Original Article

Topical Beta Blockers versus Oral Beta Blockers for Treatment of Periocular Infantile Haemangioma

PJO – Official Journal of Ophthalmological Society of Pakistan

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ABSTRACT

Purpose: To determine the safety and efficacy of topical versus systemic (oral) beta-blockers in the treatment of infantile haemangiomas involving periocular region at early proliferative stage.

Study Design: Quasi experimental study.

Place and Duration: This study was done at Paediatric Ophthalmology Department, College of Allied Vision Sciences, Mayo Hospital, Lahore from December 2020 to June 2021.

Methods: A total of 26 patients were divided into two groups. Group A was given oral beta blockers and Group B topical beta blockers for infantile hemangioma. Oral propranolol in the dose of 1mg/Kg twice daily was given to Group A and increased to 2mg/Kg twice daily after two weeks. In Group B Timolol maleate 0.05% solution was given to be rubbed on the affected skin for five seconds twice a day. Patients were monitored for any local or systemic adverse effects. Response of patients to therapy was observed for next four months. Before and after therapy, Hemangioma Activity Score was used to record the proliferative activity, change in size of lesion and color.

Results: The mean age of patients was 26.0± 14.5 months in group A and 25.4±12.0 months in group B respectively. There was a significant improvement in the HaemangiomaAactivity Score (P < 0.001) within the same group after treatment. However, difference between the two groups was not statistically significant (P value 0.78).

Conclusion: In early proliferative stage of infantile hemangioma, oral and topical beta-blockers are equally effective.

Keywords: Hemangioma, Adrenergic Beta-Antagonists, Propranolol, Timolol.

How to Cite this Article: Nisa ZU, Khan HZA, Choudhary S, Mahmood H. Topical Beta Blockers Vversus Oral Beta Blockers for Treatment of Periocular infantile Haemangioma. 2026;42(3):275-280.
Doi: 10.36351/pjo.v42i3.2344

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Received: January 07, 2026
Revised: May 1, 2026
Accepted: May 06, 2026

INTRODUCTION

Infantile haemangiomas (IHs) account for 4-10% of the infant tumours.[1] The incidence of IHs is more in Caucasian females. Superficial haemangiomas are confined to cutaneous level while deeper ones show penetration into subcutaneous tissue.[2] Although IHs undergo spontaneous involution, but they can producecosmetic disfigurement to visual loss secondary to ptosis, strabismus, astigmatism, anisometropia, exposure keratopathy and optic nerve compression.[3] Periocular IHs can have their systemic manifestations, as seen in Kasabach Merritt syndrome in association with thrombocytopenia and PHACES syndrome (P = anomalies of posterior fossa, H = hemangioma both cutaneous and visceral, A = arterial lesions in head and neck region, C = cardiac abnormalities involving major blood vessels, E = eye and endocrine abnormalities,S = sternal anomalies)

characterized by involvement of brain, heart and other major organs.[4]IHs in periocular region should be investigated thoroughly especially for systemic associations.[5] Doppler ultrasonography and Magnetic resonance imaging techniques are investigations of choice. The proliferative stage is characterized by hyper vascularity on Doppler scan.[6] Symptomatic periocular IHs require intervention.Treatment modalities available in this regard are corticosteroids, immunomodulators, lasers, surgical resection, whereas oral and topical beta blockers being the most recent ones and all of them carry some associated risk of adverse effects.[7,8]

Ppropranolol, a non selective beta blocker has proven to be very potent in comparison to other treatment modalities especially in terms of possible side effects and cost effectiveness.[9] As orally given propranolol predisposes to hypotension, hypoglycaemia bradycardia and bronchospasm, it becomes even more hazardous if given to infant, as in that case monitoring is not easy especially where mothers have to do it themselves. Several studies prove that oral propranolol in paediatric patients is linked to side effects, though none of them mentioned complications severe enough to stop the treatment.[10] Topical beta blockers are possible alternative now a daysforsuperficial and cutaneous lesions. Although topical instillation of 0.5% timolol is associated with systemic absorption but theoretically speaking chances of adverse effects are very low.[11] A multicentred trial in Sindh Pakistan has shown promising results of topical timolol 0.5% when applied to superficial His.[12]

To provide a simple, safe and cost-effective approach to deserving population, we evaluated oral and topical beta blockers' effectiveness in treating superficial periocular haemangiomas as first line therapy.

