Propranolol and Periocular Capillary Hemangiomas: Assessment of Refractive Effect

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ABSTRACT

Purpose: To assess the effects of systemic propranolol on refractive error in infants with periocular capillary hemangiomas.

Methods: A single-center study of consecutive patients with capillary hemangiomas treated with systemic propranolol. Refractive data were analyzed using Long’s matrix formalism and the methods of Harris and Kaye.

Results: Seventeen patients were included. At 6 months postoperatively, hemangioma size reduced from 3,214 to 1,806 mm$^3$ (standard deviation: 4,122 to 2,441). Mean refractive error in the affected eye significantly reduced: -1.25/0.38 × 36 (95% confidence intervals: -5.08/1.20 × 90 to 1.64/1.43 × 180, $P = .048$) with a smaller change ($P = .06$) in the unaffected eye of -1.01/+0.31 × 3.16 (95% confidence intervals: -4.02/+1.12 × 180 to +1.49/+0.51 × 90).

Conclusions: Propranolol produced a clinically significant reduction in the infants’ refractive error and anisometropia. The reduction in the total refractive error and anisometropia has not been evident in previous analyses, which have concentrated on the change in the “cylinder” as the principal outcome measure.

INTRODUCTION

Infantile capillary hemangiomas are vascular lesions that can occur in many possible sites. They characteristically exhibit rapid growth soon after birth, when they can be small in size or barely visible. The incidence of capillary hemangioma has been reported as 2.6% in a study involving more than 1,000 newborns with a prevalence as great as 10% in children younger than 1 year. Females are more often affected, with a reported female-to-male ratio of 3:2. The regression rate of hemangioma has been reported as 30% at 3 years, 60% at 4 years, and 76% at 7 years of age. They are well recognized around the eye and can vary in size from dot-sized lesions involving the eyelids to extensive hemangiomas with resulting closure of the palpebral aperture. This can lead to amblyopia through visual deprivation, mechanically induced astigmatic refractive errors, and anisometropia. Although the natural history of the lesion itself is often favorable without treatment, the resulting effects of amblyopia warrant early treatment and quick resolution, if possible.

The treatment of periocular hemangioma has traditionally involved the use of steroids. Propranolol has more recently been described in numerous retrospective studies, having been serendipitously used in patients with periocular hemangiomas.
found to be effective. It has also been reported that the use of propranolol leads to a reduction in astigmatism.\textsuperscript{7,8} These reports have used the cylinder component of the refractive power as a measure of the refractive effect. In particular, the cylinder has been analyzed in isolation from the rest of the refractive power. Although changes in the cylinder have been described, the changes in the total refractive power have not been taken into account. There have been numerous reports demonstrating the problems and statistical flaws treating the cylinder in isolation, whether as a vector (direction) or scalar (ignoring the axis) number.\textsuperscript{9-11}

In addition, although the cylinder has an astigmatic component, it also has a spherical component and does not fully represent astigmatism.\textsuperscript{12} For example, a cylinder of 1 diopter (D) has a “spherical equivalent” of 0.5 D. Measurement of the total refractive power is clearly necessary for measuring anisometropia, which is a significant risk factor for amblyopia. Use of the spherical equivalent is insensitive for refractive powers, which have prominent astigmatic components.\textsuperscript{9-14} For example, if two patients have refractive errors of +1/+2 × 90 in the right eye and +1/0 in the left eye, +2/0 in the right eye and +1/0 in the left eye, respectively, they will, by using the spherical equivalent, be mistakenly presumed to have the same inter-eye difference or no anisometropia. Furthermore, because the components of refractive powers co-vary,\textsuperscript{9,11,13,15} it is necessary to analyze the components of refractive errors dependently and not as independent variables. Therefore, this study analyzes the changes in the refractive errors of infants with periocular capillary hemangioma who have been treated with systemic propranolol.

**PATIENTS AND METHODS**

A retrospective review of all cases of periocular hemangiomas treated with propranolol between June 2009 and February 2012 was undertaken. The study was performed in a tertiary referral pediatric ophthalmology department. Cases were identified from a locally kept database. At presentation, the location, size, and duration of the capillary hemangioma was recorded. Comorbidities and any contraindication to propranolol therapy, such as airway disease or congenital heart disease, were noted. Objection to occlusion, visual behavior, and visual acuity, if possible, were measured using preferential looking methods. Cycloplegic refraction and funduscropy were performed 40 minutes after instillation of 1% cyclopentolate or atropine 1% for heavily pigmented irides.

