HHS Public Access

Author manuscript

Intern Med Rev (Wash D C). Author manuscript; available in PMC 2020 April 21.

Published in final edited form as:

Intern Med Rev (Wash D C). 2016 October ; 2(9): . doi:10.18103/imr.v2i9.221.

Beta Blockers in the Treatment of Periocular Infantile Hemangiomas: A Review

Ann Q Tran, MD[1], **Catherine J Choi, MD, MS**[1], **Sara T Wester, MD, FACS**[1]

[1]University of Miami – Bascom Palmer Eye Institute, Department of Ophthalmology

Abstract

Infantile hemangiomas (IH) are the most common benign tumor of infancy, and in the periocular region can be associated with permanent visual impairment from amblyopia. Previous treatment options included systemic and local corticosteroids, surgical excision, laser therapy, and in rare cases immunomodulatory therapy, many of which had variable outcomes with undesirable side effect profiles. Since their initial use for IH in 2008, beta blockers have become the mainstay of therapy for periocular IH due to their excellent clinical efficacy and tolerability. While the exact mechanism of action of beta blockers in IH has not been fully elucidated, both oral and topical therapy have demonstrated low rates of adverse events and improved outcomes in the management of periocular IH. This review summarizes the most recent studies on the clinical outcomes, management, and guidelines for the treatment of periocular IH with topical and oral beta blockers.

Keywords

Infantile hemangioma; capillary hemangioma; periocular hemangioma; beta blockers; propranolol; timolol

Introduction

Infantile hemangiomas (IH) are the most common benign tumor of infancy with an estimated incidence of 4 – 5%, which has been increasing over the past 30 years.[1–2] Risk factors for IH include female gender, premature deliveries, placental abnormalities, low birth weight, in vitro fertilization and a positive family history.[2] The majority of lesions appear in the head and neck region but can also involve the trunk, extremities and the genital or perineal area. While complete regression is seen in 75 to 90% of children by age 7, significant morbidity can result from functional impairment depending on the anatomic location, or disfigurement from scarring and ulceration.[3–4]

Corresponding Author: Sara T Wester, MD, FACS, University of Miami, Bascom Palmer Eye Institute, 900 NW 17th St. Miami, FL, 33136, SWester2@med.miami.edu, Phone: 305-326-6132, Fax: 305-326-6443.

Contributions

Ann Q Tran – Original authorship

Catherine J Choi and Sara T Wester – Conception and final revision

Conflict of interest

No conflicting relationships exist for any author

Periocular IH more specifically can lead to anisometropic astigmatism, ptosis, proptosis, lid margin abnormalities, strabismus, globe displacement, tear duct obstruction and permanent vision loss from amblyopia.[5] As many as 60% of infants with periocular IH are at risk for developing some degree of amblyopia as the proliferation of IH tends to coincide with visual development; prompt treatment is thus necessary in these cases to prevent permanent vision loss.[5–6] In a population-based study, periocular IH occurred in 1 in 1586 live births, with the highest prevalence in female and Caucasian patients.[3] Interestingly, in patients with periocular IH, a second hemangioma was present elsewhere in the body in 20% of cases.[3]

Historically, treatment options included systemic and local corticosteroids, laser, surgical excision, and immunomodulatory therapy.[7–9] Cortico-steroid injections have inherent risks including optic neuropathy, permanent skin hypopigmentation, damage to the surrounding tissues from atrophy or necrosis, retrobulbar hemorrhage, and even blindness from ophthalmic artery occlusion or retinal embolization.[8, 10–11] Surgical excision can be complicated by scarring, and complete excision is often difficult due to the un-encapsulated nature of IH. Both surgery and laser require general anesthesia in children, which carries with it the risks of intraoperative cardiovascular or pulmonary events and potential long-term neurotoxic effects.[12] Immunomodulators such as interferon-α, cyclophosphamide and imiquimod serve as a final resort treatment options given their extensive potential systemic side effects including myelosuppression, transaminitis, infertility, hemorrhagic cystitis and skin damage.[13–15]

In 2008, Léauté-Labrèze incidentally noted regression of steroid-refractory IH lesions in two patients being treated with oral propranolol for cardiac complications (obstructive cardio-myopathy and heart failure from compressive intracervical lesion).[16] In both patients, the IH continued to regress following the steroid taper. After this initial observation, an additional nine patients with disfiguring IH underwent propranolol treatment with response within a day. Since this discovery, many retrospective case series as well as a randomized clinical trial have evaluated the safety and efficacy of oral propranolol as first-line therapy for the treatment of periocular IH.[17–26] More recently, several case series have also evaluated topical beta blocker therapy with timolol for periocular IH with promising results.[27–31] Herein, we summarize the literature and treatment recommendations for the use of oral and topical beta blockers in periocular IH.

