

Combined Oral and Topical Beta Blockers for the Treatment of Early Proliferative Superficial Periocular Infantile Capillary Hemangioma

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ABSTRACT

Purpose: To evaluate the safety and efficacy of combined oral and topical beta blockers for the treatment of superficial periocular infantile hemangioma at the early proliferative stage.

Methods: This was a randomized, controlled comparison trial involving 25 patients. Patients were randomly enrolled into two groups: the topical and systemic treatment and systemic treatment only groups. The topical and systemic treatment group was treated with oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and timolol maleate 0.5% gel. The systemic treatment only group received oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and simple eye ointment to be applied to the lesion. The Hemangioma Activity Score was used to record the proliferative activity of the hemangioma. The main outcomes of the study were the change in the hemangioma size, the proliferative activity, and the treatment side effects.

Results: At the end of the treatment period, the Hemangioma Activity Score was significantly improved in both groups from their values before treatment. However, the score obtained after treatment was significantly better in the topical and systemic treatment group ($P < .05$). Regarding the response to treatment, 10 and 3 cases in the topical and systemic treatment and systemic treatment only groups, respectively, showed a good response, with a significant difference between the two groups ($P < .50$). There were no recorded seri-

ous local or systemic complications during treatment in either group.

Conclusions: The results from combining topical with oral beta blockers showed that topical beta blockers are of additive value in treating superficial periocular infantile hemangioma in the early proliferative stage.

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INTRODUCTION

Infantile hemangiomas are benign vascular endothelial neoplasms characterized by a bright red surface and occur in up to 4% of children by the age of 1 year. They are usually small at the time of birth and enlarge rapidly during the first few months of the newborn's life, eventually shrinking slowly over time.^{1,2}

Therapeutic options include corticosteroids, pulse dye laser, topical imiquimod, beta blockers, and surgery, with recent emphasis on corticosteroids and beta blockers.

The efficacy of propranolol, a non-selective beta blocker, in the treatment of infantile hemangiomas has been investigated since 2008.³⁻⁵ Numerous reports have suggested that oral propranolol holds high promise for infantile hemangioma treatment,⁶⁻⁹ and other reports have focused on the effect of topical beta blockers with promising results.^{10,11}

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The aim of this study was to evaluate the safety and efficacy of combined oral and topical beta blockers for the treatment of superficial periocular infantile hemangioma at the early proliferative stage.

PATIENTS AND METHODS

This was a randomized, controlled comparison trial involving 25 patients. Patients were recruited from the Eye Outpatient Department at Menoufia University Hospital, Egypt, between August 2008 and August 2011.

Eligible patients were infants aged older than 4 months. Inclusion criteria were a clinical diagnosis of capillary hemangioma, clinical evidence of functional visual impairment, otherwise normal eye examinations, and parents willing to attend the eye clinic at the timing required by the study design. Exclusion criteria were evidence of eye pathology or chronic eye diseases, a history of previous hemangioma treatment, a previous ocular surgical treatment, deep hemangiomas, or a history of systemic medical conditions, including asthma or cardiovascular disorder.

Data collected from patients included age, ocular and medical history, medications, allergies, and family history of eye diseases. Patients had baseline assessments during their visit before the start of treatment, including pupillary reaction, preferential looking testing, assessment of eye movement, dilated fundus examination with an indirect ophthalmoscope, and cycloplegic refraction.

All patients had a full pediatric assessment, including complete physical examination, regional ultrasonography, blood tests with a complete blood cell count and coagulation profile, and a computed tomography scan if there was evidence of possible intracranial extension.

The randomization process used four opaque envelopes in two containers. One container contained two envelopes marked with either "T" for topical and systemic treatment or "S" for systemic treatment only. The other container contained two envelopes with the name of two patients eligible for treatment. The two patients were randomized to one of the procedures by asking an independent person to choose one envelope from each container.

The study protocol was approved by the Ethical Committee of Menoufia Medical School and adhered to the tenets of the Declaration of Helsinki. The study protocol was explained to the parents and written informed consents were obtained.

