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CLINICAL STUDY

Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol

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Abstract

Purpose **To evaluate the optical and anatomical effects of oral propranolol treatment for infantile periocular capillary haemangioma.**

Methods **All children diagnosed with infantile capillary haemangioma in 2008–2010 at a tertiary paediatric medical centre underwent comprehensive evaluation, including imaging, by a multidisciplinary team followed by oral propranolol treatment. Clinical follow-up was performed regularly until the lesions disappeared. Main outcome measures included changes in anatomical extraocular extension, refractive sphere and cylindrical power, and spherical equivalent in the involved eye before and after treatment and between the two eyes.**

Results **A total of 30 patients (8 male; mean age at diagnosis, 1.6 ± 2.8 months) participated. The lesions affected the left eye in 53.3% and were located preseptally in 83.3%. Four patients (13.3%) received steroids before propranolol. A treatment dosage of 2 mg/kg per day was started at mean age 5.0 ± 4.5 months, 3.3 ± 4.3 months from disease onset. Side effects occurred in 11 patients and warranted a dose reduction (to 1 mg/kg per day) in 3 and treatment termination in 1. Findings were significant for mean reduction in involved extraocular area ($P < 0.0001$), post-treatment reduction in mean cylindrical power in involved eyes ($P = 0.02$), pre- and post-treatment differences in mean cylindrical power between involved and uninvolved eyes ($P = 0.02$ and $P = 0.01$, respectively), and post-treatment change in absolute values of mean spherical power between involved and uninvolved eyes ($P = 0.025$).**

Conclusions **Early diagnosis of infantile periocular capillary haemangioma and prompt treatment with propranolol lead to a significant reduction in the involved ocular area, in astigmatism, and prevent ocular/facial disfiguration/deformation, without rebound. Propranolol is recommended as the preferred treatment compared with other accepted therapies.**

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Introduction

Infantile periocular capillary haemangioma is the most common benign vascular tumour of the eyelids/orbits in babies, with an incidence of 1.1–2.6% in full-term neonates and 4–10% in infants aged <1 year.[1,2] It is more common in females (female/male 4.1 : 2.5), premature infants, and twins. The natural history of the lesion consists of a proliferative phase, lasting from 3 to 6 months up to 24 months, followed by a period of stabilization and spontaneous involution that lasts from a few months to several years. Complete regression occurs in 60% of patients by age 4 years and in 76% by age 7 years.[3,4] Overall, 10% of these patients require intensive treatment during the proliferative period because of a life-threatening

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location, local anatomical and functional complications, or facial-disfiguring risks.[5–7]

The exact aetiology of capillary haemangiomas is unclear, with involvement of angiogenic and vasculogenic factors.[8] In the angiogenesis pathway, new blood vessels arise from remodelling of pre-existing vasculature. Accordingly, capillary haemangiomas are composed of endothelial cells, mast cells, macrophages, and cellular factors such as the angiogenesis-related receptor E-selectin intergrins, $\alpha V\beta 3$ and $\alpha 5\beta 1$, and basic fibroblast growth factor (bFGF).[9,10] The proliferative phase is characterised by elevated levels of vascular endothelial growth factor and insulin-like growth factor 2, which promote lesion growth from existing vessels.[11,12] The vasculogenesis pathway is implicated by findings that the early endothelial structures and the cellular part of these structures originate from mesoderm-derived haemangioblasts that function as progenitors for haematopoietic and endothelial cells. The proliferation and involution phases are controlled by various regulators and include molecular, cellular, and hormonal changes.[11,12]

Focal infantile periocular capillary haemangioma is associated with a 46–80% rate of severe complications.[13] It can cause ptosis, displacement of the globe, and mechanical deformation of the immature sclera and cornea, leading to anisometropic astigmatism and refractive amblyopia.[13–15] In severe cases, it can cause disfiguring proptosis, exposure keratitis, compressive optic neuropathy, and facial/lid deformation.[16,17]

First-line therapy with corticosteroids: systemic (oral and intravenous), through local intralesional injection, periorbital infusion, or combined intralesional and posterior sub-Tenon's infusion yielded anatomical and refractive improvement.[18–20] However, prolonged treatment with several sessions sometimes required general anaesthesia for proper administration, and posed a risk of serious ocular and systemic side effects.[21] In cases of steroid-resistant lesions, second-line therapy with interferon-*á* and vincristine had an almost 100% success rate, but adverse reactions ranged from minor to very severe.[8,22] In 2008, Léauté-Labrèze *et al*[23] reported that propranolol administered for decreased cardiac output in a child with a capillary haemangioma led to permanent regression of the lesion. This finding was confirmed in another report of 11 children treated with propranolol for capillary haemangioma.[24,25]

The aim of this study was to determine the efficacy and advantages/disadvantages of propranolol treatment for infantile periocular capillary haemangioma and to evaluate propranolol-induced anatomical and functional changes in the lesion.