Pathophysiology of infantile hemangiomas

The pathophysiology of IH has not yet been fully elucidated. It involves the proliferation of benign endothelial cells and pericytes, and this capillary unit structure is the source of its more common name “capillary hemangioma.” The existing theories regarding the pathogenesis of IH can be summarized into three main categories.[32] The first hypothesis suggests that IH cells are “embolized” from the placenta in utero, given the similar histochemical markers (GLUT-1, Lewis Y Antigen, FcyRII, and Merosin+) found in IH and placental blood vessels. Others propose that somatic gene mutations in hemangioma stem cells cause hyperactivity of VEGF-receptor signaling, leading to downstream proliferation of endothelial cells. Lastly, it has been shown that hypoxia may serve as an independent driving factor for vascular proliferation.[32] This theory is supported by the epidemiologic data related

to low-oxygen environments in low birth weight infants, advanced maternal age, and the additional association with retinopathy of prematurity.

Diagnosis and classification of periocular infantile hemangiomas

Diagnosis of periocular IH is based on clinical appearance. There is no clear consensus or recommendation regarding the role of MRI imaging in orbital IH to date.[33–34] In a small case series evaluating the MRI characteristics of IH, common features included the presence of flow voids, lobulated appearance, hypo-intense T1 signals and hyper-intense T2 signals.[23] Other imaging modalities such as ultrasound have also been beneficial in the longitudinal follow-up of periocular IH, and can be used to document lesion regression in response to treatment without the need for patient sedation.[11] Ultrasound of IH typically demonstrates high internal reflectivity with irregular acoustic echoes. The authors find imaging other than ultrasound unnecessary in the absence of clear evidence of orbital involvement of the lesion. It is important to note, however, that in early cases patients should still be monitored closely and further imaging should be used judiciously with signs of progression.

The rate of IH growth can vary with some lesions having a slow indolent course and others growing rapidly. IHs characteristically undergo a rapid proliferation phase, followed by a period of stabilization where the lesion may remain quiescent, and finally a spontaneous involution phase.[32] Eighty percent of IH undergo a proliferation phase in the first 3 months of life, reaching its final size by 5 months.[4]

Periocular IH can be described by depth of skin involvement (deep, superficial or mixed) or location (localized or segmental involvement). Superficial hemangiomas involve the outer layers of the skin and typically present as bright red vascular lesions while deep hemangiomas grow below the cutaneous plane into the subcutaneous tissue and have a bluish vascular appearance.[35] Segmental lesions are spatially confined in one area while localized lesions have a cluster of IHs residing in one large anatomic territory. Interestingly, similar growth rates are seen between these two types within the first 6 months.[4] Overall, regardless of the subtype, the size and location are critical for predicting the degree of ocular complications, as visual prognosis is worse in periocular IH of the upper eyelid or greater than 1 cm in size.[5]

Mechanism of action of beta blockers

The exact mechanism of action of beta blockers in IH remains elusive. Propranolol has non-selective antagonistic effects on β-adrenergic receptors. It is thought that propranolol may trigger vasoconstriction within the lesion thereby changing the color and decompressing the hemangioma.[16] Additionally, beta blockers likely modulate angiogenic peptides, changing the signal transduction pathway and inhibiting further development of hemangiomas.[36] Other research supports non-specific activity of beta blockers that can initiate apoptosis of capillary endothelial cells, as well as a downstream effect of decreased renin production.[36]

Indications for initiating treatment

Given the diversity of presentation of IH, it is important to review the indications for starting therapy. Areas considered at risk for disfigurement or functional complications require immediate therapy: periocular IH with or without occlusion of the visual axis, areas prone to ulceration such as the axillary or perineal region, lesions near the nose leading to nasal obstruction or near the lips resulting in difficulty with oral intake, and large IH in the mammary regions for girls.[33–34] Smaller lesions, even at high-risk locations, can be monitored with interval follow-ups based on the age of the patient (age in months = follow-up interval in weeks).[33–34]

