Management of infantile periorbital hemangiomas: a revisit

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Background
Although infantile hemangioma is a common benign childhood tumor, it is still one of the challenging problems.
Aim
The current prospective study aimed to evaluate the effect of local propranolol gel in the treatment of infantile periorbital hemangioma.
Patients and methods
A prospective study in the period of 4 years from January 2012 to December 2016 was carried out on infants with periorbital hemangioma with a follow-up period of a minimum of 1 year. All infants underwent a fine-needle histopathological sample. All patients who proved to be capillary hemangioma were divided into two groups. Group I included those patients who were treated with topical timolol maleate gel from 4 to 30 weeks. On the other hand, group II included those patients who underwent a local corticosteroid therapy in the form of clobetasol 0.05% gel for a similar period. Posttherapy clinical and histopathological assessment took place in both groups. The obtained data were statistically analyzed.
Results
Twenty-eight patients were enrolled in the study. They were 18 women and 10 men with the ratio of women to men being about 2 : 1. In 21 infants, the tumor shrank in a period of 4–10 weeks after topical timolol administration. On the other hand, those who underwent local corticosteroid therapy showed a longer period for the shrinkage of the tumor; the *P* value is less than 0.003.
Conclusion
Local timolol gel therapy is superior to topical corticosteroid therapy with a wide range of safety and less side effects. Moreover, its cost-effectiveness is acceptable compared with other modalities such as laser therapy. The number of the study materials are limited; yet, it may be an indicator for a road map of managing infantile periorbital hemangiomas. Further studies with a larger population may be needed, as the problem deserves a full citizenship in the world of pediatric research.

Keywords:
clobetasol, hemangiomas, infantile, periorbital, timolol maleate

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Introduction

Hemangiomas are one of the most commonly encountered benign tumors in infants. It may be considered as the most common eyelid and orbital tumors of childhood. Its management is still a challenging dilemma for pediatricians, ophthalmologists, surgeons, and dermatologists. Although being benign periorbital may lead to many complications including strabismus and it may end up with an irreversible loss of vision, if not promptly treated [1–3].

Approximately, one among 10 children is affected by capillary hemangioma with a varying severity [4]. Most of hemangiomas may be clinically diagnosed not requiring any biopsies [5].

The main goal of treating eyelid or orbital hemangiomas is to reduce its size aiming at the resolution of occlusion, reduction in astigmatism, and prevention of pupillary occlusion. Those with occlusion are at higher risk for severe residual amblyopia and require prompt and definitive treatment [6].

Several modalities have existed for treating hemangiomas including corticosteroid therapy whether topically or by intralesional injection,

interferon alfa, laser, immunomodulators, embolization, surgery as well as beta blockers whether topically or systemically. However, therapeutic options for the management of periorbital superficial hemangiomas are still limited [7,8].

The current prospective study aimed to evaluate the experience in the management of infantile periorbital hemangioma seen in multidisciplinary sections to find an answer for a highly debatable issue.

Patients and methods

This prospective study was performed in a period of 4 years from January 2011 to December 2014. It was carried out on infants with periorbital hemangiomas. The ethics committee of our institute research board (IRB) approved the study when a formal informed written consent was obtained and signed by children's legal care takers prior to their participation in the study. Included in the study were all children with histopathologically proved capillary hemangiomas while other histological types were excluded. Also excluded were those children who had undergone any previous treatment and/or ulcerated lesions. Patients underwent a true-cut biopsy for histopathological assessment before the start of treatment. All biopsies were taken under general anesthesia; most of them were about 1×2 mm and extended through the full depth of the corium, including subcutaneous tissue in lesions with deep components. Specimens were processed and stained by conventional H&E stains. Special stains including Masson's Trichrome, Verhoeff Van Gieson's, and reticulin were used whenever needed. The studied patients were divided into two groups. The first one (group I) included those patients who were treated with topical timolol maleate gel (a beta-blocker component) that was applied twice daily on to the surface of the hemangioma. This treatment continued for a period of 60 weeks. On the other hand, group II included those children who were treated with topical clobetasol 0.05% gel (corticosteroid component) with the same technique for the same period. All children were photographed weekly emphasizing on the lesion color and size before the starting of the study until the end using a high-resolution 25-megapixel camera. Photographs were saved and then randomized and evaluated blindly by two academic associates without knowing any clinical or chronological information about the used treatment modality. They used a visual analog scale. Clinical response was assessed according to a previously described scale from 1 to 4 [9]. This scale included: score 1 when the reduction in the lesion size is less than 25%. Score 2 is considered when the reduction ranged from 25 to 50%; score 3 50 to 75% reduction (good response). The excellent response is expressed as a score 4 when more than 75% of the lesion size is reduced. Posttherapy clinical and histopathological assessment took place in both groups. As previously described [5], we evaluated the therapeutic effect of both drugs. The obtained results were rated as 'markedly effective,' 'effective,' or 'invalid.' 'Markedly effective' means the rapid shrinkage of the tumor after treatment and almost complete involution during the follow-up. 'Effective' means some shrinkage of the tumor.

