Oral Propranolol for Treatment of Periocular Infantile Hemangiomas

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Objective: To evaluate the efficacy and adverse effects of oral propranolol for treatment of periocular infantile hemangioma.

Methods: Participants were treated with oral propranolol 3 times daily, with outpatient monitoring of adverse effects. The starting dosage was 0.5 mg/kg/d for 1 week, then 1 mg/kg/d for the following week, then 2 mg/kg/d for the remaining duration of treatment. Serial examinations and external photography documented the size of the hemangiomas. Complete ophthalmic examinations included assessing for amblyopia with cycloplegic refraction and visual diagnostic testing. Amblyopia was treated with part-time occlusion therapy.

Results: Nineteen periocular hemangiomas from 17 children (71% girls) were studied. The median age at the start of treatment was 4.5 months (interquartile range, 2.2-5.6 months). The median treatment duration was 6.8 months (interquartile range, 4.1-7.2 months). Treatment with oral propranolol reduced the size of all hemangiomas. Median change in the surface area was 61% (interquartile range, 32%-64%) of the original size. Mild rebound growth that did not necessitate retreatment was found in 2 patients (12%). One patient (6%) experienced a benign episode of bradycardia. Seven patients (41%) had amblyopia.

Conclusions: Oral propranolol for treatment of infantile hemangiomas was effective in all patients, with 33% reduction in astigmatism and 39% reduction in surface area. Vision equalized in all but 1 child, who receives ongoing amblyopia therapy. Our results suggest that early treatment with propranolol is remarkably effective in treating and preventing loss of visual acuity associated with periocular infantile hemangiomas.


Infantile hemangiomas are benign tumors that appear shortly after birth. They usually begin to involute spontaneously in early childhood. Whereas most are small and of mild cosmetic concern, infantile hemangiomas can cause significant morbidity. Large focal or segmental hemangiomas can cause severe disfigurement. Involvement of structures of the head and neck can lead to airway obstruction and feeding difficulties. Periocular hemangiomas may cause vision loss secondary to amblyopia induced by astigmatism, ptosis, or globe displacement.

In the past, various treatments have been used for infantile hemangiomas, such as corticosteroids given topically, orally, and via intralesional injection. Corticosteroids have significant systemic adverse effects, including growth retardation, failure to thrive, adrenal suppression, cushingoid weight gain, hypertrichosis, behavioral changes, and gastrointestinal upset. Complications of intralesional corticosteroid injections include focal fat atrophy, thinning of the skin, skin hypopigmentation, cataracts, glaucoma, and central retinal artery emboli. Less commonly used therapies for hemangiomas include pulsed dye laser, surgical excision, alfa-interferon, and vincristine.

In 2008, Léauté-Labrèze et al reported the successful treatment of severe infantile hemangiomas with oral propranolol. The incidental discovery occurred when 2 patients with large airway hemangiomas were prescribed propranolol to treat high-output cardiac failure. They noted a remarkable decrease in the size of the hemangiomas within days and reported an additional 9 patients who also responded to oral propranolol.

We report our experience with 17 patients with periocular infantile capillary hemangiomas who were treated with oral propranolol. The goal of our study was to evaluate the efficacy and adverse effects of this treatment.

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A retrospective medical record review was performed on patients who were treated with oral propranolol for periocular infantile hemangiomas. All 17 infants included in the study had been examined in the ophthalmology and dermatology clinics at St Louis Children’s Hospital. The Washington University Institutional Review Board granted approval before the onset of the study. Health Insurance Portability and Accountability Act (HIPAA) compliance was maintained throughout the study.

Demographic information, age at first visit to clinic, age at start of treatment, duration of treatment, and indication for treatment were recorded. Documentation of hemangioma size included detailed drawings and photography. Due to the non-gaussian distribution of data, the median and interquartile range (IQR) were used for statistical analysis.

