SJIF Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 9
Issue: 4
Page N. 139-145
Year: 2025

Original Article www.wjahr.com

COMPARISON BETWEEN INTRALESIONAL BLEOMYCIN AND TRIAMCINOLONE IN THE TREATMENT OF CAPILLARY HEMANGIOMA AMONG PROPRANOLOL NON-RESPONDERS IN MOSUL CITY

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Article Received date: 10 February 2025 **Article Revised date:** 30 February 2025 **Article Accepted date:** 20 March 2025

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ABSTRACT

Background: Capillary hemangiomas can be treated in different ways depending on the location of the hemangioma, how large it is, and whether or not it is causing vision problems. Currently available treatment options include laser therapy, surgery, chemotherapeutic drugs (bleomycin, vincristine, and alpha-interferon), systemic or intralesional corticosteroids, or a mix of them. Every choice has certain restrictions because of negative consequences. **Objectives:** Is to compare the efficacy of intralesional bleomycin and intralesional triamcinolone among non-responders to propranolol therapy in terms of size reduction and side effects. **Methods:** A nonrandomized controlled trial was conducted in the Department of Pediatric Surgery at Ibin Al Atheer Hospitals**, f**rom January 2024 to February 2025. The study included children aged 0-14 years with uncomplicated cutaneous capillary hemangiomas who presented to the outpatient department or were admitted to the hospital. The study excluded children with infected hemangiomas, solid organ hemangiomas, contraindications to oral propranolol and prior treatment for the same lesion. The questionnaire includes five sections, section one for demographic information, section two for intervention used, section three for patient clinical presentation information and section four for response details of the lesion and part five for complication of the intervention used. **Results:** The study included 148 infants with infantile cutaneous hemangioma. Of them; 98 (66.22%) patients were respond to propranolol treatment, while 30 (20.27%) patients are partial respondents and 20 (13.51%) patients were not respond to propranolol treatment. Among the patients with inadequate response (partial and non-respondents) which are 50 patients, the mean ± standard age was 3.23 ± 0.71 years. The majority of them (64%) are from the age group of less than 1 year. Moreover; 31 (62%) patients were females and 19 (38%) were males with female to male ratio was 1.63. Bleomycin shows better response rate than triamcinolone (P value <0.001). With significantly less dose of drug need for bleomycin group (P value <0.001). **Conclusion:** In children with partial or no response to oral propranolol, intralesional bleomycin is more effective than intralesional triamcinolone. Triamcinolone and propranolol may have similar mechanisms of action when compared to bleomycin, as non-responders to propranolol may similarly have poor reactions to triamcinolone. Bleomycin could offer extra benefits to those on propranolol.

KEYWORDS: Infantile hemangioma, Bleomycin, Triamcinolone, Mosul, Iraq.

1. INTRODUCTION

A capillary hemangioma, also known as a "strawberry" birthmark, is a benign tumor composed of malformed capillary vessels.[1] Although they may not be present at birth, capillary hemangiomas typically show up during the first six months of life.[2] They normally grow quickly until the age of 12 months, after which they begin to decline in size between 12 and 15 months.[3] Most of capillary hemangioma disappear completely by the age of five or six years.[3-4] Nevertheless, despite the fact that they often resolve spontaneously, they are a major contributor to morbidity in children because they trigger problems like ulceration, bleeding, itching, and scarring; as a result, about 40% of children need additional care.[5-6]

Capillary hemangiomas are more frequent among preterm babies and girls.[7] They can be detected at any body part.[8] They typically grow on the eye's eyelids, the orbit, the conjunctiva, and eye's surface.[9] Visual impairment may result from capillary hemangiomas on the eyelid.[9-10] As the hemangioma expands, it may press

against the eye's surface, changing the eye's shape and causing astigmatism.[9-11] If the hemangioma causes the eyelid to drop (ptosis) and impede vision, it might cause focusing issues and amblyopia.[11-12]

Capillary hemangiomas can be treated in different ways depending on the location of the hemangioma, how large it is, and whether or not it is causing vision problems.[13] Currently available treatment options include laser therapy, surgery, chemotherapeutic drugs (bleomycin, vincristine, and alpha-interferon), systemic or intralesional corticosteroids, or a mix of them. Every choice has certain restrictions because of negative consequences.[14-15]

Propranolol is now used as a first line of treatment for capillary hemangiomas.[16] Other beta blocker medications like atenolol have also been shown to be safe and helpful in treating hemangiomas. If the hemangioma is superficial (on the surface) or small, then a beta-blocker eye drop, such as Timolol can be rubbed directly on the skin of the hemangioma instead of taking the medicine by mouth.[17] However, some patients need further therapeutic measures because they either do not respond to propranolol or respond partially to it.[16-17]

Previous studies indicate that corticosteroids and bleomycin intralesional therapy can be useful for infantile hemangiomas.[18-20] However; there are few studies comparing corticosteroids and bleomycin in treatment of infantile hemangioma, especially in Iraq. As a result, the purpose of this study was to compare the efficacy of intralesional bleomycin and intralesional triamcinolone among non-responders to propranolol therapy in terms of size reduction and side effects.