The obtained data were statistically analyzed.

Statistical analysis

Upon data completion and validation, data had been transported from Excel to the statistical software Statistical Package for the Social Sciences, version 21, for statistical analysis. Both descriptive and analytic inferential statistics were conducted. A P value of less than or equal to 0.05 was the significance level for all statistical tests. Categorical variables had been presented as counts and proportions (percentage) and continuous variables were presented as mean±SD. In univariate analysis for comparison and correlation between variables of interest versus different categorical variables, χ^2 as well as independent t-test was applied. Multivariate analysis was conducted as well, where odds ratio with significance level and 95% confidence interval were reported.

Results

Twenty-eight patients with capillary hemangioma were enrolled in the study. They were 18 women and 10 men with the ratio of women to men being about 2 : 1. Their age ranged from 2 up to 32 months with a mean of 18±4.7. Table 1 shows the descriptive criteria and demographic data of all patients.

Table 1 Descriptive data of the patients

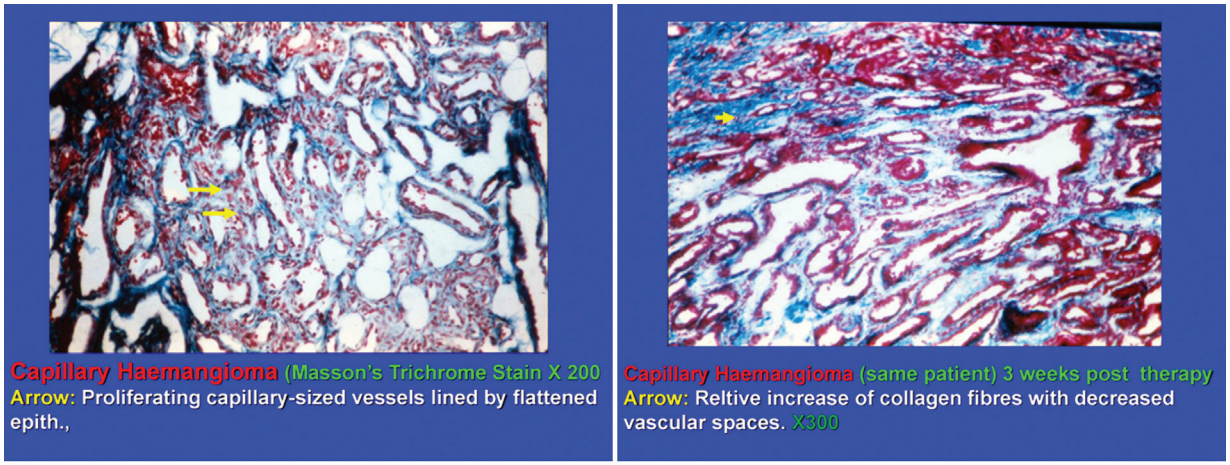
	Clobetasol (N=14)	0.5% timolol maleate (N=14)
Sex [n (%)]		
Male	10 (35.7)	24 (25.81)
Female	18 (64.3)	69 (74.19)
Age at initial treatment (month)		
Median	7.4	7.4
Range	2–12	2–12
Gestational age (weeks)		
Median	37	37
Range	36–38	36–38
Age of the mother		
Median	28	28
Range	24–45	24–45

They were followed up for a period of 24–40 months after the stoppage of therapy.