The Department of Cardiology at St Louis Children’s Hospital was consulted regarding the treatment regimen. Based on their years of experience with oral propranolol, we determined that treatment could safely be performed on an outpatient basis. All patients were treated with oral propranolol 3 times daily. The starting dosage was 0.5 mg/kg/d for 1 week, then 1 mg/kg/d for the following week, then 2 mg/kg/d for the remaining treatment period. If the patient had been born prematurely, treatment was delayed until he or she reached 2 to 3 months of age and any cardiac or pulmonary disease had resolved. Patients were not routinely screened via electrocardiography or echocardiography except 1 patient with PHACES (posterior fossa abnormalities, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sternal clefting) syndrome. At the initial examination, patients were tested via blood pressure screening. Parents were counseled regarding possible adverse effects and instructed to feed their infant every 4 hours and to call us immediately if lethargy, cool and clammy skin, or breathing difficulty occurred. During the monthly follow-up examinations, blood pressure was not checked if the patient was asymptomatic. Treatment was discontinued when the response reached a plateau and the patient became older than 1 year. The dosage of oral propranolol was tapered during a 4-week period.

Ophthalmologic examinations included assessment of visual fixation preference, eyelid function and ptosis, extraocular motility, anterior segment, dilated funduscopic, and cycloplegic refraction. Additional assessment of visual acuity included spatial sweep visual-evoked potentials and Cardiff preferential-looking tests.

The astigmatic difference was calculated by subtracting the cylinder measurement in the affected eye from the cylinder measurement in the unaffected eye. Significant amblyogenic factors included a difference of 1.50 diopter (D) or greater in astigmatism (in accordance with the preferred practice pattern of the American Academy of Ophthalmology6), ptosis, eyelid contour changes at risk of causing occlusion, strabismus, or globe displacement. Amblyopia was treated with part-time occlusion of 1 to 2 h/d with adhesive eye occluders over the healthier eye.

Photographs were taken at treatment onset, throughout treatment, and at the conclusion of treatment. These photographs were analyzed digitally to determine surface area (the greatest diameter multiplied by the perpendicular diameter) of the superficial hemangiomas. The corneal diameter of the individual was chosen as a common measurement by which to gauge treatment progress. The posttreatment surface area was subtracted from the pretreatment surface area for each patient.

A total of 17 children (71% girls) were included in the study. Sixteen (94%) were white. One patient had been adopted and her past medical history was unknown. Four (24%) patients had been born prematurely, and none had ongoing cardiac or pulmonary disease. No special monitoring was performed. The median age at the start of treatment was 4.5 months (IQR, 2.2-5.6 months). The median treatment duration was 6.8 months (IQR, 4.1-7.2 months) for the 9 patients who completed treatment before analysis.

A total of 19 periocular hemangiomas were analyzed: 8 (42%) on the upper eyelid, 4 (21%) on the lower eyelid, 3 (16%) on the medial canthus, 2 (11%) on the glabella, and 2 (11%) in the orbit. Eight were located around the right eye and 9 around the left eye. Eight hemangiomas were superficial, 6 were deep, and 5 were mixed. Two hemangiomas were segmental.

Treatment with oral propranolol produced a rapid reduction in the size of all hemangiomas, with parents reporting softening and lighter coloration within days (Figure 1). Nine children had photographs of adequate quality taken to analyze surface area change. Me-
Dian change in the surface area at the end of treatment was 61% of the original size (IQR, 32%-64%). Mild rebound growth that did not necessitate treatment was found in 2 patients, but none had significant enlargement. Two patients did not return for follow-up. The Table contains treatment and outcome details.

Adverse effects were generally mild, and no serious adverse effects occurred. One patient (6%), after 5 months of treatment, experienced brief episodes of bradycardia measuring between 60 and 69 beats per minute while hospitalized for treatment of an airway hemangioma. The episodes occurred during sleep and spontaneously resolved. Treatment with propranolol was discontinued. The cardiologist concluded that the episodes were benign because the electrocardiographic findings showed no abnormalities. Treatment with propranolol was resumed uneventfully at the previous dosage.

Seven patients (41%) had amblyopia based on the results of fixation preference and visual diagnostic testing. The median astigmatic difference was 0.25 D (IQR, 0.13-1.25 D). Four patients (24%) had an astigmatic difference of 1.50 D or greater, and all had amblyopia (Figure 2 and Figure 3). After treatment, those with astigmatism of greater than 1.50 D experienced a median reduction in astigmatism of 0.66 D (33%) (IQR, 0.13-1.25 D). Eleven patients (65%) had ptosis, 3 patients (18%) were at risk of occlusion amblyopia owing to eyelid contour changes, and 2 patients (12%) had globe displacement. Visual acuity equalized after occlusion therapy in all but 1 patient whose condition has improved but is still undergoing treatment. Seven patients had previously not responded favorably to corticosteroids. Five patients had received topical clobetasol propionate, 0.05%, applied twice daily to the lesion. Two patients had received oral prednisone.