Periocular IH, in particular, warrants close and early evaluation with an ophthalmologist or oculoplastic surgeon due to the risk of potential compromise of vision from amblyopia. IH can induce amblyopia by applying direct pressure on the globe with resultant corneal astigmatism, by causing partial or complete obstruction of the visual axis leading to deprivation amblyopia, or by producing misalignment of the extraocular muscles known as strabismus preventing binocular fusion.[5] These complications have been reported at variable rates of incidence ranging from 43% to 80% among patients with untreated periocular IH).[35, 37] Other possible ocular complications associated with periocular IH include optic nerve compression secondary to mass effect in orbital IH, exposure keratopathy, and tear duct obstruction.[35]

Contraindications to use of beta blockers

Contraindications to propranolol therapy include premature infants less than 5 weeks of age, infants weighing less than 2 kg, history of cardiogenic shock or heart failure, heart rate less than 80 beats per minute, hypotension with blood pressure less than 50/30 mmHg, greater than first degree heart block, bronchial asthma or hypersensitivity to propranolol.[38] Precautions should be taken in infants with poor feeding given the risk of hypoglycemia and hypoglycemic seizures. Extra precautions should be also taken in infants with PHACE syndrome (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities) due to their head and neck arterial anomalies, placing them at a higher risk of stroke from labile blood pressures when using non-selective beta blockers.[39] Prior to starting propranolol treatment, PHACE syndrome patients may benefit from MRI/MRV of the head and neck and echocardiogram to assess for underlying structural abnormalities, and should be followed closely by cardiology.

Routine screening and monitoring recommendations

While the authors as ophthalmo-logists do not initiate oral beta blocker treatment in the office, the following treatment guidelines are typically used by the referring pediatrician or pediatric cardiologist.[33–34] Initial examination for infants undergoing oral propranolol treatment should include a thorough history and physical documenting any wheezing, heart murmurs, poor feeding, dyspnea, tachypnea and diaphoresis. Baseline vital signs, cardiac and pulmonary exams should be performed.[33–34] EKGs should be obtained for infants with heart rates below the normal range for age, family history of congenital heart disease,

maternal history of connective tissue disease or personal history of arrhythmias.[33–34] Screening echocardio-grams may not be necessary in normal infants as structural and functional heart disease have not be associated with uncomplicated IH.

One to two hours after administering the first dose of propranolol, heart rate and blood pressure measurements should be monitored as propranolol effects typically peak two hours after administration.[33–34, 40] If these values are abnormal, the vital signs should be recorded until they normalize. Infants who are less than 8 weeks old with co-morbid conditions should be monitored in an inpatient setting for the first three doses to ensure that the infant tolerates the treatment. Infants older than 8-weeks with adequate support can be monitored in the outpatient setting.[33–34] Studies utilizing Holter monitoring for bradycardia and arrhythmias are likely unnecessary in otherwise healthy patients with IH older than 12 weeks of age.[41]

In practice, there is a wide variability in baseline screening, pre-treatment cardiac testing and imaging, and beta blocker dosing among providers. A survey of pediatric dermatologists found that 96% of providers prescribed oral propranolol for treatment of IH but 75% of providers did not follow consensus guidelines.[42] Only 56% of providers monitored vital signs after the first dose and only half continued to monitor vital signs thereafter. Primary care providers should recognize high-risk infants for appropriate referrals and expedite their initial consultation with appropriate specialists.[4] Currently, many ophthalmo-logists work closely with pediatricians who aid in the administration and monitoring of beta blocker therapy.