During the follow-up period of 1–6 months after timolol treatment in group I, 10 out of 14 (71%) showed an excellent response to treatment with a score of 4. The infants had a tremendous reduction in the hemangioma size and volume of about 95%. These patients expressed a fade in the color from being red to light pink or even normal skin color. This was verified by the histopathological assessment. The remaining four (29%) patients were categorized as a score 3 showing a good response to therapy with reduction in size and color of about 60–70%. In this group, no significant changes neither in the heart rate nor in local or systemic adverse effects of the beta blocker were recorded in any case (Figs 1–6).

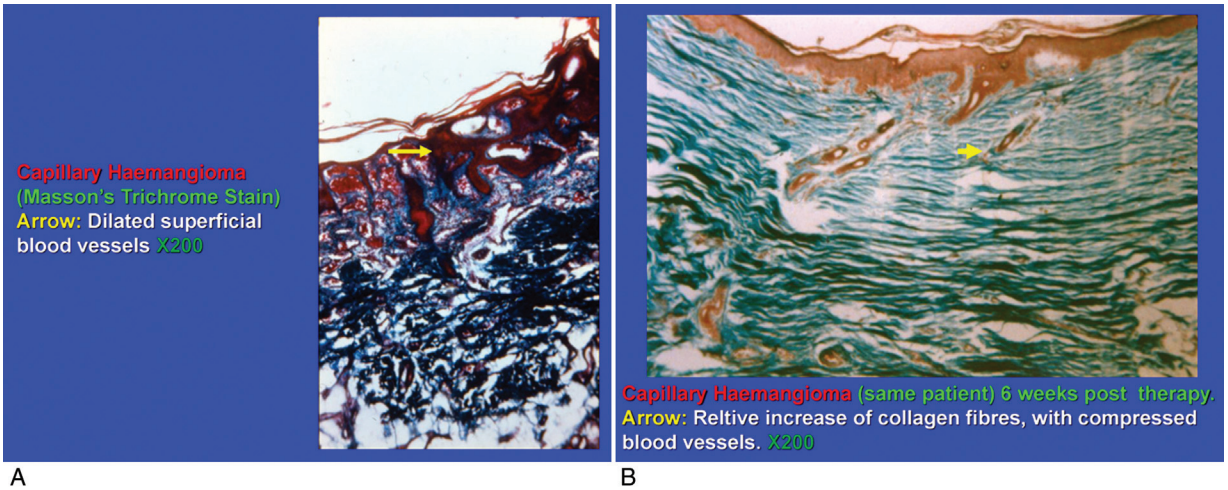
In group II, where clobetasol was applied six out of 14 (43%) had a score of four showing an excellent response to treatment. In the remaining eight patients, three had a score of 3 with good response to therapy. Two patients had a poor score of 2 while one patient was categorized as score 1 with no response to therapy. These data were also histopathologically verified. A statistically significant difference was recorded among the infants in groups I and II ($P<0.001$).

Figure 1



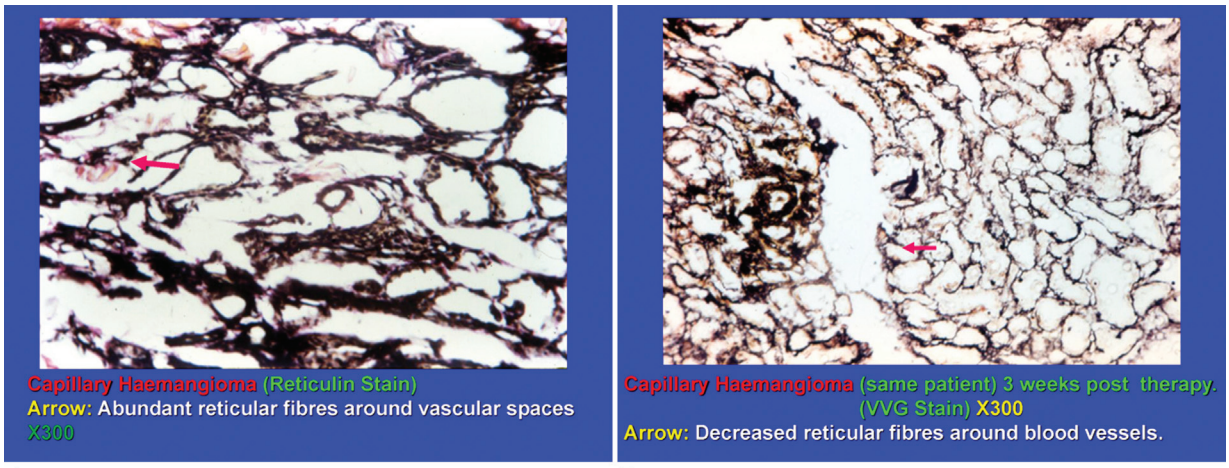
(a) Capillary hemangioma (Masson's Trichrome Stain, ×200). Arrow: proliferating capillary-sized vessels lined by a flattened epithelium. (b) Capillary hemangioma (same patient) 6 weeks posttherapy. Arrow: relative increase of collagen fibers with decreased vascular spaces (×300).

