

Different Pharmacological Modalities for the Treatment of Cutaneous Hemangioma: A Randomized Controlled Trial

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ABSTRACT

Hemangiomas are commonly seen benign tumors in pediatric dermatology, affecting neonates and infants. They manifest in stages and can require medical or surgical intervention in certain cases. Management modalities include conservative observation only, corticosteroids, cytotoxic drugs, beta blockers, and Lasers. This 3-year prospective randomized controlled study involved pediatric patients with hemangiomas of different types. Patients were divided into groups based on treatment: intralesional propranolol, topical propranolol, intralesional bleomycin, topical bleomycin, intralesional corticosteroids, and topical corticosteroids. Treatment responses were evaluated using clinical assessments and a grading system. Clinical assessments were performed at baseline and follow-up visits by evaluating lesion size, severity, and symptoms. A standardized grading system (e.g., mild, moderate, severe) was used to assess treatment response and disease progression. The study included 84 patients with varying hemangioma types. Treatment interventions showed comparable efficacy across groups, with no significant differences in age distribution, initial tumor size, or post-therapy outcomes observed. Topical and intralesional bleomycin, propranolol, and corticosteroids demonstrated similar effectiveness, regardless of patient age or tumor size. The study underscores the efficacy of various treatment modalities, including intralesional and topical applications of propranolol, bleomycin, and corticosteroids, in managing hemangiomas among pediatric patients. The findings indicate comparable effectiveness across these interventions, with no significant differences in treatment outcomes based on patient age, initial tumor size or tumor size after treatment. Further research and long-term follow-ups are warranted to refine treatment strategies and optimize outcomes for pediatric patients with hemangiomas.

Keywords: *Efficiency, Cutaneous hemangioma, Treatment*

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INTRODUCTION

One of the most common benign dermatological tumors in paediatrics is haemangioma. Its prevalence among neonates ranges from 1% to 2.6%. Prevalence increases among infants under one year to 10–12%¹. Its origin is from vascular endothelium; it appears during the first months of life, yet not necessarily at birth. It goes through different stages in its natural history, such as the proliferative phase (endothelial proliferation and hypercellularity), the stationary phase, and the involuting phase (slow regression), which is what happens to almost all haemangiomas. We can classify infantile haemangioma as superficial capillary, deep cavernous, or mixed haemangioma^{2,3}.

Spontaneous resolution is the common fate of infantile haemangioma, conservative observational management is the rule. However, there are instances when medical and/or surgical intervention becomes necessary. These situations include a large haemangioma, repeated bleeding, ulceration, or infection, or a haemangioma that is located in a deep organ and affects the function of the organ. Nevertheless, when indicated, there are different available treatment modalities for infantile haemangioma. Among these modalities, the first line is corticosteroids with their different routes, whether topical, intralesional, or systemic. Topical and intralesional steroids can be used for superficial, low-risk, small-sized (diameter of 1–2 cm) lesions^{1,4-7}. The second option is to use cytotoxic drugs like cyclophosphamide, bleomycin, and interferon alfa-2a and -2b. This is especially useful for complicated haemangiomas that don't get better with steroids. Intralesional bleomycin was used in children less than one year in a study conducted by Hassan et al. and proved to be effective and safe. The outcome was 24% of patients had complete resolution, yet it had reported superficial and systemic complications⁸.

Recently, the use of beta blockers has proven to be both effective and safe. This can either be topical timolol, propranolol ointment, oral propranolol, or oral atenolol. A study reported that out of 197 patients treated with beta blockers, 97% had complete resolution; some of those treated have treatment failure when on corticosteroid trial therapy. These medications proved to have a high safety profile, with only mild hyperkalaemia reported in about 3 patients^{9,10}. However, other treatment modalities can include laser and light therapy, surgical resection (for ulcerated lesions), and negative pressure wound therapy¹⁰. This study aimed to assess the efficacy and response of bleomycin, administered topically or intralesionally, in treating different histological types of haemangiomas compared to conventional treatments such as propranolol and corticosteroids.