Dosing of oral beta blockers

Most dosing recommendations for oral propranolol were historically based on anecdotal experience of providers only. Some initial consensus recommendations based on non-randomized clinical studies were to start at 0.33 mg/kg of propranolol administered every 8 hours (1mg/kg/day). If the dose was not tolerated, it was reduced and gradually increased until the patient can tolerate 0.33 mg/kg; if the dose was tolerated, it was increased to 0.66 mg/kg every 8 hours (2mg/kg/day).[33–34] Recommended maximum target dose among studies ranged from 1 to 3 mg/kg/day, with an average dose of 2 mg/kg/day administered three times a day.[33–34]

In 2015, Léauté-Labrèze conducted the first multicenter, randomized, double-blinded phase II/III clinical trial assessing the efficacy and safety of oral propranolol in pediatric patients.[26] A total of 460 infants (ages 35–150 days) were randomized to 1 mg/kg/day or 3 mg/kg/day divided into twice daily dosing over a three or six-month period. Propranolol was titrated weekly by starting at 1 mg/kg/day, increasing to 2mg/kg/day at week one, and reaching a final dose of 3 mg/kg/day by week two.[26] A higher percentage of patients had complete or nearly complete regression after six months of treatment compared to three months of treatment.[26] The results of this study led to the FDA approval of Hemangeol™, an oral solution of propranolol, for the treatment of proliferating IH.[38] Hemangeol™ protocol recommends starting at 1.2 mg/kg/day with gradual titration to 2.2 mg/kg/day then maintenance dose of 3.4 mg/kg/day over a six-month period divided in half for twice daily

dosing.[38] To reduce the risk of hypoglycemia, the medication should be administered during or after routine feeding times.

Rebound growth after propranolol discontinuation has been reported in 25% of patients, requiring modification of treatment.[41] Discontinuing therapies prior to 9 months of treatment had a 2.4-fold higher odds of rebounding (OR 2.4, 95% CI 1.3 – 4.5; P=0.04) compared to those who received treatment for 12 to 15 months.[43]

Clinical response to oral beta blockers

Many case series and more recent clinical trials thus far have demonstrated the clear efficacy of oral beta blockers in the treatment of IH.[17–26] Even patients who had failed prior corticosteroid treatment responded to propranolol, including a child outside of the mean proliferative phase.[18, 25] In the randomized control trial by Léauté-Labrèze, 88% of patients in the propranolol treatment arm showed improvement after 5 weeks of treatment regardless of the dosage, compared to 5% in the placebo group.[26] Fifty-two percent of infants receiving a lower dose of 1 mg/kg/day of propranolol for 6 months had improvement. Ten percent of patients required re-treatment during follow-up.

Given the high response rate, tolerable side effect profile, and rapid onset of regression, most practitioners have switched to oral beta blockers as first-line treatment for IH. A recent meta-analysis of 18 different studies revealed 95% clearance of IH with oral propranolol and only 43% with oral corticosteroids.[44] There was also evidence suggesting that IH treated with beta blockers had better improvement in color lightening and flattening based on five studies that commented on the appearance of IH.[45]

More specifically for periocular IH, oral propranolol has been shown to have significant benefit in decreasing the rates of visual complications reported in many retrospective case series.[17, 18, 20, 21, 22, 25, 46, 47] Median reduction in surface area of periocular IH was 61% (range 32% – 64%) after propranolol treatmeant.[21] Quanti-fication of refractive changes of children before and after treatment showed a significant decrease in mean astigmatic power from 1.0 ± 1.1 D to 0.6 ± 0.7 D.[25] The refractive error of patients with anisometropic astigmatism showed improvement in both the affected and the unaffected eye, consistent with the process of emmetropization that occurs during infancy.[22]

Other studies have focused on developing risk stratification and monitoring tools for ambylogenic risk from periocular IH.[47] In one study, a single diopter value (DFE-δ) proportional to amblyogenic risk was calculated based on diopters of refractive anisometropia. DFE-δ constant at the start of propranolol treatment was 1.54 (±0.62D) compared to 0.39 (±0.38D) at the end of treatment.[47] While this calculation was based on data from only nine children, such methodology may aid in the quantification of treatment outcomes of propranolol in the future.

