

The Role of Intralesional Bleomycin in the Management of Cutaneous Infantile Hemangioma

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ABSTRACT:

BACKGROUND:

Infantile hemangioma, although often small after birth, it tends to follow a proliferative phase in which the growth may be rapid and unpredictable. Besides, its involution often takes many years to happen causing psychological problems and embarrassment to the parents as well as their child.

OBJECTIVE:

To evaluate the efficacy of intralesional bleomycin in the management of infantile cutaneous hemangiomas and to assess the possible side effects and complications of this treatment modality.

PATIENTS AND METHODS:

A prospective study done in Iraq over the period from October 2014 to December 2015, were 28 patients with cutaneous infantile hemangiomas had been treated by intralesional bleomycin injection, 0.25-0.5 unit/kg/dose, administered subcutaneously. The enrolled patients were divided depending on lesion size at time of presentation into two groups; those with hemangiomas less than 12 cm² and others with lesions greater than 12 cm². The lesions were measured serially and monitored with photos for follow up and documentation. Side effects were also recorded. Lesion's response was graded into five grades according to the final size after treatment.

RESULTS:

The mean age of the studied patients was 13.5±11.2 months (3 months to 4 years). The mean number of injections given was 3.7±0.7(3 to 5), and the mean total dose administered was 3.8±1.5 units/patient(2.5 to 9). Complete involution (>90% reduction in the size of the hemangioma) was recorded in 9(32.1%) children. Twelve (42.9%) children were reported to achieve 75-90% reduction in the size of the hemangioma. In 6(21.4%) children, there was a 50-75% reduction in the size of the lesion, and only 1 patient had <25% reduction in the size of the lesion. The mean follow up period was 5.8±2.1 months (3 to 10 months). Hyperpigmentation was the most common complication and was reported in 11(42.3%)patients.

CONCLUSION:

Intralesional bleomycin is an effective option in the treatment of cutaneous infantile hemangioma

KEYWORDS: intralesional, bleomycin injection, cutaneous, infantile, hemangioma.

INTRODUCTION:

The terms "infantile hemangioma" and "hemangioma of infancy" are used to describe a specific group of vascular tumors that arise during infancy and demonstrate characteristic clinical and histologic features.⁽¹⁾ Infantile hemangiomas arise during the first year of life and are considered the most common tumor of infancy. They develop in 4-5% of infants, with

the majority of lesions noted within the first several weeks of life⁽²⁾.

Infantile hemangiomas usually follow a course of proliferative, involuting and involuted phases.

The proliferative phase is marked by rapid growth for the first 6-8 months that typically plateaus by age of 10-12 months⁽⁴⁾. The involuting phase occurs from age 1 to 5-7 years during which time the tumor slowly regresses. This phase is notable for fading color of the tumor from crimson to a dull purple, accompanied by deflation of the tumor size⁽⁵⁾.

In the final involuted phase, 50% of patients have nearly normal skin in the area of prior lesion. Patients with larger tumors can have lax or redundant skin and yellowish discoloration⁽⁵⁾.

Systemic and local corticosteroids were considered first line therapy for decades⁽⁴⁾.

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Propranolol, a nonselective beta blocker, has been recognized as an important therapeutic option and in most centers, has become the first line of therapy⁽⁵⁾. Vincristine can be effective in the treatment of infants with complicated lesions that do not respond to corticosteroids⁽⁶⁾. The application of laser therapy has been useful in the management of superficial lesions and hemangiomas in certain locations such as the upper eyelid when visual obstruction is a concern⁽⁴⁾. Surgical excision is often reserved for involuted lesions with residual scars, pedunculated lesions, localized periorbital hemangiomas and for slowly involuting hemangiomas in cosmetically concerning locations⁽⁷⁾.