MATERIALS AND METHODS

Study design: This 3-year prospective randomized controlled study was conducted at 3 different institutional hospitals.

Study population: Initially, all hemangiomas underwent histological assessment to ascertain their types of hemangiomas. Accordingly, they were divided into (capillary, mixed, and cavernous). Children aged from 3 months up to 14 years who suffered from any of the 3 hemangioma types were included in the study, excluding those who suffered from any associated structural anomalies, who had any complications at the time of examination, who were previously treated for hemangiomas with failed treatment, and who had painful lesions and/or periorbital infections.

Study groups and interventions: Participants were randomly assigned to study groups using a computer-generated randomization sequence. Allocation was concealed using sealed opaque envelopes to ensure

unbiased assignment. Patients were divided into 3 main groups (28 patients each). Each group is further subdivided into two subdivisions (A and B) groups. In Group 1A, patients with variable types of hemangiomas underwent intralesional propranolol therapy. The volume of the drug was calculated in relation to the lesion size; for every cm of the lesion, 0.2 ml was injected. The maximum intralesional injection volume did not exceed 1 ml per injection session. Patients of this group individually underwent a thorough clinical assessment of cardiac and respiratory systems before, during, and post-injection. They were kept under strict observation for the first 24 hours post-therapy. Their blood pressure and heart rate were assessed hourly. Moreover, blood glucose was measured among those who showed irritability and/or distress. After discharge, they were followed up weekly during the first month, then every two weeks during the second month. Further evaluation was done every 4 weeks during the following 4 months post-injection. Investigators blindly assessed all patients without knowing the type of injected drugs. Hemangioma size was clinically measured, and color photographs were taken to document the lesion size in mm before, during, and after therapy. The response to treatment was evaluated after the end of the last therapeutic session. A scale for assessment was set as excellent, good, fair, and poor. This was assessed when the intralesional session stopped. An excellent grade was considered when achieving complete resolution. A good grade means a reduction of size ≥ 50 percent. A fair grade means a reduction of less than 50 percent. Hemangiomas that didn't respond to treatment or even worsened are graded as poor.

In Group 1B, a propranolol hydrochloride ointment was prepared at 1 percent concentration. It was applied twice daily in a thin layer (1.5 mg/cm², or 15 μ g propranolol/cm²) to the hemangioma. A follow-up study of the patients was performed by serial photographs before, during, and after using the ointment. The grading system for evaluating therapy efficacy was the same as in Group 1A.

In Group 2A, similarly to Group 1, all patients underwent a meticulous clinical assessment of the respiratory system before the injection. Moreover, careful monitoring for any pulmonary fibrosis was done during and after the intralesional injection. Fifteen milligrams of bleomycin powder were used, dissolved in 15 ml of normal saline to yield a concentration of 1 mg per ml. In superficial small capillary lesions, direct intralesional injection was performed using a 27-gauge needle. The total administered dose did not exceed 1 mg per kilogram. However, in 3 patients with proliferating cavernous hemangioma, the dosage was raised (up to 3 mg per kilogram in 1 patient). No pulmonary complications were recorded. However, for large lesions, multiple needles of a slightly larger gauge (23) were used for serial injections. Post-therapy assessment was done using standardized color photographs with the same grading system similar to what was used in Group 1A.

In Group 2B, bleomycin ointment was used. It was prepared as 0.25 units per ml. An ointment of 0.5 ml was used to treat superficial hemangioma (capillary and mixed), yet higher doses of 0.5 units per ml were used to treat the proliferative type (cavernous hemangiomas). Parents were advised to apply it to the lesion to avoid affecting the healthy skin surrounding hemangiomas. The ointment was initially used once daily for 1 to 2 weeks. The dose was adjusted based on each individual's response. After this period, the dose may continue if the response is not satisfactory, or it will be tapered gradually to 3 to 4 times weekly if the response is satisfactory. In Group 3A, intralesional corticosteroid therapy was employed. Triamcinolone acetonide, prepared at 40 mg per ml, was injected directly into the hemangioma lesions. The dosage per injection did not exceed 3 mg per kilogram,

as previously described in managing problematic cases. Patients and their guardians were briefed on the procedure and potential side effects. The injections were administered by trained medical personnel using a sterile technique to minimize the risk of infection. Following each injection, patients were monitored for immediate adverse reactions, and post-procedural care instructions were provided. Subsequent injections were scheduled based on the individual's response and clinical progress. Regular follow-up assessments were conducted to evaluate treatment efficacy and monitor for any complications. The goal of this therapeutic approach was to induce regression and reduce the size and vascularity of the hemangioma lesions, ultimately improving their cosmetic appearance and minimizing associated symptoms.