Topical Beta Blockers

Over 28 studies have also evaluated the use of topical beta blockers such as timolol maleate solution 0.5%, timolol maleate 0.25–0.5% gel, propranolol 1% ointment and propranolol 3%

hydrochloride gel in the treatment of IH, of which 7 were focused on periocular IH.[27] Adequate absorption of topical drops and gel has been demonstrated in serum and in urine.[27] In some cases, occlusive dressings with beta blocker gels may further enhance absorption and result in superior effects.[48]

In an observational case series of 7 superficial periocular IH, timolol maleate 0.5% given twice a day for a duration of 1 to 6 months led to a 55 to 95% volume reduction in lesion size.[49] Most patients responded to treatment 4 to 8 weeks after initiation and none of the children reported significant local or systemic side effects. A case of a rare episcleral hemangioma treated with timolol maleate 0.5% twice a day also regressed completely after 5 months of treatment without rebound growth a year after discontinuing the medication.[29]

It is important to note that in the authors' experience, superficial periocular IH are more likely to respond to topical therapy than deeper lesions, but some deeper lesions may show adequate response as well.[50–51] In certain cases without immediate amblyopia risk, it is therefore reasonable to initiate a trial of topical timolol first prior to escalating to oral therapy. For other cases of deeper lesions, the combination of oral and topical beta blockers can also be considered. In a retrospective study of 89 infants with various types of IH, propranolol 2 mg/kg/day divided into two doses and timolol maleate 0.5% gel three times a day were administered over 9 months.[30] One hundred percent of patients benefited from regression of the lesion by color, surface consistency, firmness and depth. Limited adverse effects such as cold extremities (3.4%), agitation (2.2%) and diarrhea (2.2%) were seen during the first 6 months of treatment. Only one patient relapsed after treatment.

Side effects of beta blockers

Both oral and topical beta blockers carry the potential for adverse side effects that should be monitored in children. A review of 1175 patients in 85 papers at the pediatric consensus conference in 2011 reported the most common side effects as sleep disturbances (3.7%), asymptomatic hypotension or hypertension (2.8%), somnolence (2.2%), cool or mottled extremities (1.7%) and pulmonary symptoms (1.4%).[33] The most common adverse reactions in the randomized clinical trial by Léauté-Labrèze were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting, occurring in less than 10% of patients.[26] Severe side effects such as cardiac disorders, hypoglycemia, bradycardia, alopecia or urticaria occurred in less than 1% of patients. Less than 2% of patients discontinued treatment due to side effects. There was no significant difference in the side effect profile at the higher dosage of propranolol (3mg/kg/day).[26]

To minimize the risk of these side effects, practitioners are advised to take precautions with initiation and discontinuation of therapy (as outlined previously) and to instruct caregivers of the associated risks. Propranolol may induce hypoglycemia by its receptor properties in a dose-dependent manner, and feeding should be monitored.[33–34] Bronchospasm can occur in the setting of an acute viral illness while on propranolol, which may thus be temporarily discontinued for the duration of the acute illness. Cardiovascular effects should be monitored with vital signs based on outpatient and inpatient criteria outlined above.

Topical beta blockers have differing side effects depending on the method of delivery: ocular versus topical dermal application. When given to the eye, apnea, asthma, lightheadedness, bradycardia, and dissociated behavior have been reported in small numbers in pediatric glaucoma applications.[52] Topical dermal administration of beta blockers has been associated with pruritis causing excoriations and erosions and sleep disturbances in some cases.[28, 30] The majority of these side effects were not found to be bothersome in prior studies.

Conclusion

The use of oral and topical beta blockers has dramatically lowered risks and improved outcomes in the treatment of periocular IH. Treatment should be individually tailored to each patient with close collaboration between the ophthalmologist and the pediatrician, and pre-treatment work-up may be indicated prior to initiation of therapy depending on the child's risk profile. Vital sign monitoring during the initiation of therapy is advisable. The recommended target dose of oral propranolol ranges from 2 mg/kg/day to 3 mg/kg/day. For topical beta blockers, timolol maleate 0.5% has been used in studies with good effect for superficial IH. Overall, the adverse reactions from these medications occur infrequently and are less severe than those with prior treatment modalities such as oral corticosteroids and immuno-modulators. Both oral and topical beta blockers are thus the mainstay of treatment for IH today and represent a major change in the clinical management of this common but potentially serious condition.