Patients and methods

Setting

A retrospective, comparative, interventional study design was used. The study group comprised children diagnosed with an extensive capillary haemangioma in the proliferative phase from June 2008 to June 2010 and treated with propranolol. The study was conducted at the Schneider Children's Medical Center of Israel, a university-affiliated tertiary hospital. The protocol was approved by the Institutional Review Board of the Rabin Medical Center, Beilinson Hospital, and approval was confirmed by the directorship of the Schneider Children's Medical Center of Israel.

Pretreatment procedure

All patients underwent pretreatment evaluation by a multidisciplinary team consisting of a paediatrician, paediatric ophthalmologist, orthoptist, paediatric dermatologist, and radiologist. The ophthalmic examination included the size and extent of the lesion (periorbital and orbital), facial/ocular disfiguration, intraocular pressure measured using a Tono-Pen XL (Medtronic Solar, Jacksonville, FL, USA), funduscopy performed using an indirect ophthalmoscope, and cycloplegic refraction examination with two successive administrations of cyclophenolate 0.5% with phenylephrine 2.5%, 10 min apart. The orthoptic evaluation included ocular motility, duction, version, and vergence, as well as the alternate prism cover test or Hirschberg's test. The dermatological evaluation covered the extent, size, colour, and rigidity of the lesion. Most of the children also underwent magnetic resonance imaging with contrast material to determine the full periocular extension of the lesion.

The criteria for propranolol treatment were a mutually confirmed diagnosis of infantile periocular capillary haemangioma by a paediatric ophthalmologist and dermatologist and findings of partial/total occlusion of the visual axis, pressure, or displacement of the eye globe, or significant refractive anisometropia, proptosis, and disfiguring malformation of the eyelids and face. Patients with other ocular or neurological problems or craniosynostosis were excluded, as were patients with other periorbital and orbital vascular or lymphatic lesions, known allergy to propranolol, and asthma or other upper respiratory tract disease.

Candidates for systemic oral propranolol therapy were referred for thorough cardiac evaluation, including electrocardiography and echocardiography, to rule out contraindications. In addition, digital colour photographs were taken of the periorbital involvement; findings were analysed using the NIH Image J software,

version 14.3U (NIH, Bethesda, MD, USA), a public domain program, downloaded from the NIH website (http://rsbweb.nih.gov/ij).[26] The involved area was determined by circling the lesion area in free hand and then measuring all diseased areas in centimetres squared. Owing to lapses in patient cooperation, the photographs were not always taken from the same distance, and the lesion sometimes appeared larger or smaller in successive images. Therefore, to standardise measurements, we used the corneal horizontal diameter, white to white, as a constant 11.5-mm scale for each photograph (Figure 1).

Treatment

Before onset of propranolol treatment, parents/guardians were given a detailed explanation of the disease, the treatment plan, and potential side effects of the drug, and all signed an informed consent form to participate in the study.

Propranolol, 2 mg/kg per day in two doses, was initiated with supervision either in the Day Care Unit or during 24 h hospitalisation in one of the paediatric departments. Blood pressure, pulse rate, and blood glucose levels were monitored during hospitalisation and again during clinic follow-up after 1 week and then every 6–8 weeks for the duration of the systemic therapy. After cessation of therapy, ocular follow-up continued for several months depending on the clinical abnormality. In addition, at each routine medical visit, the dermatological evaluation was repeated, together with ophthalmic/orthoptic evaluations of vascular lesion size, ocular anterior and posterior segments, visual axis, ptosis, ocular motility, misalignment, and cycloplegic refraction. Patients with significant refractive anisometropia (mainly astigmatism) or partial occlusion of the visual axis were prescribed glasses; those older than 4 months were also given anti-amblyopia treatment. The preoperative cardiac evaluation and periorbital digital imaging were repeated at the last follow-up visit. Treatment tolerance was determined according to the findings of the ophthalmologist and the dermatologist and parental reports of side effects. Systemic adverse effects were measured by the paediatrician, including blood pressure, glucose level, and pulse rate. In cases of severe early and late systemic side effects or life-threatening effects of propranolol, the ophthalmologist and dermatologist weighed the need to lower the dosage or discontinue therapy.