Patients were randomly enrolled into two groups. The combined treatment group was treated with oral propranolol (1 mg/kg/d initially, increased to 2 mg/kg/d gradually in 2 weeks) and timolol maleate 0.5% gel (Timogel; Orchidia Pharmaceutical Industries, Cairo, Egypt), with two drops applied to the lesion twice daily and gently rubbed against the entire surface with the little finger for 5 seconds. Parents were instructed on how to apply the topical treatment during their visit before the start of treatment. The systemic treatment only group received oral propranolol (1 mg/kg/d initially, increased to 2 mg/kg/d gradually in 2 weeks) and simple eye ointment (Martindale Pharmaceuticals Limited, Buckinghamshire, United Kingdom) to be applied to the lesion. The treatment was stopped when the child reached 12 months of age in a tapering dose during the course of 1 week.

Infants were admitted for the first week of therapy, when potential complications such as bradycardia, diarrhea, hypoglycemia, or hyperkalemia were monitored and managed accordingly. They were then observed every 4 weeks at the eye outpatient clinic, where photographs were taken at each visit. All examinations before and after treatment were performed by independent investigators who were masked to the type of treatment used.

The main outcome of the study was the change in lesion size, the proliferative activity, and the treatment side effects. Response to treatment was categorized as good (lesion decrease $\geq 50\%$), moderate (lesion decreased $< 50\%$), or poor (no response to therapy or increased in size). The Hemangioma Activity Score of 1 to 12 was also used to record the proliferative activity of the hemangioma before treatment and at the end of the follow-up period, at which point two independent investigators scored the proliferative activity of hemangioma by evaluating the extent of deep swelling, color of the infantile hemangioma, and ulceration based on images captured at the start and end of treatment (**Table 1**).

Statistical analysis was performed using SPSS software (version 16; IBM Corporation, Armonk, NY). A paired *t* test was used to detect the difference between data obtained before and after treatment in the study groups, and the independent sample test was used to calculate the difference between both groups in numerical variables. The Pearson chi-square test was used to calculate the difference between the groups in categorical variables.

RESULTS

Twenty-five patients (13 males and 12 females) were included in this study, 13 in the topical and systemic treatment group and 12 in the systemic treatment only group. The mean age at the start of treatment in the combined treatment group was 5.18 ± 1.12 months, and the mean treatment duration was 6.92 ± 1.12 months. In the systemic treatment only group, the mean age at the start of treatment was 5.13 ± 1.11 months and the mean treatment duration was 7.53 ± 1.11 months. There were no significant differences between the two groups regarding the gender of patients, the age at the start of treatment, or the duration of treatment (Table 2).

The mean value for the Hemangioma Activity Score at the start of treatment was 4.59 ± 1.04 and 4.80 ± 0.71 in the combined treatment and systemic treatment only groups, respectively, with no significant difference between the two groups ($P = .567$) (Table 2).

At the end of the treatment period, the Hemangioma Activity Score was 1.52 ± 1.36 and 3.40 ± 0.84 in the topical and systemic treatment and systemic treatment only groups, respectively, with significant improvement in both groups from their scores obtained before treatment ($P < .05$). However, the score obtained after treatment was significantly better in the combined treatment group ($P < .05$) (Table 3).

Regarding the response to treatment, 10 and 3 cases in the combined treatment and systemic treatment only groups, respectively,

TABLE 1
Hemangioma Activity Score

Variable	Score
Swelling score	
Tense swelling	6
No tense swelling or < 50% reduction during follow-up	4
≥ 50% reduction during follow-up	2
No swelling during follow-up	0
Color	
Bright/shining redness	5
Bright/shining red edges	4
Matte red or reddish purple	3
Blue or shining deep blue	2
Gray	1
Skin-colored after activity	0
Ulceration	
≤ 1 cm ²	0.5
1 to 2.5 cm ²	1
≥ 2.5 cm ²	2

showed a good response, with a significant difference between the two groups. Three cases in the combined treatment group showed a moderate response, compared to 8 cases in the systemic treatment only group. A poor response to treatment was recorded in no cases in the combined treatment group and one case in the systemic treatment only group (Table 3).