References

1. Anderson KR, Schoch JJ, Lohse CM, et al. Increasing incidence of infantile hemangiomas (IH) over the past 35 years: Correlation with decreasing gestational age at birth and birth weight. J Am Acad Dermatol. 2016;74(1):120–6. doi: 10.1016/j.jaad.2015.08.024. [PubMed: 26494585]
2. Munden A, Butschek R, Tom WL, et al. Prospective study of infantile haemangiomas: incidence, clinical characteristics and association with placental anomalies. Br J Dermatol. 2014;170(4):907–13. doi: 10.1111/bjd.12804. [PubMed: 24641194]
3. Alniemi ST, Griepentrog GJ, Diehl N, et al. Incidence and clinical characteristics of periocular infantile hemangiomas. Arch Ophthalmol. 2012;130(7):889–93. doi: 10.1001/archophthalmol.2012.213. [PubMed: 22776927]
4. Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics. 2008;122 (2):360–7. doi: 10.1542/peds.2007-2767. [PubMed: 18676554]
5. Schwartz SR, Blei F, Ceisler E, et al. Risk factors for amblyopia in children with capillary hemangiomas of the eyelids and orbit. J AAPOS. 2006;10 (3):262–8. [PubMed: 16814181]
6. Frank RC, Cowan BJ, Harrop AR, et al. Visual development in infants: visual complications of periocular haemangiomas. J Plast Reconstr Aesthet Surg. 2010;63(1):1–8. doi: 10.1016/j.bjps.2008.08.045. [PubMed: 19097831]
7. Ni N, Guo S, Langer P. Current concepts in the management of periocular infantile (capillary) hemangioma. Curr Opin Ophthalmol. 2011;22(5):419–25. doi: 10.1097/ICU.0b013e32834994b4. [PubMed: 21730838]
8. Friling R, Axer-Siegel R, Ben-Amitai D, et al. Intralesional and sub-Tenon's infusion of corticosteroids for treatment of refractory periorbital and orbital capillary haemangioma. Eye (Lond). 2009;23(6):1302–7. doi: 10.1038/eye.2008.300. [PubMed: 18989344]
9. Garzon MC, Lucky AW, Hawrot A, et al. Ultrapotent topical corticosteroid treatment of hemangiomas of infancy. J Am Acad Dermatol. 2005;52(2):281–6. [PubMed: 15692474]