METHODS

After approval from IRB committee **(20340/REG/KEMU/2020),** using 95% confidence level, 90% power of test with expected response to therapy for topical group as 80%[13] and oral group as 25%,[14] 26 patients were enrolled. Informed consent was taken from parents of all patients. Both male and female patients, diagnosed with superficial and subcutaneous haemangiomas in periocular region were included in the study. Patients with deep orbital haemangioma, previous haemangioma treatment, ocular surgical treatment and children with systemicdiseases,i.e., asthma, cardiovascular disorder, PHACES syndrome, etc., were excluded from the study. Patients were divided into two groups (Group A and Group B), 13 in each group. Group A was given oral beta blockers and Group B, topical beta blockers. Base line examination, visual assessment was done with preferential looking test, pupillary reactions, eye movements, color and size of lesion, dilated fundus examination, cycloplegic refraction and B-scan to rule out deep orbital hemangiomas. Pediatricians and cardiologists evaluated patients to rule out any systemic associations. Infants with oral therapy were initially given a trial of propranolol under strict medical observation, to note any side effects. Mothers were counseled about proper monitoring of pulse and signs of hypoglycemia. In Group A, dose of oral propranolol was 1mg/KgBD which was increased to 2mg/Kg BD after two weeks. In Group B patients were given timolol maleate 0.05% solution to rub on the affected skin for five seconds twice a day. Patients were monitored for any local or systemic adverse effects. Response of patients to therapy was observed for next four months.

Before and after therapy, Hemangioma Activity Score (Table -1) was used to record the proliferative activity, change in size of lesion and color. The Response to the Treatment was categorized as good (lesion decreased to $> 50\%$), fair (lesion decreased to $\leq 50\%$) and poor (no response or increase in size). The data was entered and analyzed in SPSS version 28. Paired sample t-test was applied for comparison after four months of treatment. P value ≤ 0.05 was considered as significant.

RESULTS

There were 26 patients (18 females and 8 males), 13 in each group. In Group A, two (15%) were males and 11(85%) were females. While in Group B,six(46%) were males and seven (54%) were females. The mean age at initial stage of the treatment was 26.0± 14.5 months in Group Aand25.4 ± 12.0 months in Group B.

The indication for hemangioma treatment was astigmatism in three (23.1%), ptosis in five (38.5%) and painful lesion with cosmetic disfigurement in five (38.5%) patients in Group A. Whereas in Group B, astigmatism was in eight (61.5%), ptosis in two (15.4%) while disfiguring painful lesion was present in three (23.07%) patients. In Group A upper eye lid

haemangiomas were present in eight (61.5%), lower lid was involved in three (23.1%) and medial canthal haemangioma seen in two (15.4%) of patients. In Group B, nine (69.2%) patients presented with upper lid haemangiomas, lower lid hemangiomawas seen in three (23.1%) and medial canthal involvement in one (7.7%) patient. The response to treatment was good in eight (61.5 %) patients in both groups showing > 50% of improvement. Fair response was detected in four (30.8%) in Group A and three (23.1%) in Group B. One (7.7%) patient in Group A and two (15.4%) patients in Group B showed poor response to the therapy.

Table 1: *Haemangioma Activity Score.*

Haemangioma Activity Score[17] Variable	**Score**
Swelling score	
No swelling during follow-up	0
≥50% reduction during follow up	2
No tense swelling or < 50% reduction	4
Tense swelling	6
Colour	
Skin coloured/ or gray on crying only	0
Gray	1
Blue or shining deep blue	2
Matte red or reddish purple	3
Bright/ shining red edges	4
Bright / shining redness	5
Ulceration	
≤ 1 cm^2	0.5
1 to 2.5 cm^2	1
≥ 2.5cm^2	2

Table 2: *Haemangioma activity Score and Response to Treatment Comparison between two groups.*

Variable	**Group A (Oral)**	**Group B (Topical)**	**P value**
Haemangioma activity score[a]	2.5 ± 2.10	2.23 ± 2.00	0.79[b]
Response to treatment			0.78[c]
Good	8 (61.5%)	8 (61.5%)	
Fair	4 (30.8%)	3 (23.1%)	
Poor	1 (7.7%)	2 (15.4%)	

[a]Values are presented as mean ± standard deviation.
[b] Independent *t*test .
[c]Chi square test.

After four months of treatment, the Haemangioma Activity Score was 2.50 ± 2.10 and 2.23 ± 2.00 in Group A and B, respectively, whereas there was no significant difference in response to treatment among two groups (P value 0.78) as shown in (Table 2). Table 3shows the comparison of both the groups pre and post treatment with their hemangioma activity score, mean and standard deviation values.