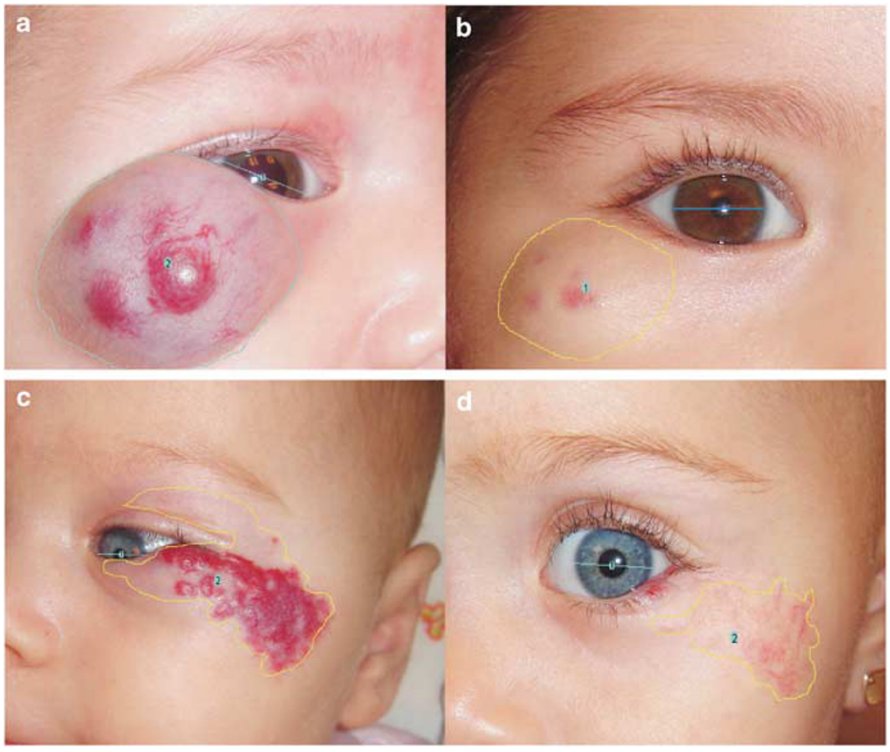

Figure 1 Infantile periocular capillary haemangioma before and after propranolol therapy. (a, b) Patient 1: A 4-month-old child with demarcated severe right perioculary capillary haemangioma, before and after a 6-month course of propranolol. The significant lesion shrinkage as measured by the corneal diameter scale (white to white) must be noted. (c, d) Patient 2: A 5-month-old child with demarcated severe left periocular capillary haemangioma, before and after a 6-month course of propranolol. The significant lesion shrinkage as measured by the corneal diameter scale (white to white) must be noted.

Data collection

Patient files were reviewed for the following data: age at initiation and termination of treatment, interval from appearance of the lesion to start of therapy, duration of therapy, dosage, total/partial treatment, changes in the three refractive parameters in the involved and healthy eyes and from before to after treatment, side effects of treatment, need for suppurative ocular treatment after systemic therapy, and absolute changes in the involved area after treatment.

A successful treatment result was defined as significant reductions in lesion size (>50%), lesion extension (>50%), disfigurement, and the three refractive parameters (namely spherical power, cylinder power, and spherical equivalent) in the involved eye *vs* the healthy eye.

Statistical analysis

The Wilcoxon-matched pairs signed-rank test was used to analyse anatomical (lesion-related) and functional (refraction) changes from baseline to after treatment within each involved eye and between the involved and healthy eyes. We also analysed the absolute changes in sphere and cylindrical power and spherical equivalent. A *P*-value of 0.05 was considered significant. All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 17.0.0; Professional Statistics release 6.29/2010, SPSS Inc., Somers, NY, USA).

Results

In all, 30 infants (8 male and 22 female) met the study criteria. Their characteristics are shown in Table 1. The mean age at diagnosis was 1.6 ± 2.8 months (range 0.25–15 months). The lesion affected the left eye in 53.3% of patients and was located preseptally in 83.3%. Four patients (13.3%) were treated briefly with steroids before propranolol. The mean age at treatment initiation was 5.0 ± 4.5 months (range 1.0–7.0 months), and the mean interval from diagnosis to start of therapy was 3.3 ± 4.3 months (range 0.25–16.5 months). The mean duration of treatment was 7.3 ± 3.5 months (range 1.5–15.0 months), and the duration range of follow-up after cessation of therapy was 6–10 months.