In Group 3B, topical corticosteroid therapy was used as betamethasone titration (Diprolene AF cream twice daily). The period of continuing or stopping therapy was related to the treatment response.

Ethical approval: The study protocol was approved by the institutional ethics committee (KFU-2025-ETHICS3043). Data were collected according to local laws, which were compatible with the Helsinki Declaration principles. Written informed consent was individually obtained for every patient by parents or guardians.

Statistical analysis: Data were analyzed using the Statistical Package for Social Science software (SPSS), version 29. Continuous data were presented using the median and interquartile range (IQR) as the data were not normally distributed. Categorical variables were presented as frequencies and percentages. Mann Whitney test and Kruskal-Wallis's rank sum test were used to examine the difference in continuous variables. Fisher's exact test was used to examine the difference in proportion across study variables. The significance level was assigned as p-value less than 0.05.

RESULT

This study involved 84 pediatric patients with hemangiomas. The median age was 39 months (IQR: 18, 64). The interventions applied included intralesional bleomycin (19%), intralesional corticosteroid therapy injection (19%), intralesional propranolol injection (19%), topical propranolol (14%), topical bleomycin (14%), and topical corticosteroid (14%).

The median size of the tumor before therapy was 4.15 cm (3.40, 5.95) and 1.00 cm (0.20, 2.83) after it, with the majority falling under the excellent category at 40%, followed by good at 33%, satisfactory at 18%, and poor at 8.3%, Table 1.

The age distribution among the groups revealed median ages of 42 months for the bleomycin group, 34 months for the corticosteroid group, and 43 months for the propranolol group, with no significant differences observed ($p=0.8$). The median initial tumor sizes prior to therapy were 4.25 cm for bleomycin, 3.85 cm for corticosteroid, and 4.60 cm for propranolol, with no statistically significant difference noted ($p=0.4$). After therapy, the median tumor sizes were 1.10 cm for bleomycin, 0.90 cm for corticosteroid, and 1.43 cm for propranolol, indicating no significant difference ($p=0.4$). Post-therapy tumor size reduction was categorized, revealing outcomes for bleomycin as 39% excellent, 29% good, 18% satisfactory, and 14% poor; for corticosteroid, 43% excellent, 36% good, 14% satisfactory, and 7.1% poor; and for propranolol, 39% excellent, 36% good, 21% satisfactory, and 3.6% poor ($p=0.9$) (Table 2).

The medians of the initial tumor sizes before therapy were as follows: 5.00 cm for intralesional bleomycin, 3.70 cm for intralesional corticosteroid therapy injection, 4.85 cm for intralesional propranolol

Table 1. Characteristics and Treatment Outcomes of Hemangioma patients

Characteristic	Frequency (percentage)
Median age (month)	39 (18, 64)
Intervention	
Intralesional bleomycin	16 (19%)
Intralesional corticosteroid therapy injection	16 (19%)
Intralesional propranolol injection	16 (19%)
Topical propranolol	12 (14%)
Topical bleomycin	12 (14%)
Topical corticosteroid	12 (14%)
Median size before therapy (cm)	4.15 (3.40, 5.95)
Median size after therapy (cm)	1.00 (0.20, 2.83)
Median size after therapy (category)	
Excellent	34 (40%)
Good	28 (33%)
Satisfactory	15 (18%)
Poor	7 (8.3%)

Table 2. Comparison of Treatment Outcomes with Bleomycin, Corticosteroid, and Propranolol