10. Wester ST, Johnson TE. Echographic evidence of regression of a periocular infantile capillary hemangioma treated with systemic propranolol. Ophthalmic Surg Lasers Imaging. 2011; 10;42 Online:e18–21. doi:10.3928/15428877-20110203-04.
11. Samimi DB, Alabiad CR, Tse DT. An anatomically based approach to intralesional corticosteroid injection for eyelid capillary hemangiomas. Ophthalmic Surg Lasers Imaging. 2012;43(3):190–5. doi: 10.3928/15428877-20120315-03. [PubMed: 22432604]
12. Rappaport B, Mellon RD, Simone A, et al. Defining safe use of anesthesia in children. N Engl J Med. 2011;364(15): 1387–90. doi: 10.1056/NEJMp1102155. [PubMed: 21388302]
13. Greinwald JH Jr, Burke DK, Bonthius DJ, et al. An update on the treatment of hemangiomas in children with interferon alfa-2a. Arch Otolaryngol Head Neck Surg. 1999;125(1):21–7. [PubMed: 9932582]
14. Wilson MW, Hoehn ME, Haik BG, et al. Low-dose cyclophosphamide and interferon alfa 2a for the treatment of capillary hemangioma of the orbit. Ophthalmology. 2007;114(5):1007–11. [PubMed: 17337066]
15. Jiang C, Hu X, Ma G. A prospective self-controlled phase II study of imiquimod 5% cream in the treatment of infantile hemangioma. Pediatr Dermatol. 2011;28(3):259–66. doi: 10.1111/j.1525-1470.2011.01520. [PubMed: 21615472]
16. Léauté-Labrèze C, Dumas de la Roque E, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358(24):2649–51. doi: 10.1056/NEJMc0708819. [PubMed: 18550886]
17. Haider KM, Plager DA, Neely DE, et al. Outpatient treatment of periocular infantile hemangiomas with oral propranolol. J AAPOS. 2010;14(3): 251–6. doi: 10.1016/j.jaapos.2010.05.002. [PubMed: 20603059]
18. Li YC, McCahon E, Rowe NA, et al. Successful treatment of infantile haemangiomas of the orbit with propranolol. Clin Experiment Ophthalmol. 2010;38(6):554–9. doi: 10.1111/j.1442-9071.2010.02327. [PubMed: 20491798]
19. Blatt J, Morrell DS, Buck S, et al. β-blockers for infantile hemangiomas: a single-institution experience. Clin Pediatr. 2011;50(8):757–63. doi: 10.1177/0009922811405517.
20. Fabian ID, Ben-Zion I, Samuel C, et al. Reduction in astigmatism using propranolol as first-line therapy for periocular capillary hemangioma. Am J Ophthalmol. 2011;151(1):53–8. doi: 10.1016/j.ajo.2010.07.022. [PubMed: 20970771]
21. Missoi TG, Lueder GT, Gilbertson K, et al. Oral propranolol for treatment of periocular infantile hemangiomas. Arch Ophthalmol. 2011;129(7):899–903. doi: 10.1001/archophthalmol.2011.40. [PubMed: 21402978]
22. Glasman P, Chandna A, Nayak H, et al. Propranolol and periocular capillary hemangiomas: assessment of refractive effect. J Pediatr Ophthalmol Strabismus. 2014;51(3):165–70. doi: 10.3928/01913913-20140507-03. [PubMed: 24877527]
23. Levitt M, Coumou AD, Groeneveld L, et al. Propranolol as first-line treatment in orbital infantile haemangiomas: a case series. Orbit. 2014;33(3):178–83. doi: 10.3109/01676830.2014.884148. [PubMed: 24568543]
24. Lynch M, Lenane P, O'Donnell BF. Propranolol for the treatment of infantile haemangiomas: our experience with 44 patients. Clin Exp Dermatol. 2014;39(2):142–5. doi: 10.1111/ced.12210. [PubMed: 24289272]
25. Snir M, Reich U, Siegel R, et al. Refractive and structural changes in infantile periocular capillary haemangioma treated with propranolol. Eye (Lond). 2011;25(12):1627–34. doi: 10.1038/eye.2011.233. [PubMed: 21921959]
26. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015;372(8):735–46. doi: 10.1056/NEJMoa1404710. [PubMed: 25693013]
27. Painter SL, Hildebrand GD. Review of topical beta blockers as treatment for infantile hemangiomas. Surv Ophthalmol. 2016;61(1):51–8. doi: 10.1016/j.survophthal.2015.08.006. [PubMed: 26408055]
28. Xu DP, Cao RY, Tong S, et al. Topical timolol maleate for superficial infantile hemangiomas: an observational study. J Oral Maxillofac Surg. 2015;73(6): 1089–94. doi: 10.1016/j.joms.2014.12.026. [PubMed: 25843815]