Figure 2



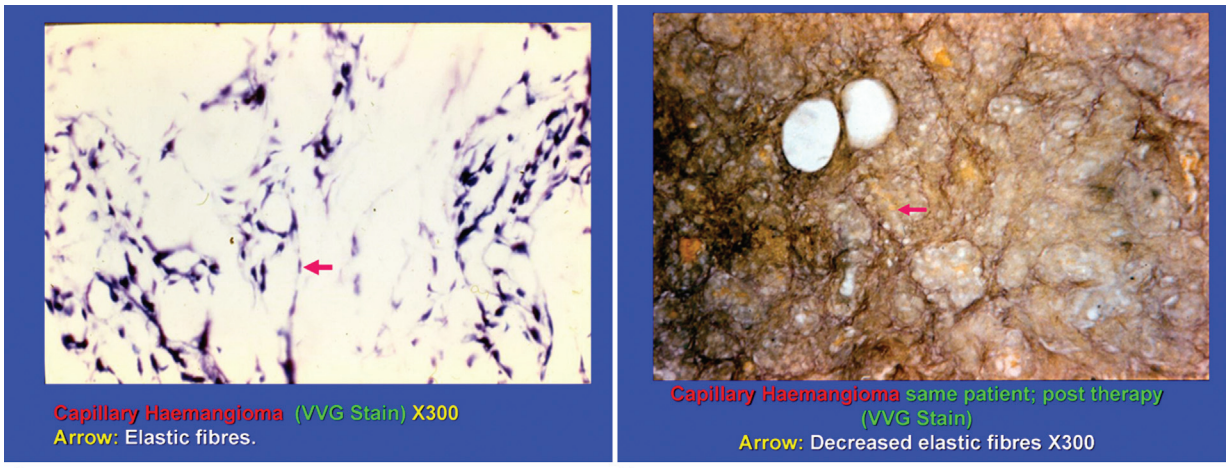
(a) Capillary hemangioma (Masson's Trichrome Stain). Arrow: dilated superficial blood vessels (×200). (b) Capillary hemangioma (same patient) 6 weeks posttherapy. Arrow: relative increase of collagen fibers, with compressed blood vessels (×200).

Figure 3



(a) Capillary hemangioma (reticulin stain). Arrow: abundant reticular fibers around vascular spaces (×300). (b) Capillary hemangioma (same patient) 6 weeks posttherapy (VVG stain) (×300). Arrow: decreased reticular fibers around the blood vessels.