2. PATIENT AND METHODS

A nonrandomized controlled trial was conducted in the Department of Pediatric Surgery at Ibin Al Atheer Hospitals**,** from January 2024 to February 2025. The study included children aged 0-14 years with uncomplicated cutaneous capillary hemangiomas who presented to the outpatient department or were admitted to the hospital. The study excluded children with infected hemangiomas, solid organ hemangiomas, contraindications to oral propranolol (e.g., bronchial asthma, cardiac abnormalities, diabetes mellitus), and prior treatment for the same lesion (oral or intralesional). A modified questionnaire was used to collect data, including sociodemographic information, natal history, and clinical history (size, site, and color of lesion upon presentation). Patients received oral propranolol at 2 mg/kg body weight in two separate doses for 3-6 months. Every month, the lesion was examined for regression in size (maximum diameter). Before starting propranolol medication, all patients underwent a thorough history, clinical examination, and baseline testing to identify any potential contraindications. Ultrasonography with color Doppler was used to diagnose hemangioma when clinical diagnosis was uncertain.

Children were categorized into three groups according to their clinical response to oral propranolol:

• Responders: who experienced more than 50% reduction in lesion size following therapy.
• Partial responders: who saw a 25%-50% reduction in lesion size following 6 months of treatment.
• Non-responders: who experienced less than 25% lesion size reduction after 6 months of treatment.

Only partial and non-responders were eligible for intralesional treatment. Participants were randomly assigned to Group A or Group B based on their response status.

- Group A: Children received intralesional bleomycin at a dose of 0.5 IU/kg (up to 15 IU in a single treatment), repeated every 3-6 weeks on an outpatient basis. Following each injection, children were monitored for 24 hours for any adverse effects.
- Group B: Children got 2 mg/kg (maximum of 60 mg) of triamcinolone intralesional injection, followed by 3-6 weeks of outpatient care.

Patients were followed up at 1, 3, and 6 months after starting intralesional treatment. A comprehensive history and examination were conducted to identify any potential side effects of therapy. The maximal diameter of the lesion was measured at each follow-up. Any negative consequences that might have arisen were adequately treated. The subsequent intralesional dosage of bleomycin/triamcinolone was likewise given throughout the follow-up.

Regression in lesion size was seen at the end of six months of intralesional therapy, and it compared with the size at the start of treatment. The response was split into three groups according on the size regression percentage:

- Excellent response: More than 75% decrease in the size of lesion.
- Good response: a 25%–75% decrease in lesion size.
- Inadequate or nonexistent response: less than 25% decrease in lesion size.

Additionally, side effects from intralesional treatment were recorded and tabulated for comparison between the two groups. The clinical response and incidence of side effects following intralesional therapy were then compared to explore the effectiveness of bleomycin and triamcinolone.

Data analysis was done using SPSS (Statistical Package for Social Sciences) software version 26 (IBM Corporation, USA). Frequencies and percentages were used to represent categorical characteristics like gender and lesion location. A mean ± standard deviation was used to display continuous variables like age and lesion size. The two intervention groups' response rates and baseline characteristics were compared using the chi-square test. The groups' pre-intervention lesion sizes were compared using the independent samples t-test. P less than 0.05 was regarded as statistically significant.

3. RESULTS

The study included 148 infants with infantile cutaneous hemangioma. Of them; 98 (66.22%) patients were respond to propranolol treatment, while 30 (20.27%) patients are partial respondents and 20 (13.51%) patients were not respond to propranolol treatment. As shown in figure 3.1.

Table 3.1: Distribution of the study population according to their response to propranolol treatment.