A protocol for propranolol therapy for this study was determined in collaboration with cardiologists and approved by the Clinical Development Evaluation Group of the hospital. Prior to initiation, a complete pediatric examination including weight, blood pressure and pulse rate, and electrocardiogram and echocardiogram was performed by dedicated pediatricians. All patients were admitted to the inpatient day care ward for initiation of treatment.

The propranolol dose used was 1 mg/kg three times a day. After each dose, blood pressure, pulse, and respiratory status were monitored, the frequency of which depended on change in these values compared to baseline reading. The first day’s treatment (three doses) was all given in the hospital. If the treatment was well tolerated, the patient was discharged with the same dose with outpatient follow-up. Subsequent appointments involved checking vital signs such as blood pressure, pulse rate, and weight. The dose and frequency of propranolol administration was adjusted according to the infants’ weight and clinical response. Parents were questioned about the presence of side effects of propranolol therapy, in particular dyspnea and wheeze. Cycloplegic refraction was performed at each visit. A tapering of the individual patients’ propranolol dose regimen was adjusted according to the clinical appearance of the hemangioma, visual behavior, and refractive error of both the affected and fellow eye.

Refractive data were collected preoperatively and at 1, 3, and 6 months, and 1 year postoperatively. Patients with missing data were excluded.

**Analysis of Refractive Data**

Refractive data were transformed into Long’s matrix formalism\textsuperscript{16} and statistical analysis using the methods of Harris\textsuperscript{17-19} and Kaye and Harris.\textsuperscript{20-21} Long\textsuperscript{16} showed that refractive data can be transformed into four independent components given by

\[
\begin{align*}
    f_{11} &= S + C \sin \theta A \\
    f_{12} &= -C \sin A \cos \theta \\
    f_{21} &= -C \sin A \cos \theta \\
    f_{22} &= S + C \cos \theta A
\end{align*}
\]

and \( f_{22} = S + C \cos \theta A \) where \( f_{11} \) is the cell in the first row and first column \( f_{12} \) is the cell in the first row and second column and \( f_{21} \) is the cell in the second row and first column. Therefore,
For a thin lens, this simplifies further as \( f_{12} = f_{21} \) so that \( S/C_A \) can be written as

\[
S/C_A = \frac{f_{11} f_{22}}{f_{12} f_{21}} = \frac{S + C \sin^2 A - C \sin A \cos A}{-C \sin A \cos A \left( S + C \cos^2 A \right)}
\]

For example, if one considers the sum of two refractive powers, \(+2/+2_{45}\) and \(+1/+1_{180}\), each can then be transformed to: \(+2/+2_{45} = [2 + 2 \sin^2 45°, 2 + 2 \cos^2 45°] = [3 - 1 - 3, 3 + 1 + 1] = [1 2, 2] \). These can then be simply added together as follows: \([3 - 1 3] + [1 0 2] = [4 - 1 5]\), which after transforming back gives \(+3.38/+2.24_{32}\). The usefulness of this method is that it can be applied to large datasets to provide means, standard deviations, confidence intervals, and statistical tests. Using Long’s formalism\(^{16}\) and the methods of Harris\(^9,10,17-19\) and Kaye and Harris\(^21\) allows one to calculate the total mean standard deviation, upper and lower confidence intervals, and standard error of the mean. The data are therefore presented in standard notation as the mean standard deviation and 95% confidence intervals.

**Astigmatism**

It is important to note that a cylinder is not the same as astigmatism. Indeed, if one accepts the concept of there being a spherical equivalent, then it follows that a cylinder has a spherical component. Consider a refractive power of \( S/C_A \). It follows that

\[
S/C_A = [S + C/2] + [S/C_A - (S + C/2)]
\]

which simplifies to

\[
S/C_A = [S + C/2] + [- C/2 / C_A]
\]

that is, \( S/C_A = \text{Nes} + \text{JCC}. \)\(^{12,22}\) Thus, for example, if one applies this to a cylinder, we have

\[
C_A = \frac{C_2 / 2 - C/2}{C_A}
\]

or a cylinder of \(+1_{90}\) yields a nearest equivalent sphere of \(+0.5\) and a Jackson crossed cylinder (JCC) of \(-0.5/+1_{90}\). This method was used to measure the astigmatism present in the refractive errors.