A total of 26 babies (86.7%) underwent maximal treatment of 2 mg/kg per day. In all, 11 patients (36.6%) had side effects of treatment according to their medical files. In three of them (10.0%), the dose was partially decreased (to 1 mg/kg per day) because of severe wheezing, difficulty breathing, and loss of appetite; two of the three patients also had diarrhoea and vomiting. No change in dosage was made in the remainder, in whom adverse effects included transient episodes of sleep problems (three patients), restlessness (three patients), or fever (two patients). Treatment was stopped in one patient (3.3%) because of a respiratory tract infection. There were no abnormal findings on intensive monitoring of blood pressure, pulse rate, and blood glucose level.

Table 1 Clinical data of 30 infants with PICH

Characteristics	*Number (%)*
Sex, n *(%)*	
Male	8 (26.7)
Female	22 (73.3)
Laterality, n *(%)*	
Right	12 (40)
Left	16 (53.3)
Bilateral	2 (6.7)
Location, n *(%)*	
Preseptal	25 (83.3)
Preseptal + intraorbital (extraconal)	3 (10)
Preseptal + intraorbital (extraconal + intraconal)	1 (3.3)
Preseptal + intraconal and intracranial	1 (3.3)
Mean age at diagnosis (months)	
Mean ± SD	1.6 ± 2.8
Range	0.2–15.0
Age at treatment initiation (months)	
Mean ± SD	5.0 ± 4.5
Range	1.0–17.0
Interval from diagnosis to treatment (months)	
Mean ± SD	3.3 ± 4.3
Range	0.5–16.5
Duration of treatment (months)	
Mean ± SD	7.3 ± 3.5
Range	1.0–15.0
Follow-up after cessation of therapy (months)	6–10
Lesion size (cm^2)	
Mean ± SD	12.7 ± 21.7
Range	1.21–108.15

Anatomical improvement was noted within 2–4 days of initiation of treatment in all patients: the lesion became paler and softer, and there was some shrinkage in lesion size, thickness, and extension. These parameters continued to improve longitudinally until the end of treatment. The periorbital photographs of 24 patients (80%) were appropriate for the digital calculation program. The findings revealed a mean diseased periorbital area of 12.7 ± 21.7 cm^2 before therapy and 6.0 ± 9.5 cm^2 after therapy, for a reduction of >50% ($P<0.0003$) (Table 2). Treatment was stopped when the

Table 2 Refraction and anatomical results of oral propranolol treatment for infantile periocular capillary haemangioma

Parameter	*Before treatment*	*After treatment*	*Improvement*	P-*value**
Spherical power (*D*)	1.9 ± 1.6	1.3 ± 0.6	31%	0.13
Cylindrical power (*D*)	1.0 ± 1.1	0.6 ± 0.7	41%	0.02
Spherical equivalent (*D*)	1.8 ± 1.6	1.3 ± 0.8	28%	0.1
Involved area (cm^2)	12.7 ± 21.7	6.0 ± 9.5	52.5%	<0.0003

*Wilcoxon-matched pairs signed-rank test; $P \leq 0.05$ was considered significant.

Table 3 Differences in refractive parameters between the involved and healthy eyes before and after treatment

Parameter	*Before treatment*				*After treatment*			
	Involved eye	*Healthy eye*	*Difference (%)*	P-*value**	*Involved eye*	*Healthy eye*	*Difference (%)*	P-*value**
Mean spherical power (*D*)	1.9 ± 1.6	1.3 ± 2.0	30.0	0.9	1.3 ± 0.6	1.2 ± 1.0	9.1	0.13
Mean cylinder power (*D*)	1.0 ± 1.1	0.5 ± 0.6	50.0	0.02	0.6 ± 0.7	0.3 ± 0.5	47.0	0.01
Mean spherical equivalent	1.8 ± 1.5	1.8 ± 1.5	1.5	1.0	1.3 ± 0.8	1.3 ± 0.7	0.8	0.8

*Wilcoxon-matched pairs signed-rank test; $P \leq 0.05$ was considered significant.

lesion shrank to the point that it was nearly flat and had almost disappeared, with only mild residual skin colour changes and residual superficial telangiectasia, and no lid/facial disfiguration.

