although bleomycin injection show great response even after first injection, side effect of bleomycin is more. In comparison with other modalities of treatment, cost of vial is more expensive than other types such as corticosteroid and bleomycin vial is stable after its dissolve for only 24 hours at room temperature or 48 hours when refrigerated.

#### Conclusion:

Intralesional injection of bleomycin is safe, highly effective tool in the treatment of different sizes of IH and has minimal and controllable local or systemic adverse effects. Intralesional bleomycin

injection was more clinically effective but less cost-effective than other modalities such as Intralesional corticosteroids in treating IHs.

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