Figure 4



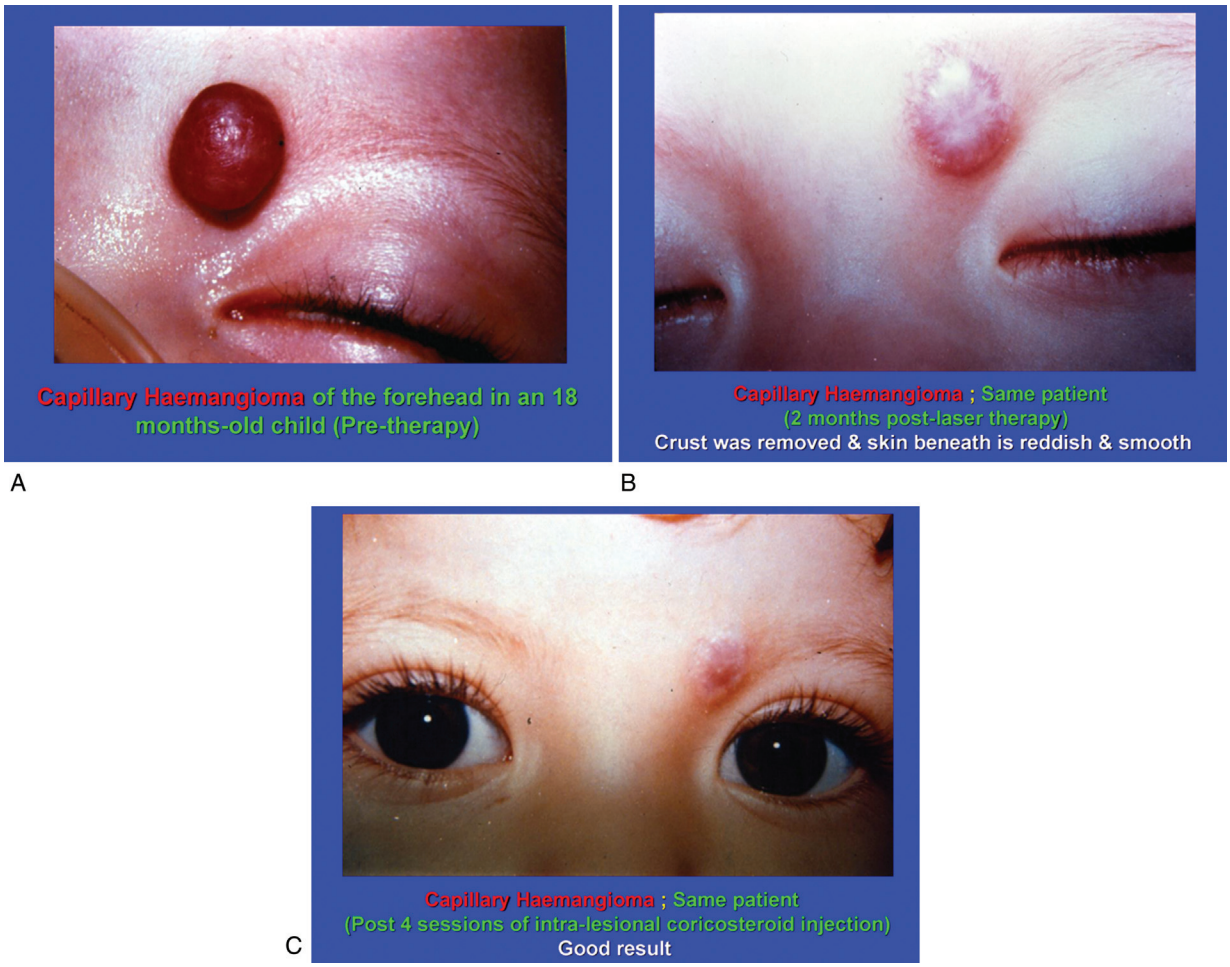
(a) Capillary hemangioma (VVG stain) (×300). Arrow: elastic fibers. (b) Capillary hemangioma same patient; posttherapy (VVG Stain). Arrow: decreased elastic fibers (×300).

Discussion

Infantile hemangioma is a common benign tumor in the head and the neck. They typically pass through different phases. The initial one is of a proliferative type that usually starts during the first 2 weeks of life. Consequently, followed by a plateau phase before turning into a phase of involution that usually begins within the first year of life to continue until the age of 4–6 years. Therefore, most of the superficial hemangiomas doesn't need treatment except for those occurring in certain critical anatomical sites. Periorbital hemangiomas are among those who need a prompt therapy due to its dangerous consequences that might end up with blindness [10–12].

Capillary hemangiomas are the most common eyelid and orbital tumors of childhood. Periorbital hemangioma attracts special attention because of the potential danger of impairing the visual development. The most common ocular complication of periocular capillary hemangiomas in infants is visual loss secondary to amblyopia. The cornea deformation and astigmatism caused by tumor oppression is the main cause of amblyopia [7,13–15].

Figure 5



(a) Capillary hemangioma of the forehead in an 8-month old child (pretherapy). (b) Capillary hemangioma (same patient) 6 weeks after the therapy. (c) Capillary hemangioma; same patient (6 months post therapy), the skin beneath is reddish and smooth.

The main objective of treating periorbital hemangiomas should be the control of tumor growth, prompt tumor shrinkage, and release tumor oppression on the cornea as soon as possible in order to avoid the occurrence of astigmatism and subsequent amblyopia [7].