Bleomycin is a cytotoxic antitumor antibiotic derived from the fungus *Streptomyces Verticillus*, as a systemic chemotherapeutic agent. It acts by inducing apoptosis in rapidly growing immature cells with specific sclerosing effect on vascular endothelium⁽⁸⁾. It has low toxicity and is associated with minimal immunosuppression and myelosuppression. Bleomycin can be administered intralesionally by means of subcutaneous injection and is proven to be an exciting modulator of vascular anomalies. This nonsurgical and scarless treatment option has the added advantage of predictable and significant response rates in hemangiomas and vascular malformations⁽⁹⁻¹⁰⁾. Bleomycin hydrolase, that inactivates bleomycin, is present in all organs but in lower concentrations in the skin and lungs. This explains why the side effects of bleomycin are predominantly cutaneous and pulmonary⁽¹²⁾.

PATIENTS AND METHODS:

which 0.25-0.5 unit/kg/session was given depending on patient's age and size of the lesion. A single dose of 10 units per session (a total dose of 70 units per course) was never exceeded in this study.

Transcutaneous injection was performed through non-affected normal skin to avoid bleeding and then advanced into the hemangioma in subcutaneous and deep tissue planes. Bleomycin was injected slowly in radial fashion until the hemangioma became pale or swollen. Most patients experienced unremarkable post-injection period and were discharged 1-2 hours after treatment with paracetamol syrup prescribed for analgesia.

The treatment course consisted of 3 injections given at 3 weeks interval. A second course could be given if the lesion had complications or if it was large in size.

A prospective study over the period from October 2014 to December 2015 enrolling 28 patients with cutaneous infantile hemangiomas during their proliferative and involuting phases with associated complications including ulceration, bleeding and obstruction as well as lesions at or near vital structures. Patients with lesions at the involuted phase and those with visceral lesions were excluded from the study. Other exclusion criteria include patients whom parents refuse the treatment modality, neglect or miss a treatment dose and patients with sensitivity to bleomycin documented after the first session. Parents received extensive counseling regarding likely outcomes and possible side effects of treatment as part of informed consent.

History and clinical data including age, gender, weight and address were obtained. Clinical examination of each patient was done with emphasis on the lesion's location, size (in cm²) and number as well as any associated complication.

The diagnosis of cutaneous hemangiomas was confirmed clinically in all patients. Besides routine necessary investigations, an ultrasound was obtained in patients with multiple lesions. Chest X-ray was done for every patient before starting treatment as a baseline study to assess any pulmonary complication related to bleomycin after completing treatment.

All patients with cutaneous hemangiomas were treated with intralesional bleomycin injection. Dosage regimens were in accordance with previous studies in

Patients were divided into 2 groups depending on lesion's size; those with lesions <12cm and others with lesions >12cm to assess whether the initial size of the hemangioma was a factor affecting response to treatment.

The response rate to treatment was graded as follows:

1. complete resolution implying > 90% reduction in lesion's size
2. 75-90% reduction in lesion's size
3. 50-75% reduction in lesion's size
4. 25-50% reduction in lesion's size
5. less than 25% reduction in lesion's size

Colored photographs were taken for every patient before, during and after completion of treatment. Complications were also recorded during the follow-up period.

Data were analyzed using the (SPSS) version 20. Pearson's chi-square test was used to assess relations between categorical variables.

BLEOMYCIN IN CUTANEOUS INFANTILE HEMANGIOMA

McNemar chi-squared statistics with Yates correction was used to assess effectiveness of treatment. P-Value less than 0.05 was used as the alpha level of significance.

RESULTS:

Five (17.9%) of the studied patients were males whereas 23(82.1%) were females. 18(64.3%) of the patients were infants at time of presentation while the other 10(35.7%) were more than 1 year of age.

19 (67.8%) patients were presented with hemangiomas $<12\text{cm}^2$ in size and 9 (32.2%) patients had lesions $>12\text{cm}^2$.

The mean age was 13.5 ± 11.2 (3-48) months, and the mean weight was 10.1 ± 3.8 (5-18) kg.