Characteristic	Bleomycin, N = 28	Corticosteroid, N = 28	Propranolol, N = 28	p-value
Age in month	42 (19, 64)	34 (16, 57)	43 (24, 65)	0.8
Tumor Size before therapy (cm)	4.25 (3.18, 6.05)	3.85 (3.30, 5.80)	4.60 (3.80, 6.08)	0.4
Tumor Size after therapy (cm)	1.10 (0.18, 2.65)	0.90 (0.15, 1.93)	1.43 (0.28, 3.00)	0.4
Tumor Size after therapy (category)				
Excellent	11 (39%)	12 (43%)	11 (39%)	0.9
Good	8 (29%)	10 (36%)	10 (36%)	
Satisfactory	5 (18%)	4 (14%)	6 (21%)	
Poor	4 (14%)	2 (7.1%)	1 (3.6%)	

injection, 4.30 cm for topical propranolol, 3.75 cm for topical bleomycin, and 3.95 cm for topical corticosteroid ($p=0.7$). The median ages of the groups were 28 months, 35 months, 35 months, 48 months, 49 months, and 33 months, respectively ($p=0.4$). The median values of post-therapy tumor sizes were 0.75 cm, 0.85 cm, 2.25 cm, 0.72 cm, 1.20 cm, and 1.00 cm, respectively ($p=0.5$). The post-therapy outcomes were classified as excellent, good, satisfactory, and poor, with varying percentages across treatments. Intralesional bleomycin resulted in 56% excellent, 25% good, 13% satisfactory, and 6.3% poor outcomes. The outcomes of intralesional corticosteroid therapy injection were as follows: 50% excellent, 31% good, 13% satisfactory, and 6.3% poor. The outcomes of intralesional propranolol injection were as follows: 38% were excellent, 44% were good, 19% were satisfactory, and 0% were poor. The outcomes of topical propranolol were as follows: 42% were excellent, 25% were good, 25% were satisfactory, and 8.3% were poor. Topical bleomycin resulted in 17% excellent, 33% good, 25% satisfactory, and 25% poor outcomes. Topical corticosteroids resulted in 33% excellent, 42% good, 17% satisfactory, and 8.3% poor outcomes ($p=0.8$) (Table 3).

The median ages of patients receiving these treatments were 48, 49, and 33 months, respectively ($p=0.4$). The initial tumor diameters before therapy were 3.75 cm to 4.30 cm, and no significant difference was observed among the groups ($p=0.5$). There was no statistically significant difference observed ($p=0.7$) in the post-therapy tumor diameters, which ranged from 0.72 cm to 1.20 cm. The post-therapy outcomes were classified as excellent, good, satisfactory, and poor. Topical propranolol demonstrated 42% good, 25% satisfactory, 25% unfavorable, and 8.3% excellent outcomes. The outcomes of topical bleomycin were as follows: 33% were good, 25% were satisfactory, 25% were poor, and 17% were excellent. In terms of outcomes, topical corticosteroids demonstrated 42% good, 25% satisfactory, 25% poor, and 8.3% excellent results ($p=0.8$) (Table 4).

Topical ($p=0.4$) and intralesional ($p>0.9$) corticosteroids, propranolol, and bleomycin did not exhibit any statistically significant association with the age of patients. Similarly, topical or intralesional bleomycin, propranolol, and corticosteroids were not associated with tumor size before treatment ($pp=0.5$, $p=0.6$) or after treatment ($pp=0.7$, $p=0.2$) (Table 5).