TABLE 2
Baseline Data^a

Variable	Combined Treatment Group	Systemic Treatment Only Group	P
Age (mo)	5.18 ± 1.12	5.13 ± 1.11	.912 ^b
Sex			.835 ^c
Male	7	6	
Female	6	6	
Duration of treatment (mo)	6.92 ± 1.12	7.53 ± 1.11	.185 ^b
Hemangioma Activity Score at the start of treatment	4.59 ± 1.04	4.80 ± 0.71	.567 ^b

topical and systemic treatment group = treated with oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and timolol maleate 0.5% gel (Timogel; Orchidia Pharmaceutical Industries, Cairo, Egypt); systemic treatment alone group = treated with oral propranolol (1 mg/kg per day initially, increased to 2 mg/kg per day gradually in 2 weeks) and simple eye ointment

^aValues are presented as mean ± standard deviation.

^bt test.

^cChi-square test.

TABLE 3

Hemangioma Activity Score and Response to Treatment Comparison

Variable	Combined Treatment Group	Systemic Treatment Only Group	P
Hemangioma Activity Score ^a	1.52 ± 1.36	3.40 ± 0.84	.001 ^b
Response to treatment			.03 ^c
Good	10 (76.9%)	3 (25%)	
Moderate	3 (23.1%)	8 (66.7%)	
Poor	0 (0%)	1 (8.3%)	

combined treatment group = treated with oral propranolol (1 mg/kg/d initially, increased to 2 mg/kg/d gradually in 2 weeks) and timolol maleate 0.5% gel; systemic treatment alone group = treated with oral propranolol (1 mg/kg/d initially, increased to 2 mg/kg per day gradually in 2 weeks) and simple eye ointment

^aValues are presented as mean ± standard deviation.
^bt test.
^cChi-square test.

There were no recorded serious local or systemic complications during treatment in either group. However, transient hypoglycemia was recorded in 3 cases in the form of sweating, shakiness, and tachycardia in the first week of treatment (2 and 1 case in the topical and systemic treatment and systemic treatment only groups, respectively). The cause of hypoglycemia was relative deficient nutrition because of an upper respiratory tract infection that was managed by the pediatricians. Propranolol therapy was continued with the same dose with no other reported hypoglycemic manifestations later on.

DISCUSSION

Therapeutic options for the treatment of infantile hemangioma include intralesional injection of steroids, systemic steroids, immunomodulators, and most recently beta blockers.¹³⁻¹⁶

Each therapeutic option has its own benefits and drawbacks. Systemic steroid therapy showed some benefit in diffuse or orbital lesions; however, rebound growth after discontinuation and significant side effects such as increased risk for growth delay, immunosuppression, behavioral disturbances, and adrenal insufficiency made this therapy suboptimal.^{13,14}

Intralesional steroids have proven to be efficacious in diminishing the size of the lesion rapidly within 2 weeks of injection in many cases; however, possible side effects include corticosteroid particle embolization due to high injection pressure, ophthalmic artery occlusion, retinal embolization and central retinal artery occlusion, eyelid hypopigmentation, linear subcutaneous fat atrophy, sclerodermiform linear atrophy, eyelid necrosis, periocular calcification, cushingoid features, growth deceleration, and adrenal suppression.^{15,16}

Immunomodulators such as cyclophosphamide and interferon alpha-2a have also been tried systemically. However, the treatment course takes several months, leading to significant adverse effects such as bone marrow suppression and hepatotoxicity.¹⁷

Beta blockers, either applied topically or used systemically, constitute a new and promising treatment modality. The exact mechanism by which propranolol shrinks infantile hemangioma is unknown. Various explanations have been proposed, including vasoconstriction, decreased expression of vascular endothelial growth factor and beta fibroblast growth factor genes, apoptosis of capillary endothelial cells, blockage of the G protein-coupled receptor kinases Leu41, reduced matrix metalloproteinase-9, and effect on differentiation of mesenchymal stem cells.¹⁸