Twenty four (85.7%) hemangiomas were situated in the head and neck; of these lesions 19 were $<12\text{cm}^2$ and the other 5 were $>12\text{cm}^2$. Only 4 (14.3%) hemangiomas were located in peripheral locations and all of these were $>12\text{cm}^2$. Table(1).

Table 1: Relation between lesion size and site among patients with Hemangioma.

Variables	Size of lesion				Total		p value
	< 12 cm ²		> 12 cm ²				
	No.	%	No.	%	No.	%	
Lesion site							
Cheek	5	26.3%	1	11.1%	6	21.4%	0.108 NS
Neck	5	26.3%	0	0.0%	5	17.9%	
Forehead	3	15.8%	1	11.1%	4	14.3%	
Periocular	2	10.5%	2	22.2%	4	14.3%	
Perioral	2	10.5%	1	11.1%	3	10.7%	
Periaural	2	10.5%	0	0.0%	2	7.1%	
Extrimities	0	0.0%	2	22.2%	2	7.1%	
Back	0	0.0%	1	11.1%	1	3.6%	
Trunk	0	0.0%	1	11.1%	1	3.6%	
Total	19	100%	9	100%	28	100%	
Chi-square test, NS= not significant at 0.05 level							

The mean number of injections given was 3.7 ± 0.7 (3-5), and the mean dose of bleomycin given was 3.8 ± 1.5 units (2.5-9). The mean

duration of follow-up to reach complete resolution or healing of complicated lesion was 5.8 ± 2.1 months (3-10).

Table 2: Mean differences between study groups regarding the number of injections, Bleomycin dose and follow-up duration.

Parameters	Size of lesion Mean $\pm$ SD (range)		Total Mean $\pm$ SD (range) N=28	p-value
	$<12\text{cm}^2$ N=19	$>12\text{cm}^2$ N=9		
Number of injections	3.4 ± 0.5 (3-4)	4.3 ± 0.5 (4-5)	3.7 ± 0.7 (3-5)	$<0.001^*$
Dose of Bleomycin (IU)	3.3 ± 0.9 (2.5-5.5)	4.8 ± 2.1 (2.5-9)	3.8 ± 1.5 (2.5-9)	0.016*
Duration of follow up (months)	4.7 ± 1.2 (3-8)	8.1 ± 1.8 (5-10)	5.8 ± 2.1 (3-10)	$<0.001^*$
Independent t-test, * Significant at 0.05 level				

Twenty one (75%) patients achieved $>75\%$ reduction in the size of the hemangioma, of whom 9 were judged to have complete involution ($>90\%$ reduction in the size of the lesion). 6(21.4%) patients had achieved 50-75% reduction in the

size of their lesions and 1 (3.6%) child achieved less than 25% reduction in the size of the hemangioma. No patients were categorized to achieve 25-50% reduction in the size of their lesions. Table (3).

Table 3: Relation of lesion size with response rate and post-injection complications

ariables	Size of lesion				Total		p value
	< 12 cm ²		> 12 cm ²				
	No.	%	No.	%	No.	%	
Response rate							
Reduction in size > 90% (Complete resolution)	7	36.8%	2	22.2%	9	32.1%	0.299 NS
Reduction in size 75% - 90%	7	36.8%	5	55.6%	12	42.9%	
Reduction in size 50% - 75%	5	26.4%	1	11.1%	6	21.4%	
Reduction in size < 25%	0	0.0%	1	11.1%	1	3.6%	
Post-injection complications							
Hyperpigmentation	7	41.2%	4	44.4%	11	42.3%	0.155 NS
Fever	4	23.5%	2	22.2%	6	23.1%	
Hypopigmentation	5	29.4%	0	0.0%	5	19.2%	
Flu-like illness	1	5.9%	1	11.1%	2	7.7%	
Ulceration	0	0.0%	2	22.2%	2	7.7%	
Total	19	100%	9	100%	28	100%	
Chi-square test, NS= not significant at 0.05 level							

Hyperpigmentation was the most common complication and was reported in 11 patients, while hypopigmentation was reported in 5 patients. Low grade fever was documented in 6 patients and was subsided with paracetamol syrup. Flu-like illness was reported in 2 patients.