Response	Frequency	Percent
Respondents	98	66.22
Partial respondents	30	20.27
Non-respondent	20	13.51

Among the patients with inadequate response (partial and non-respondents) which are 50 patients, the mean ± standard age was 3.23 ± 0.71 years. It's evident that the age group of less than 1 year was prevalent among 32 (64%) patients, followed by the age groups of 1-3 years, 4-5 years, 6-8 years and 9 to 14 years with 8(16%) patients, 5 (10%) patients, 3 (6%) patients, 3 (6%) patients and 2 (4%) patients respectively. Moreover; 31 (62%) patients were females and 19 (38%) were males with female to male ratio was 1.63. Furthermore; 32 (64%) patients was born at term, while preterm and post-term delivery were prevalent among 11 (22%) patients and 7(14 %) respectively. Additionally; 37 (74%) patients had head and neck lesions while 7 (14%) had extremity lesions and 4 (8%) patients had trunk lesions. From the other hand; 33 (66%) patients were presented due to cosmetic disfigurement, while feeding problem, visual disturbance and nasal obstruction complaints was presented by 6 (12%) patients, 8 (16%) and 3 (6%) patients respectively. Lastly; 40 (80%) patients had 2-5 cm lesion size, 7 (14 %) patients had less than 2 cm lesion size and 3 (6%) patients had lesion size of more than 5 cm. As shown in figure 3.2.

Table 3.2: Demographic information and clinical presentation of the study population.

Variable	Number	Percent
Age (years):		
Less than 1	32	64
1-3	8	16
4-5	5	10
6-8	3	6
9-14	2	4
Gender:		
Female	31	62
Male	19	38
Natal history:		
Preterm	11	22
Term	32	64
Post-term	7	14
Site of lesion:		
Head and neck	37	74
Extremities	7	14
Trunk	4	8
Presenting complaints:		
Cosmetic disfigurement	33	66
Feeding problems	6	12
Visual disturbances	8	16
Nasal obstruction	3	6
Size of lesion (cm):		
Less than 2	7	14
2-5	40	80
More than 5	3	6

Table 3.3 shows comparison between the study groups regarding different demographic and clinical presentation variables. No statistically significant difference was founded between the study groups regarding; patients' ages, patients' gender, natal history, site of lesions, presenting complaints and size of lesion (P value > 0.05) for all of these variables.

Table 3.3: Comparison between the study groups regarding demographic information and clinical presentation.

Variable	Group A (Number =30)		Group B (Number =20)		P value
	Number	Percent	Number	Percent	
Age (years):					
Less than 1	17	56.66%	13	65%	0.551
1-3	6	20%	3	15%	
4-5	3	10%	2	10%	
6-8	2	6.67%	1	5%	
9-14	2	6.67%	1	5%	
Gender:					
Female	18	60%	13	65%	0.238
Male	12	40%	7	35%	
Natal history:					
Preterm	6	20%	5	25%	0.392
Term	20	66.67%	12	60%	
Post-term	4	13.33%	3	15%	
Site of lesion:					
Head and neck	23	76.67%	14	70%	0.522
Extremities	4	13.33%	3	15%	
Trunk	3	10%	3	15%	
Presenting complaints:					
Cosmetic disfigurement	19	63.33%	14	70%	0.427
Feeding problems	4	13.33%	2	10%	
Visual disturbances	5	16.67%	3	15%	
Nasal obstruction	2	6.67%	1	5%	
Size of lesion (cm):					
Less than 2	4	13.33%	3	15%	0.728
2-5	24	80%	16	80%	
More than 5	2	6.67%	1	5%	

Table 3.4 explores comparison between the study groups regarding different response variables. Statistically significant difference results were found between the study groups regarding response result, in other word; bleomycin group shows better results (P value <0.001). Moreover; statistically significant difference result was found again between the study groups regarding dose of drug with less dose need for bleomycin group (P value <0.001). Lastly no statistically significant difference was found regarding the duration of treatment (P value = 0.298).

Table 3.4: Comparison between the study groups regarding response variables.

Variable	Group A (Number =30)		Group B (Number =20)		P value
	Number	Percent	Number	Percent	
Excellent	21	70%	5	25%	**<0.001**
Good	6	20%	6	30%	
Poor	3	10%	11	45%	
Dose of drug, mean ± Standard deviation (IU/mg)	3.2 ± 0.3		3.9 ± 1.8		**<0.001**
Duration of treatment, mean ± Standard deviation (weeks)	21.3 ± 2.5		21.5 ± 3.2		0.298

Table 3.5 illustrates various complications which were occurred with both of the study groups. Out 30 patients treated by bleomycin 12 (30%) patients developed complications versus out of 20 patients treated by triamcinolone 7 (35%) patients developed complications (P value = 0.427). Among the group of bleomycin; 6 (15%) patients developed skin hyperpigmentation, while 2 (6.67%) patients developed either hypopigmentation, hypertrophic scar and superficial ulcer respectively. From the other hand; among the group of triamcinolone; 4 (20%) patients developed skin redness and 1 (5%) patient develop either lipoatrophy, hypertrichosis and sterile abscess respectively.