A total of 21 patients (70%) underwent cycloplegic refraction examinations. The refractive changes are shown in Tables 2 and 3. Analysis revealed a significant reduction of 40.5% in mean cylindrical power in the involved eye after treatment compared with baseline ($P = 0.02$). There was a non-significant reduction of 31% in spherical power ($P = 0.13$), and a non-significant decrease of 28% in mean spherical equivalent ($P = 0.1$) (Table 2). A significant difference was noted in mean cylindrical power between the involved and uninvolved eyes both before and after treatment ($P = 0.02$ and $P = 0.01$, respectively) (Table 3). The difference in absolute values of the refractive error changes before *vs* after treatment in the involved eye (mean -0.6 ± 1.4) and healthy eye (mean -0.2 ± 1.7) revealed a significant difference in the mean sphere (*D*) ($P = 0.025$). No significant refractive change was found in the healthy eye at any point.

Three patients (10%) were prescribed anti-amblyopia treatment consisting of a patch over the healthy eye with or without glasses.

There were no events of hypotension, bradycardia, or hypoglycaemia during treatment. There was no deterioration in anatomical or refractive parameters after cessation of treatment, during the post-treatment follow-up period.

Discussion

This study indicates that propranolol is the recommended treatment for babies with a massive periocular capillary haemangioma in the proliferative phase. The administration of propranolol at a steady dose of 2 mg/kg per day significantly reduced the anatomical and functional pathology, thereby preventing refractive amblyopia and ocular/facial disfiguration or deformation within a short time, without rebound. Side effects were relatively few and treatable.

Researchers are seeking appropriate replacements for steroids as the first-line therapy for infantile periocular capillary haemangioma, especially in patients with combined refractory periorbital and orbital disease.

Propranolol is a non-selective β-blocker. It has been found to have a beneficial effect on infantile periocular capillary haemangioma, but the underlying mechanism is unknown.[26,27] Three possibilities have been proposed: (1) a vasoconstrictive effect caused by β-2-adrenergic receptor binding in capillary endothelial cells; (2) decreased expression of genes controlling such angiogenic factors as VEGF and bFGF that modify signal transduction in the RAF-mitogen-activated protein kinase pathway; and (3) hypoxia-induced capillary-endothelial cell apoptosis. Propranolol may affect capillary haemangiomas at the proliferative or involution stages. Studies have reported a propranolol-reduced structural regression in capillary haemangiomas, together with dramatic functional refractive improvement, within 1–4 days of drug initiation.[27–32] Léauté-Labrèze *et al*[24] were the first to describe rapid anatomical shrinkage already 24 h after treatment initiation in 11 babies. After the lesion flattened, patients were able to satisfactorily open their eyes; there was no visual impairment. Taban and Goldberg[32] administered propranolol to a 6-year-old girl with a capillary haemangioma who had failed to respond to steroids. Improvement was noted after a few days. The lesion

ultimately disappeared completely, with no regrowth. Similarly, in a study of 17 infants with propranolol-treated capillary haemangioma, Al Dhaybi *et al*[33] observed a reduction in lesion size within 2 months in all cases. In our study, patients showed marked improvement within 2–4 days of treatment initiation. The colour of the lesion faded, and it became softer and smaller. Missoi *et al*[34] and Haider *et al*[35] reported on 17 children who were treated orally from age 4.5 months and age 3 weeks to 12 months, respectively. Anatomical improvement was observed within a few days. Cheng *et al*[36] (5 patients) and Fridman *et al*[37] (10 patients) observed anatomical improvement in most cases within 1 day and 1 week, respectively.

The mean duration of treatment in our study was 7.3 ± 3.5 months, which is longer than that reported by others: 6.5 months in the 11 patients treated by Léauté-Labréze *et al*,[24] and 5.5 months in the 17 patients treated by Al Dhaybi *et al*[33] This difference may be related to the considerably greater number of participants in our study and our more frequent monitoring and calculations of the anatomical changes. We also used a specific digital imaging software to delineate the new lesion limits after regression and calculated the involved area at each measurement.[25] In this manner, we were able to objectively and directly pace the healing process. To the best of our knowledge, this technique has not been used in other studies as part of the regular clinical follow-up of patients with propranolol-treated capillary haemangioma. By the end of treatment, the mean diseased area had decreased significantly ($P < 0.0003$), with minor residual skin pigmentary changes and superficial telangiectasis.