No patient in the study had pulmonary fibrosis after completion of the treatment. Table (3). Overall complete resolution occurred in 9 (32.1%) patients, 7 (36.8%) of them had lesions < 12cm² and 2(22.2%) had lesions > 12cm² prior to treatment.

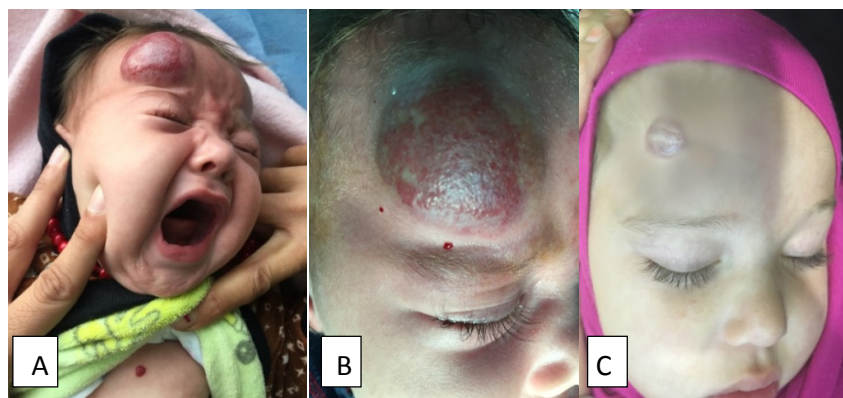


Figure 1: (A) 5 months old female with large IH (size >12 cm²) on the forehead. (B) After the first treatment session. (C) 7 months later, when treatment course was completed (75-90% reduction in size).

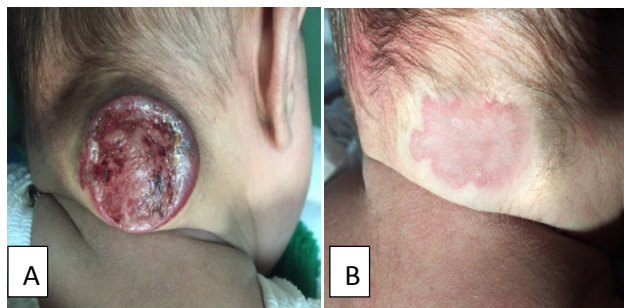


Figure 2: (A) 6 months old female infant with posterior neck ulcerating IH with size $>12\text{ cm}^2$. (B) 4 months later after treatment with $>90\%$ reduction in size



Figure 3: (A) 9 months old male with large proliferative right cheek IH with size $>12\text{ cm}^2$. (B) when he was 15 months old after treatment with IBI with complete resolution but hyperpigmented scar.

DISCUSSION:

Awareness and parent's expectation about their child's look is a growing problem to the pediatrician and pediatric surgeon enhancing them to better, earlier and more effective treatment of these troublesome pathological lesions that affect both the parents and their child specially when the child is growing to reach school age.

In this study, 23(82.1%) patients were females. This goes with the findings of Pienaaer et al⁽⁸⁾ and Sainsbury et al⁽⁹⁾ who reported that the female patients were 83.3% and 84.6% respectively. These findings prove the fact that infantile hemangiomas develop more frequently in females⁽¹⁾.

In this study, 18(64.35%) patients were infants at time of presentation. This goes with Saitta et al⁽¹⁰⁾ and Pienaar et al⁽⁸⁾ who reported that 68% and 63% of their patients were infants respectively. This may be explained by the natural history of hemangiomas in children which usually follows a proliferative phase during the first year of life causing them to increase in size well enough to

bring the attention of the parents as well as their anxiety and cosmetic concern about their child.