In several studies, oral propranolol has shown remarkable regression in patients with eyelid capillary hemangiomas up to 5 years of age.¹⁹⁻²¹

Holmes et al.²² studied 31 consecutive patients with rapidly proliferating infantile hemangioma with visual functional impairment or cosmetic disfigurement who were treated with propranolol as a first-line treatment. All patients had cardiovascular work-ups before treatment and began propranolol 3 mg/kg/d. A rapid halt in hemangioma proliferation was observed in 100% of patients and significant regression in 87% of patients. The treatment was well tolerated and had few side effects.²²

In a study by Sans et al.,²³ propranolol was administered to 32 children after clinical and ultrasound evaluations, with a starting dose of 2 to 3 mg/kg/d, given in two or three divided doses. Treatment was continued and the children were reevaluated after 10 days of treatment and then every month. Im-

mediate effects on color and growth were noted in all cases. Objective clinical and ultrasound evidence of longer-term regression was observed in 2 months. Relapses were mild and responded to re-treatment. Side effects were limited and mild.²³

Topical beta blockers have also been shown to be effective for cutaneous capillary hemangiomas. The major advantages of topical timolol are their availability, cost, ease of administration, and minimal risk of drug-related adverse events, especially when applied to the face and, in particular, the periorbital area.¹⁰

Chakkittakandiyil et al.¹⁰ were the first to publish the results of a large retrospective cohort study involving 73 patients from five centers. Patients were treated with timolol maleate 0.1% (15% of cases) or 0.5% gel forming solution (85% of cases). All patients except one improved. Results were better in cases of superficial hemangioma, with the use of 0.5% timolol and duration of treatment longer than 3 months.¹⁰

Another small retrospective, consecutive, non-randomized trial involving 23 cases was designed by Chambers et al.¹¹ to evaluate the efficacy of topical 0.25% timolol maleate gel for the treatment of periorbital infantile hemangioma. Thirteen patients received timolol, and 10 were observed. In the treated group, a good to moderate response was observed in 92.3% of cases, compared to 10% of cases in the observation group. Results were better in the treated group in cases of superficial hemangioma.¹¹

At the end of treatment in the current study, there was a significant improvement in both groups regarding the Hemangioma Activity Score from their values obtained before treatment ($P < .001$ in both groups). However, the score obtained after treatment was significantly better in the topical and systemic treatment group ($P < .001$). Also, the topical and systemic treatment group had a significantly better response to treatment than the systemic treatment only group ($P < .03$).

The efficacy of topical timolol maleate gel in the relatively young age group of the current study supports previously noted observations that timolol maleate gel may be more effective during the early proliferation stage. In a randomized controlled trial, Chan et al.²⁴ enrolled 41 patients with superficial infantile cutaneous hemangioma. Fifteen of the 19 infants receiving treatment and 17 of the 22 infants receiving placebo completed the study. There was a significantly higher proportion of treated infantile hemangiomas that reduced in size by more than 5% at weeks 20 and 24, and the predicted proportion of infantile

hemangioma volume change was also significantly less for treated infantile hemangiomas from week 16 onward when compared with the placebo group.²⁴

Hypoglycemia is the most frequent and insidious side effect observed with oral propranolol by most investigators.²⁵ In the current study, propranolol-induced hypoglycemia occurred in 3 cases in both groups at the start of therapy and was immediately managed by the pediatric team. There were no other recorded complications during the follow-up period.

The limitations of this study included the small number of patients and the short follow-up period. This was mainly because of the strict inclusion criteria. Cases with deep infantile hemangioma and cases that were exposed to previous treatment modalities were excluded from the study. A multi-center study design would be the best option to overcome the issue of a small patient number.

The results from combining topical with oral beta blockers showed that topical beta blockers are of additive value in treating infantile hemangioma. More studies are necessary to explore the possibility of using the same regimen, or even the topical treatment alone, in cases of deep and diffuse infantile hemangioma.

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