<table>
<thead>
<tr>
<th>Patient No./Age at Treatment</th>
<th>Treatment Duration, mo</th>
<th>Site Type of Hemangioma</th>
<th>Size (Width), cm</th>
<th>Response, % of Original Surface Area</th>
<th>Cause of Amblyopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/4 2</td>
<td>R LE</td>
<td>Superficial</td>
<td>2.1</td>
<td>62</td>
<td>NA</td>
</tr>
<tr>
<td>2/2 Lost to follow-up</td>
<td>L LE</td>
<td>Superficial</td>
<td>1.4</td>
<td>26</td>
<td>NA</td>
</tr>
<tr>
<td>3/5 Ongoing</td>
<td>R UE</td>
<td>Deep</td>
<td>1.1</td>
<td>63</td>
<td>NA</td>
</tr>
<tr>
<td>4/7 Ongoing</td>
<td>L medial canthus</td>
<td>Superficial</td>
<td>1.3</td>
<td>63</td>
<td>NA</td>
</tr>
<tr>
<td>7/4 Ongoing</td>
<td>L UE</td>
<td>Superficial</td>
<td>1.0</td>
<td>9</td>
<td>Astigmatism, ptosis</td>
</tr>
<tr>
<td>8/3 Ongoing</td>
<td>R UE</td>
<td>Mixed</td>
<td>1.3</td>
<td>51</td>
<td>NA</td>
</tr>
<tr>
<td>9/4 Ongoing</td>
<td>Glabella</td>
<td>Deep</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10/7 Ongoing</td>
<td>L UE</td>
<td>Superficial segmental</td>
<td>5.0</td>
<td>61</td>
<td>Ptosis</td>
</tr>
<tr>
<td>11/7 Ongoing</td>
<td>R medial canthus</td>
<td>Superficial</td>
<td>0.9</td>
<td>71</td>
<td>NA</td>
</tr>
<tr>
<td>12/4 Ongoing</td>
<td>L and R UE</td>
<td>Superficial segmental, PHACES</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>13/5 Ongoing</td>
<td>L LE</td>
<td>Mixed</td>
<td>1.9</td>
<td>66</td>
<td>Astigmatism, ptosis</td>
</tr>
<tr>
<td>14/5 Ongoing</td>
<td>R medial canthus</td>
<td>Mixed</td>
<td>2.4</td>
<td>38</td>
<td>Ptosis</td>
</tr>
<tr>
<td>15/12 Ongoing</td>
<td>L UE</td>
<td>Mixed</td>
<td>NA</td>
<td>NA</td>
<td>Ptosis</td>
</tr>
<tr>
<td>16/5 Ongoing</td>
<td>L LE</td>
<td>Deep</td>
<td>NA</td>
<td>NA</td>
<td>Ptosis</td>
</tr>
<tr>
<td>17/25 Ongoing</td>
<td>R orbit, L periorbit</td>
<td>Deep</td>
<td>NA</td>
<td>NA</td>
<td>Ptosis, astigmatism, globe displacement a</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; LE, lower eyelid; NA, not applicable; PHACES, posterior fossa abnormalities, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sternal clefting; R, right; UE, upper eyelid.

a Ongoing amblyopia treatment.

Figure 2. Child aged 25 months with deep hemangiomas in the right orbit and left periorbit. A, Before oral propranolol treatment—note right gaze preference and inability to wear eyeglasses due to the protruding hemangioma. B, Four months after the start of oral propranolol treatment—note straight gaze and ability to wear eyeglasses.
Use of topical and oral corticosteroids was discontinued when treatment with oral propranolol was initiated. Four patients had undergone intralesional corticosteroid injection (2-mL mixture of 6 mg/mL betamethasone sodium phosphate and 40 mg/mL triamcinolone acetonide for 3 patients; dosage unknown for the fourth patient). The time between corticosteroid injection and initiation of oral propranolol treatment for those patients was 1 month, 2 months, 9 months, and unknown. Two patients experienced a Cushingoid habitus adverse effect (1 after intralesional injection and 1 while taking oral prednisone). One patient experienced hypertrichosis after intralesional injection.