Table 3. Comparison of Treatment Outcomes by Administration Type

Characteristic	Intralesional bleomycin, N = 16	Intralesional corticosteroid therapy injection, N = 16	Intralesional propranolol injection, N = 16	Topical propranolol, N = 12	Topical bleomycin, N = 12	Topical corticosteroid, N = 12	p-value
Tumor Size before therapy (cm)	5.00 (3.18, 6.98)	3.70 (3.28, 5.60)	4.85 (4.03, 6.08)	4.30 (3.78, 5.60)	3.75 (3.25, 5.20)	3.95 (3.38, 5.80)	0.7
Age in month	28 (16, 56)	35 (12, 57)	35 (17, 62)	48 (41, 73)	49 (33, 68)	33 (18, 60)	0.4
Tumor Size after therapy (cm)	0.75 (0.10, 2.25)	0.85 (0.15, 1.93)	2.25 (0.21, 2.93)	0.72 (0.30, 3.30)	1.20 (0.95, 3.30)	1.00 (0.55, 2.05)	0.5
Tumor Size after therapy (category)							
Excellent	9 (56%)	8 (50%)	6 (38%)	5 (42%)	2 (17%)	4 (33%)	0.8
Good	4 (25%)	5 (31%)	7 (44%)	3 (25%)	4 (33%)	5 (42%)	
Satisfactory	2 (13%)	2 (13%)	3 (19%)	3 (25%)	3 (25%)	2 (17%)	
Poor	1 (6.3%)	1 (6.3%)	0 (0%)	1 (8.3%)	3 (25%)	1 (8.3%)	

Table 4. Comparison of Treatment Outcomes for Topical Propranolol, Topical Bleomycin, and Topical Corticosteroid

Characteristic	Topical propranolol, N = 12 ¹	Topical bleomycin, N = 12 ¹	Topical corticosteroid, N = 12 ¹	p-value ²
Age in month	48 (41, 73)	49 (33, 68)	33 (18, 60)	0.4
Tumor size before therapy (cm)	4.30 (3.78, 5.60)	3.75 (3.25, 5.20)	3.95 (3.38, 5.80)	0.5
Tumor size after therapy (cm)	0.72 (0.30, 3.30)	1.20 (0.95, 3.30)	1.00 (0.55, 2.05)	0.7
Tumor size after therapy (category)				
Excellent	5 (42%)	2 (17%)	4 (33%)	0.8
Good	3 (25%)	4 (33%)	5 (42%)	
Poor	1 (8.3%)	3 (25%)	1 (8.3%)	
Satisfactory	3 (25%)	3 (25%)	2 (17%)	

Table 5. Comparison of Treatment Outcomes for intralesional Propranolol, intralesional Bleomycin, and intralesional Corticosteroids

Characteristic	Intralesional bleomycin, N = 16 ¹	Intralesional corticosteroid therapy injection, N = 16 ¹	Intralesional propranolol, N = 16 ¹	p-value ²
Age in month	28 (16, 56)	35 (12, 57)	35 (17, 62)	>0.9
Tumor Size before therapy (cm)	5.00 (3.18, 6.98)	3.70 (3.28, 5.60)	4.85 (4.03, 6.08)	0.6
Tumor Size after therapy (cm)	0.75 (0.10, 2.25)	0.85 (0.15, 1.93)	2.25 (0.21, 2.93)	0.2
Tumor Size after therapy (category)				
Excellent	9 (56%)	8 (50%)	6 (38%)	0.9
Good	4 (25%)	5 (31%)	7 (44%)	
Satisfactory	2 (13%)	2 (13%)	3 (19%)	
Poor	1 (6.3%)	1 (6.3%)	0 (0%)	

DISCUSSION

This study aimed to assess the efficacy of different treatment modalities in size reduction and management of hemangioma among the pediatric population. The current study involved 84 hemangioma patients with a median age of 39 months. They underwent different intervention modalities including bleomycin, corticosteroid, and propranolol via intralesional route and topical route for each of these medications. Most of these modalities achieved an excellent size reduction of the hemangioma with obvious disparity between them. The overall performance of all modalities was a median size reduction from 4.15 cm (3.40, 5.95) to 1.00 cm (0.20, 2.83).

Clinical practice guidelines recommend that at the age of one-month early intervention and referral should be considered for infants who have Infantile Hemangiomas (IH)s¹¹. Propranolol is the drug of choice at a dose of 2 to 3 mg/kg per day for systemic treatment; which typically takes at least six months and could be maintained until 12 months of age¹¹. For the management of small, thin, and superficial IHs, topical timolol is recommended. Besides, laser treatment and surgery are the best options for the treatment of residual skin changes after involution¹¹.