29. Ciudad Blanco C, Campos Domínguez M, Moreno García B, et al. Episcleral infantile hemangioma successfully treated with topical timolol. Dermatol Ther. 2015;28(1):22–4. doi: 10.1111/dth.12173. [PubMed: 25286087]
30. Ge J, Zheng J, Zhang L, et al. Oral propranolol combined with topical timolol for compound infantile hemangiomas: a retrospective study. Sci Rep. 2016;6:19765. doi: 10.1038/srep19765. [PubMed: 26819072]
31. Hu L, Huang HZ, Li X, et al. Open-label nonrandomized left-right comparison of imiquimod 5% ointment and timolol maleate 0.5% eye drops in the treatment of proliferating superficial infantile hemangioma. Dermatology. 2015;230(2):150–5. doi: 10.1159/000369164. [PubMed: 25633200]
32. Chen TS, Eichenfield LF, Friedlander SF. Infantile hemangiomas: an update on pathogenesis and therapy. Pediatrics. 2013;131(1):99–108. doi: 10.1542/peds.2012-1128. [PubMed: 23266916]
33. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013;131(1):128–40. doi: 10.1542/peds.2012-1691. [PubMed: 23266923]
34. Hoeger PH, Harper JI, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a European expert group. Eur J Pediatr. 2015;174 (7):855–65. doi: 10.1007/s00431-015-2570-0. [PubMed: 26021855]
35. Spence-Shishido AA, Good WV, Baselga E, et al. Hemangiomas and the eye. Clin Dermatol. 2015;33(2):170–82. doi: 10.1016/j.clindermatol.2014.10.009. [PubMed: 25704937]
36. Claerhout I, Buijsrogge M, Delbeke P, et al. The use of propranolol in the treatment of periocular infantile hemangiomas: a review. Br J Ophthalmol. 2011;95(9):1199–202. doi: 10.1136/bjo.2010.192245. [PubMed: 21131380]
37. Ceisler EJ, Santos L, Blei F. Periocular hemangiomas: What every physician should know. Pediatr Dermatol. 2004;21:1–9. [PubMed: 14871317]
38. U. S. Food and Drug Administration. Hemangeol safety and efficacy. 2014; 1–18; Reference ID: 3471590. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205410s000lbl.pdf
39. Siegel DH, Tefft KA, Kelly T, et al. Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (PHACE) syndrome: a systematic review of the literature. Stroke. 2012;43(6):1672–4. doi: 10.1161/STROKEAHA.112.650952. [PubMed: 22442177]
40. Cushing SL, Boucek RJ, Manning SC, Sidbury R, Perkins JA. Initial experience with a multidisciplinary strategy for initiation of propranolol therapy for infantile hemangiomas. Otolaryngol Head NeckSurg. 2011; 144(1):78–84. doi: 10.1177/0194599810390445.
41. Jacks SK, Kertesz NJ, Witman PM, et al. Experience with Holter monitoring during propranolol therapy for infantile hemangiomas. J Am Acad Dermatol. 2015;73(2):255–7. doi: 10.1016/j.jaad.2015.05.015. [PubMed: 26054433]
42. Kumar MG, Coughlin C, Bayliss SJ. Outpatient use of oral propranolol and topical timolol for infantile hemangiomas: survey results and comparison with propranolol consensus statement guidelines. Pediatr Dermatol. 2015;32(2):171–9. doi: 10.1111/pde.12435. [PubMed: 25556828]
43. Shah SD, Baselga E, McCuaig C, et al. Rebound Growth of Infantile Hemangiomas After Propranolol Therapy. Pediatrics. 2016;137(4). pii: e20151754. doi: 10.1542/peds.2015-1754. [PubMed: 26952504]
44. Chinnadurai S, Fonnesbeck C, Snyder KM, et al. Pharmacologic Interventions for Infantile Hemangioma: A Meta-analysis. Pediatrics. 2016;137(2):e20153896. doi: 10.1542/peds.2015-3896. [PubMed: 26772662]
45. Xu SQ, Jia RB, Zhang W, et al. Beta-blockers versus corticosteroids in the treatment of infantile hemangioma: an evidence-based systematic review. World J Pediatr. 2013;9(3):221–9. doi: 10.1007/s12519-013-0427-z. [PubMed: 23929254]
46. Al Dhaybi R, Superstein R, Milet A, et al. Treatment of periocular infantile hemangiomas with propranolol: case series of 18 children. Ophthalmology. 2011;118(6):1184–8. doi: 10.1016/j.ophtha.2010.10.031. [PubMed: 21292326]
47. Burne R, Taylor R; Medscape. Monitoring propranolol treatment in periocular infantile haemangioma. Eye (Lond). 2014;28(11):1281–4. doi: 10.1038/eye.2014.237. [PubMed: 25323853]

48. Moehrle M, Leaute-Labreze C, Schmidt V, et al. Topical timolol for small hemangiomas of infancy. Pediatr Dermatol. 2013;30(2):245–9. doi: 10.1111/j.1525-1470.2012.01723. [PubMed: 22471694]

49. Ni N, Langer P, Wagner R, Guo S. Topical timolol for periocular hemangioma: report of further study. Arch Ophthalmol. 2011;129(3):377–9. doi: 10.1001/archophthalmol.2011.24. [PubMed: 21403002]

50. Xue K, Hildebrand GD. Deep periocular infantile capillary hemangiomas responding to topical application of timolol maleate, 0.5%, drops. JAMA Ophthalmol. 2013;131 (9):1246–8. doi: 10.1001/jamaophthalmol.2013.4171. [PubMed: 23846584]

51. Xue K, Hildebrand GD. Topical timolol maleate 0.5% for infantile capillary haemangioma of the eyelid. Br J Ophthalmol. 2012;96(12):1536–7. doi: 10.1136/bjophthalmol-2012-302396.

52. Coppens G, Stalmans I, Zeyen T, et al. The safety and efficacy of glaucoma medication in the pediatric population. J Pediatr Ophthalmol Strabismus. 2009;46(1):12–8. [PubMed: 19213271]