Table 3: *Haemangioma Activity Score before and after treatment in Group A and Group B.*

	Group A (Oral) n=13				**Group B (Topical) n=13**			
Activity Score	**Base Line**		**Post Treatment**		**Base Line**		**Post Treatment**	
	(n)	**(%)**	**(n)**	**(%)**	**(n)**	**(%)**	**(n)**	**(%)**
0-5	0	0	12	92.3	0	0	12	92.3
6-10	12	92.3	1	7.7	13	100	1	7.7
11-15	1	7.7	0	0	0	0	0	0
Total	13	100	13	100	13	100	13	100
Mean ±SDa	8.0 ± 1.28		2.5 ± 2.10		7.3 ± 1.19		2.23 ± 2.0	
P value	< 0.001[b]				< 0.001			

[a]Values are represented as mean ± standard deviation
[b]Paired*t* test

DISCUSSION

Capillary haemangioma is a vascular tumourwhich occurs with the rapid proliferation of endothelial cells. It is a benign vascular tumour. When present in periocular region and left untreated may cause number of complications including, astigmatism, anisometropia, compressive optic neuropathy, amblyopia, exposure keratopathy and cosmetic disfigurement.[15] The ratio of female to male is 3:1, there is an association of preterm birth and low birth weight with IH. However, none of the patients in our study were preterm or with low birth weight.

In our study Hemangioma Activity Score (HAS) was utilized. It is a useful research tool to monitor response, based on standardized measurement of clinical findings of the disease.[17] Our results showed a significant improvement in capillary HAS after treatment (P < 0.001). However, there was no significant difference in response to therapy between the two groups (P value was 0.78). Our results are comparable to a prospective randomized trial conducted in Egypt on 25 patients.[14] In this study one group of patients with capillary haemangioma were given oral propranolol while other was given topical timolol. The difference regarding decrease in size of lesion when comparing propranolol patients before and after therapy (P = 0.01) and comparing timolol patients before and after treatment (P = 0.008) was

statistically significant. Hence, strengthening the results of our study that both systemic and topical beta blockers can be used effectively as first line of therapy for treating proliferative IHs. However, according to a study topical timolol is fruitful in cases of superficial and subcutaneous haemangiomas only.[18] Deep orbital haemangiomas were not included in our study.

A meta-analysis showed that topical β-blockers may replace oral propranolol as first-line therapy for superficial IH and that they were of additive value in treating mixed infantile hemangioma.[19]

Systemic corticosteroids are linked to various adverse effects, such as growth retardation and immune suppression. Whereas topical timolol is associated with minimal adverse effects; however, for patients who cannot tolerate beta-blockers, intralesional steroid injections may be considered as an alternative treatment to mitigate the side effects of systemic corticosteroids. Although topical timolol generally has few side effects, it can cause local irritation and bronchospasm in some individuals.[20]

Kashiwagura Y et al, prepared propranolol cream as primary therapy to cure IHs. A cream or gel formulation could be more efficient when compared with solution forms as it increases the contact time.[21] There was effective clinical response together with topical beta blockers and oral beta blockers in IHs than with only oral propranolol.[21] Similarly, Gong et al, reported same effectiveness with no increased risk of adverse events when compared with placebo.[22] However, sleep disruption and characteristic bradycardia are also reported.[23] In our study, small sample size could be the reason for no side effects reported. However, intralesional trial of propranolol solution, 1mg/ml at dose of 0.2ml/cm^2 proved ineffective in shrinking IHs, though no adverse events occurred.[24]

Surgical excision of infantile haemangiomas is successful only for the well-circumscribed lesions with meticulous haemostatic control.However, it should be avoided in infants as these are highly vascular tumors and risk of excessive bleeding is a serious concern. In some cases, if it is causing ulceration, or deformity to critical structures and affecting certain cosmetically sensitive areas, surgical intervention is an option.[25]

Our results are limited due to smaller sample size, short duration of study and haemangiomas of specific depth, extent and stage. Age can affect the therapeutic response to treatment; being less than 6 months at the time of treatment commencement has better response. While in our study more than half of the patients were above 6 months of age. Multicenter randomized controlled trials will give an insight into all other factors such as age-group, location of lesion, treatment duration, efficacy as well as dosage and therapeutic response.

CONCLUSION

Topical beta-blockers like oral beta-blockers are equally effective for the treatment of superficial IHs as primary therapy. There is no significant difference between both therapies when initiated in proliferative phase of superficial capillary haemangiomas.

Funding: This study was not funded by any organization.

Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(20340/REG/KEMU/2020)**

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