Table 3.5: Complications occurred following therapy among the study groups.

Complications	Number	Percent
Group A (bleomycin)	12	30%
Hyperpigmentation	6	15%
Hypopigmentation	2	6.67%
Hypertrophic scar	2	6.67%
Superficial ulcer	2	6.67%
Group B (triamcinolone)	7	35%
Redness	4	20%
Lipoatrophy	1	5%
Hypertrichosis	1	5%
Sterile abscess	1	5%

4. DISCUSSION

There have been instances of propranolol poor response, despite its effectiveness. Furthermore, little is known about the kind of infantile hemangioma that does not improve with propranolol therapy.[21] When there is little to no response, the patient must be treated with a safe alternative. It has been observed that infantile hemangiomas can be treated with intralesional (IL) bleomycin and triamcinolone injection.

The present study founded about two third of the study participants are respond to propranolol treatment, comparably; at al have shown that propranolol is an effective first‑line treatment for infantile hemangiomas response rates about 60%.[22]

This study founded that more than half of the study participants are less than 1-year age, with gradual decrease of incidence with growing of age. The study results are in the same line of Leung et al study findings which mentioned that hemangiomas frequently started as pale patches in the first few weeks of life and progress to telangiectatic or light red patches. For the next three to six months of their lives, they grow quickly, after which they begin to decline in size between 12 and 15 months.[3] From the other hand; the study founded that infantile hemangioma occurred more frequently among females than males which runs with previous prospective studies in the United States and Europe have shown that infantile hemangioma occurred more likely among females.[23-24] The specific reason behind the female preponderance is still unknown. But according to a number of studies, estrogen (E2) may be responsible for the female preponderance, and E2 signaling plays a significant role in angiogenesis. Previous studies had demonstrated that the hemangioma tissue had estrogen receptors and that the E2 level in healthy children was much lower than that in infantile hemangioma patients.[25] The majority of the propranolol non-responders founded in this study, were older than one year, which is another interesting result. Therefore, it can be said that as the age at which therapy was started increased, the responsiveness to oral propranolol declined. Studies indicate that vasoconstriction, angiogenesis suppression, and apoptosis induction are the potential mechanisms by which propranolol works during the proliferative phase of growth. As a result, it reduces lesion growth and encourages regression when initiated during the proliferative phase. Perhaps this proliferative stage had already been reached by children who did not benefit from the therapy.[26]

When it came to the partial/non-responders to propranolol, the current study discovered that the children in the bleomycin group had a significantly more excellent response to treatment than those in the triamcinolone group. The effectiveness of intralesional bleomycin in hemangiomas has been demonstrated by Ekta Narang et al study findings.[27] Bleomycin acts by causing local sclerosis in the endothelium cells, which results in a nonspecific inflammatory response.[28] Unsurprisingly, children in the triamcinolone group also received a noticeably larger mean dosage of the medication. The two medications had the same safety profile, despite bleomycin being proven to be more effective in terms of response. Comparable findings were obtained from Gulab Dhar Yadav et al.[29]

When interpreting the study findings, it is important to take into account the limitations of it. First, the results may not be as easily applicable to different populations due to the small sample size. Second, the study was only carried out at one center, which might limit the findings' external validity. However; the study strength is no previous study comparing intralesional treatment of bleomycin and triamcinolone in the treatment of infantile hemangioma patients.

5. CONCLUSION AND RECOMMENDATION

In children with partial or no response to oral propranolol, intralesional bleomycin is more effective than intralesional triamcinolone. Triamcinolone and propranolol may have similar mechanisms of action when compared to bleomycin, as non-responders to propranolol may similarly have poor reactions to triamcinolone. Bleomycin could offer extra benefits to those on propranolol. Further research is needed to validate the mechanism and improve management of children with infantile hemangioma.

ACKNOWLEDGEMENT

We appreciate the assistance offered by the medical staff at Ibin Al Atheer Teaching hospital and the thorough attention the Nineveh Directorate of Health gave to our

study project. This study could not have been done without the assistance of each of these people.

CONFLICT OF INTERTEST

About this study, the authors disclose no conflicts of interest.

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