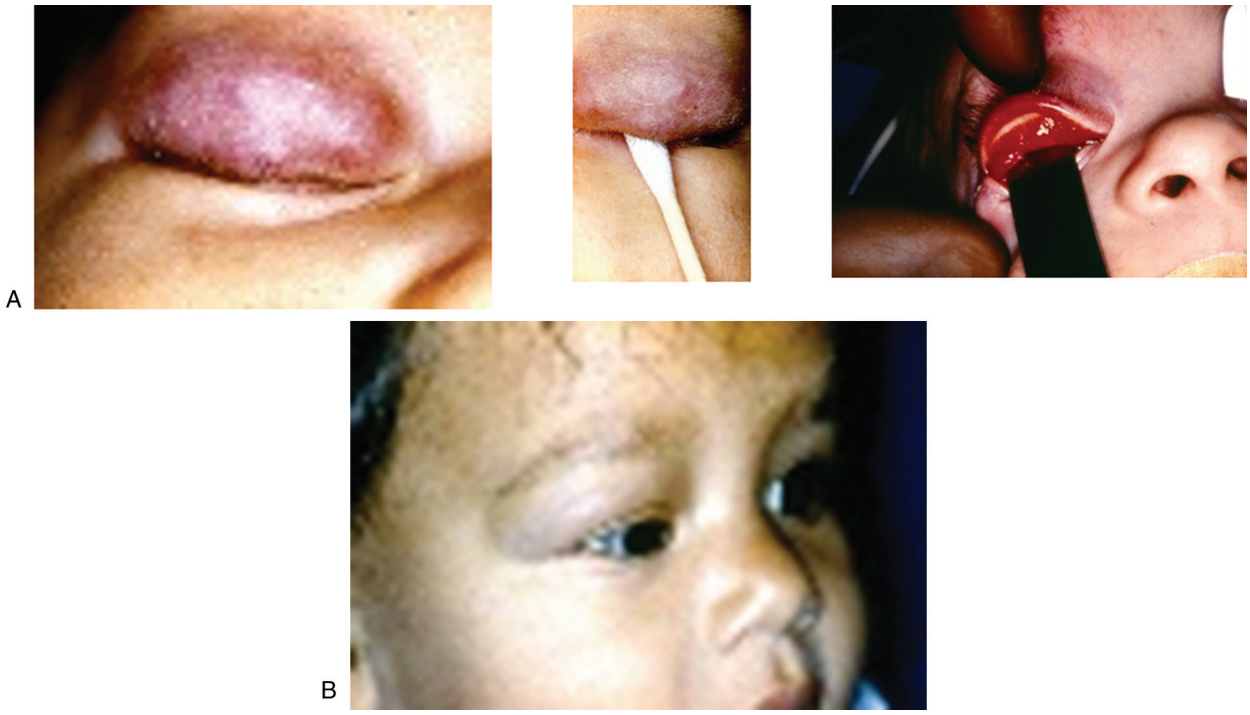
Different modalities have been lately proposed for treating periorbital hemangiomas. They include: topical timolol therapy [16–20] and topical corticosteroid therapy [21–27].

The first reported successful use of applying timolol maleate in treating superficial capillary hemangiomas of the eyelid was published in 2010 as it was used for a 4-month age infant [28]. Others also reported their experience in seven children who suffered from superficial periocular hemangiomas who were treated with topical timolol maleate at a concentration of 0.5%. They reported size and volume reduction in hemangiomas ranged from 55 to 95%. In our current study, we have applied timolol maleate 0.5% gel in 14 patients with 75–95% involution in size and color. We also reported 55–70% improvement in 10 cases. This also coincides with other published data concerning timolol maleate 0.5% topically administered in treating superficial capillary hemangiomas [8].

Nevertheless, in the clobetasol topically treated capillary hemangiomas, the involutional rate of capillary hemangioma was significantly inferior compared with the topically treated timolol group. This coincides with previously published data that support these results with no adverse effects or complications of the both drugs used as in our results [18].

It may be concluded that both timolol maleate and clobetasol can safely be used as a topical treatment for periocular hemangiomas. However, timolol maleate seems to be superior and more effective in treatment. Although the studied material is not large, it may pave the road for treating such hemangiomas. Therefore,

Figure 6



(a) Capillary hemangioma; in a 6 month male patient with vision obstruction on the right side (pretherapy). (b) Capillary hemangioma; same patient 18 months posttherapy.

further studies with a larger number of patients may be needed for a better understanding of timolol maleate effect and complications on periocular hemangiomas.

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Conflicts of interest
There are no conflicts of interest.

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