Twenty four (85.7%) of the hemangiomas were located in the head and neck while only 4(14.3%) were located in the trunk and extremities. Similar results were given by Sainsbury et al⁽⁹⁾ and Saitta et al⁽¹⁰⁾. Who reported that 82% and 84.2% of the lesions in their studies were located in the head and neck respectively. This supports the fact that infantile hemangiomas usually have an anatomic predilection to the head and neck.

The mean number of injections given for patients with lesions $< 12\text{ cm}^2$ was 3.4 ± 0.5 and for patients with lesions $> 12\text{ cm}^2$ was 4.3 ± 0.5 . The mean dose of bleomycin given for patients with lesions $< 12\text{ cm}^2$ was 3.3 ± 0.9 IU and for patients with lesions $> 12\text{ cm}^2$ was 4.8 ± 2.1 IU. The mean follow-up duration for patients with lesions $< 12\text{ cm}^2$ was 4.7 ± 1.2 months and for patients with lesions $> 12\text{ cm}^2$ was 8.1 ± 1.8 months. These significant differences between the two groups indicate that the larger the lesion's size, the bigger the bleomycin dose required, the

more frequent number of injections needed and the longer time of follow-up necessary to reach complete resolution or recovery from complications as well as parent's satisfaction.

In this study, complete response (>90% reduction in the size of the lesion) was reported to occur in 32% of the patients. This finding is similar to those of Sainsbury et al⁽⁹⁾, Omidvari et al⁽¹²⁾ and Pienaar et al⁽⁸⁾ who reported that complete response was achieved in 40%, 35% and 39% of the patients respectively. There are two reasons to choose bleomycin rather than other therapeutic modality. Bleomycin has been shown to have a sclerosant effect on the endothelial cells of the cyst wall of lymphangioma and hemangiomas⁽¹³⁾, and as an antineoplastic agent, it has an apoptotic effect on rapidly growing immature cells⁽¹⁴⁾ and thus is ideally suited to the proliferative phase of hemangiomas which usually occur during infancy.

Complete response was reported in 36.8% of the patients with lesion's size < 12cm² and in 22.2% of those with lesion's size > 12 cm². These findings have no significant difference, and go with Pienaar et al⁽⁸⁾ study in which complete response was reported in 39% of the patients with lesion's size < 12cm² and in 25% of those with lesion's size > 12cm². This proves that bleomycin is effective in reducing hemangioma regardless of the lesion's size.

All of the side effects and complications related to intralesional bleomycin in this study were statistically non-significant and not-dangerous and could be treated easily. Hyperpigmentation was the most common side effect and reported in 42.3% of the patients followed by fever (23.1%), hypopigmentation (19.2%), flu-like illness (7.7%) and skin ulceration (7.7%). These side effects were not related to lesion's size but mainly to tissue reaction in response to intralesional injection.

Pulmonary fibrosis is a delayed side effect that usually occurs three months after injection but it is age and dose related. Patients older than 50 years of age are at great risk to develop this complication. The safe cumulative dose is 250 IU given systemically at which the risk to develop pulmonary toxicity decreases to 0.5%⁽¹⁵⁾. Atwa et al⁽¹⁶⁾ reported only one patient to develop this complication among 2600 patients in his study with up to 10 years follow-up. That patient received 2 units of bleomycin/kg. In this study, 0.25-0.5 unit/kg was the standard dose given to all patients with no major side effect reported over 4 months period of follow-up.

CONCLUSION:

Intralesional bleomycin is one of the treatment modalities that should be considered in managing small as well as large cutaneous infantile hemangiomas. In the proliferative phase, more than two-thirds of children can achieve 75% reduction in the size of their lesions. Completion of treatment to reach high response rate may take several months and require reassurance and patience. Hyperpigmentation, scarring and bleeding are low risk side effects. Pulmonary toxicity and fibrosis was not reported.

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