This research demonstrated that, when evaluating the overall efficacy of various treatment modalities, irrespective of the administration method, no statistically significant difference was observed among them (p-value = 0.4). Nonetheless, the age distribution of children across various modalities shown no statistically significant difference (p-value = 0.4). Zheng et al. proposed that the selection of treatment modality should depend on the growth stage of the haemangioma. Haemangiomas in the proliferative phase are managed systemically with oral steroids, oral propranolol, and/or laser therapy. Lesions in the involutivity phase may be managed conservatively, with vigilant oversight for uncomplicated lesions potentially extending up to 18 months. Surgical procedure is warranted in cases of ulceration, scarring, or pigmented lesions. Nonetheless, treatment must be customized and personalized to meet the specific requirements of each patient¹²⁻¹⁴.

Upon examining these modalities individually, taking into account the route of administration method for each, this study found that corticosteroid treatment attained an excellent classification for size reduction in approximately 43% of cases, followed by propranolol and bleomycin, both at 39%. Topical propranolol resulted in significant size reduction in 42% of cases, whilst intralesional propranolol provided an excellent outcome in 38% of cases. Nonetheless, an excellent reduction in size was attained, with 33% efficacy from topical corticosteroids and 50% from the intralesional variant of steroids. Topical bleomycin resulted in only 17% good size reduction, whereas intralesional bleomycin attained up to 56% excellent size reduction. The literature contains numerous studies evaluating various treatment regimens to identify the most effective and safest approach for treating haemangiomas. A review and meta-analysis conducted by Ali Izadpanah et al contrasted the traditional treatment of haemangiomas with corticosteroids with the recent approach of employing non-selective beta blockers. They determined that fewer than 90% of individuals treated with corticosteroids responded to therapy, but 99% of those administered propranolol did respond. Consequently, while steroids were initially the primary treatment, beta blockers are emerging as effective and safer alternatives¹⁵⁻¹⁷. Propranolol is contraindicated in people with cardiac conditions (arrhythmias, heart failure, and cardiogenic shock), certain respiratory disorders such as asthma and reactive airway illnesses, as well as individuals with hypersensitivity to the medication¹⁸.

Surgical operations are designated for complex illnesses and individuals who do not respond to conservative and medicinal treatment^{19,20}. Additional treatments encompass laser therapy, namely

flashlamp pumped pulsed dye laser (FPDL), which is efficacious for small superficial haemangiomas; however, deep haemangiomas do not derive benefit from laser therapy due to its limitations regarding lesion depth. It inhibits the proliferation of haemangiomas in all treated patients; nonetheless, full remission was attained in merely approximately 13.8% of cases. However, for enhanced efficacy, laser therapy may be utilized in conjunction with beta blockers. Numerous unapproved techniques are documented in the literature, including medicinal therapies (procoagulants, pentoxifylline, and cytotoxic agents) and surgical interventions (cryosurgery, embolization, and sclerotherapy)²¹⁻²⁴.

This study is limited by lacking a control group who treated conservatively to compare the different interventional modalities to the watchful management. It also lacks groups that treated surgically or using laser and other kind of interventions for complicated and deep organs hemangiomas.

CONCLUSION

This prospective study involved a representative sample of paediatric patients with haemangioma who received various treatment approaches. The results for the topical administration of propranolol, bleomycin, and corticosteroids, as well as the intralesional administration of these drugs, shown no statistically significant difference. Nonetheless, the efficacy of size reduction with corticosteroids surpassed that of propranolol and bleomycin. The size reduction outcome with intralesional corticosteroids was 50% in the excellent category, whereas the topical corticosteroids achieved a 33% excellent size reduction. Recent data indicates that beta blockers may be as effective as or more effective than corticosteroids, while also exhibiting a superior safety profile. The selection of treatment modality from the various choices must be individualized for each patient based on the stage, progression, and depth of the lesion. Vigilant oversight may be maintained, but intervention must never be postponed when warranted.

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Competing Interest: None

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