Meticulous analysis of the refractive parameters yielded several significant changes from before to after treatment in the involved eye and between the two eyes. The change in the spherical component after treatment in the involved eye (31%) was not statistically significant after treatment ($P = 0.15$), but the difference in the absolute value of the spherical component (from one time point to the next) between the involved and uninvolved eyes was significant ($P = 0.025$). For the cylindrical component, the percentage change with treatment (41%) was significant ($P = 0.02$), as were the differences between the two eyes both before treatment ($P = 0.02$) and after ($P = 0.01$). These changes in spherical and cylindrical powers in the involved eye were directly related to the shrinkage of the haemangioma, which allowed for normal globe development. Fabian *et al*,[38] in a study of three patients with a massive periocular capillary haemangioma, demonstrated the efficacy of propranolol in decreasing astigmatic error and preventing amblyopia in the involved eye. Cheng *et al*[36] and Haider *et al*[35] reported a reduction in anisometropic astigmatism after treatment in a few patients, but the difference was not statistically significant.

Our repeated cycloplegic refraction measurements helped us to analyze the status of refractive error and treatment-induced changes. We found that when the astigmatic error was high and the refractive differences between the two eyes were significant ($n = 3$, 12.5%), supplemental anti-amblyopia treatment, in the form of patching of the healthy eye with or without glasses, was successful. In addition, careful monitoring clearly revealed the point at which the cycloplegic refraction stabilized, providing an objective indicator of when to terminate systemic β-blocker therapy. It is noteworthy that the refractive status of the fellow eye did not change significantly.

We observed mostly minor side effects of sleep disturbances, agitation, and fever that were successfully managed by the paediatrician with no change in the treatment protocol. None of our patients had bradycardia, hypotension, or hypoglycaemia. We attribute this last finding to the meticulous pretreatment evaluation, followed by close monitoring during and after treatment. We had to reduce the dosage in three cases (50%) to 1 mg/kg per day because of breathing difficulties, vomiting, loss of appetite, and diarrhoea, and to discontinue treatment in one patient because of a severe respiratory tract infection. Sans *et al*[39] also reported minor side effects of propranolol, such as hypotension and wheezing, in 2 of 32 patients with infantile periocular capillary haemangioma, and Al Dhaybi *et al*[33] reported diarrhoea or sleep disturbances in 5 of 17 patients. Missoi *et al*[34] observed mild side effects in most patients, but treatment had to be discontinued in only one patient because of brief episodes of bradycardia. Haider *et al*[35] noted mild side effects (gastric problems and fatigue) in 6 of 17 patients (35.3%), which did not warrant a switch or termination of the medication.

It is noteworthy that the application of topical β-blocker solution (timolol maleate 0.5%) for superficial periocular capillary haemangioma led to significant improvement (visual axis clearance) within a few weeks.[40,41] The response times were longer, and no local or systemic adverse effects were noted.

Our study is unique in several specific parameters: (1) the large sample size, (2) long duration of treatment and follow-up (3) post-treatment ocular follow-up, (4) meticulous analysis of the refractive changes in the involved eye compared with the uninvolved eye, and (5) digital analysis of the involved area before and after treatment.

In conclusion, early and prompt administration of oral propranolol to a dose of 2 mg/kg per day is recommended for massive and deep proliferative-stage infantile periocular capillary haemangioma. The use of

propranolol in this setting requires multidisciplinary supervision by a paediatrician, paediatric ophthalmologist, orthoptist, and paediatric dermatologist. In our series, the improvements were dramatic, both structurally and functionally. Structurally, the vascular lesion disappeared without ocular/facial deformation. Functionally, spherical and astigmatic errors of refraction decreased significantly, which prevented amblyopia in the involved eye. These changes were maximal and permanent, without rebound. Side effects were mostly minor.

Summary

What was known before

- Infantile periocular capillary haemangioma is the most common benign vascular tumour of the eyelids/orbits in babies, which requires intensive treatment for local anatomical, functional, and cosmetic risks.
- Treatment with corticosteroids, interferon-α, and vincristine is unsatisfactory.
- Propranolol is the newest treatment modality.

What this study adds

- Our study is unique for the large cohort size, long duration of treatment and follow-up, post-treatment ocular follow-up, analysis of the refractive changes in the involved and uninvolved eyes, and digital analysis of the involved area before and after treatment.

Conflict of interest

The authors declare no conflict of interest.

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