**COMMENT**

In this study, propranolol was uniformly effective in decreasing the size of periocular hemangiomas, with minimal adverse effects. The success of oral propranolol for the treatment of infantile hemangioma has been reported in small case studies. Our cohort is among the largest group of patients treated with propranolol for periocular lesions. The success in our study is evidenced by the response of all patients, the 39% reduction in surface area, and the 33% reduction in astigmatism. Although all patients had periocular hemangiomas, most did not develop amblyopia. The only patient who requires ongoing amblyopia treatment was 25 months old at onset of therapy (due to having been adopted from a foreign country). Our success may be due to the highly favorable response to propranolol and treatment before the secondary effects of excess skin and amblyopia developed. Although the number of patients in our study was relatively small, the results provide further evidence of the efficacy and safety of the treatment discussed herein.

Debate has taken place regarding the most favorable method for safe initiation and monitoring of treatment with oral propranolol. Potential adverse effects include bradycardia, hypotension, bronchospasm, and hypoglycemia. Some authors have suggested hospitalization with electrocardiographic testing and inpatient monitoring of vital signs during initiation of therapy. However, given the long history of safe propranolol use in pediatric patients, we and others have advocated slow initiation and outpatient monitoring of treatment. We reviewed our treatment regimen with the Department of Cardiology at St Louis Children’s Hospital and determined that outpatient treatment could be safely performed. The results of this retrospective series suggest that outpatient treatment and monitoring can be a safe alternative to inpatient monitoring.

The limitations of our study included its retrospective nature, the lack of a control group, possible outcome bias, and a relatively small cohort. A prospective, randomized clinical trial would provide data regarding the ideal dosage of propranolol, age of initiating treatment, treatment duration, and safety profile. In addition, timolol maleate ophthalmic solution has successfully treated infantile hemangiomas (S.J.B., unpublished data, 2010), but the role of topical β-blockers has yet to be fully elucidated. In addition, research is needed regarding the mechanism by which propranolol works. Possible mechanisms include inducing vasoconstriction; decreasing the expression of 2 proangiogenic factors, vascular endothelial growth factor and basic fibroblast growth factor, through the downregulation of the RAF–mitogen-activated protein kinase pathway; and triggering apoptosis of capillary endothelial cells. Our results suggest that early treatment with propranolol is effective in treating and preventing loss of vision associated with periocular infantile hemangiomas. The ease of administration and low cost of oral propranolol make it a favorable treatment option for infantile hemangiomas. Although systemic β-blockers have the potential to cause adverse effects, the complication rate in this study was low, and monitoring was safely performed on an outpatient basis.

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In Memoriam: Joseph Lawton Smith, MD (1929-2011)

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medicine has lost a consummate clinician and educator. Joseph Lawton Smith, MD, died on January 10, 2011, at 81 years of age after complications following surgery for a broken hip.

After medical school at Duke University, residency at Wilmer Eye Institute, fellowship with David Cogan, and a stint on the Duke faculty, Lawton joined the Bascom Palmer Eye Institute in 1962 until his retirement in 1993. His tenure there included supremely detailed (“doctor-killing”) examinations and extraordinary teaching skills enhanced by his own particular lexicon. For example, to work hard was to “swing into action totalis”; excessive evaluations exemplified “a blind dog in a meat house”; new technology was "twins smitties"; and a correct answer to a question would earn you a “Now you’re talkin’, doccy.”

Lawton produced 335 articles, books, and editorials, including first reports of ischemic optic neuropathy, fundus findings in choroidal hemangiomas and Leber hereditary optic neuropathy, fluorescein angiographic findings in retinal artery occlusions and giant cell arteritis, radiation therapy for optic nerve sheath meningiomas, and ophthalmic and neurologic manifestations of Lyme disease and seronegative syphilis. In 1978 he founded the Journal of Clinical Neuroophthalmology.

Lawton’s life was dramatically changed when, in 1963, he met one of his old residency classmates, Dr Jack Cooper, who told Lawton he had given his life to Christ. As Lawton said, this “ate into his brain like a rat,” and shortly thereafter he became a Christian as well. His overriding purpose from then on was to know God more intimately, and to encourage others to find the joy and peace that he had found.

R. Michael Siatkowski, MD