**RESULTS**

Seventeen patients were included in the study, 8 of whom were male. The clinical details are summarized in Table 1. Two patients had been previously treated with steroids. No patients were excluded from propranolol treatment because of comorbidity. The mean duration of treatment was 7.2 months (standard deviation: 4.22). The only reported adverse effects were wheeze, which occurred in 4 of 17 patients, of whom 1 required cessation of treatment; the remaining 3 continued with propranolol therapy.

The refractive data before and after treatment are shown in Tables 2-3. Data at baseline and 6 months were used because of missing data from 3 patients at 12 months. There was a significant reduction in both the magnitude \( (P = .048) \) and variability \( (P = .0006) \) of the refractive error in the affected eye at 6 months following treatment. There was also a reduction in the variability \( (P = .043) \) but not the magnitude \( (P = .062) \) of the refractive error in the unaffected eye at 6 months postoperatively.

There was a slight non-significant reduction in the mean anisometric refractive error following treatment. However, there was a significant reduction in the variability of the anisometropia following treatment (Table 4).
DISCUSSION

Beta adrenergic antagonists (beta blockers) have been used clinically for almost 50 years. They have traditionally been used for treating cardiovascular disorders, but their use has increasingly widened. Propranolol was the first beta blocker with widespread use. It is a non-selective beta blocker with affinity for both beta 1 and beta 2 receptors. Due to their non-selective nature, they were noted to have extracardiac effects such as bronchospasm due to beta 2 receptor blockade. Propranolol’s possible mode of action in reducing the size of a hemangioma is thought to be through a vasoconstrictive effect as a result of beta receptor blockade. Other modes of action that have been suggested include down regulation of the rapidly accelerated fibrosarcoma–mitogen-activated protein kinase pathway leading to reduced expression of anti-vascular endothelial growth factor and basic fibroblast growth factor genes. It has also been demonstrated that beta blockers can induce apoptosis in capillary endothelial cells.

There are many clinical situations where a measure of refractive outcome is needed to determine the effectiveness of a given treatment or intervention. The effect of propranolol on the cylinder component of refractive power has been reported as varying between 0.8 and 1.5 D. Little is known about the effects on the total refractive error and degree of anisometropia following treatment, both of which are important risk factors for the development of amblyopia. In addition, if the authors have treated the cylinder as an independent scalar or vector value, which is not only statistically flawed but may also produce an inaccurate representation of

**TABLE 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Month 0</th>
<th>Difference From Months 0 to 6</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sphere</td>
<td>Cylinder Axis</td>
<td>Sphere</td>
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<tr>
<td>Mean</td>
<td>2.37</td>
<td>+0.68 × 98</td>
<td>-1.25</td>
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<tr>
<td>Mean astigmatism</td>
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<td>-0.19</td>
</tr>
<tr>
<td>SD</td>
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<td>-0.16</td>
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<td>-0.27 × 37</td>
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**SD** = standard deviation; **CI** = confidence interval

*The mean refractive error, SD, upper and lower 95% CI, and mean astigmatism. Mean astigmatism was calculated by subtracting the spherical equivalent from the refractive power.*

*The mean refractive error, SD, upper and lower 95% CI, and mean astigmatism. Mean astigmatism was calculated by subtracting the spherical equivalent from the refractive power.*
the true effect, the cylinder subtraction method may overestimate the level of statistical significance when applied to the changes in astigmatism. In addition, it is intuitively obvious and demonstrated well by subjective clinical refraction that cylindrical and spherical lens components are not independent variables. Therefore, it is essential to be able to analyze the complete or whole refractive error, treating the sphere, cylinder, and axis as dependent, rather than independent, parameters. Refractive data are conventionally expressed as sphere/cylinder x-axis, from which it is apparent that there are three components, which are co-dependent.\textsuperscript{15,17-21,27,28} Despite this, there is a tendency to treat each component independently. For example, consider the following two refractive powers, $+2/+2_{90}$ and $+1/+1_{180}$. If they were to be added together, what would the result be? There are three possibilities depending on whether each component is treated independently or dependently. If they are treated independently as scalar values, this leads to the following situation:

\[
\begin{array}{c|c|c}
 Sphere & Cylinder & + \\
 \frac{2}{3} & \frac{2}{3} & \frac{2}{3} \\
 \end{array}
\]

or $(+2/+2_{90}) + (+1/+1_{180}) \neq +3/+3$, which is incorrect.\textsuperscript{22} If they are treated independently as vectors, this leads to

\[
\begin{array}{c|c|c}
 Sphere & Cylinder & + \\
 \frac{1}{2} & \frac{1}{2} & \frac{1}{2} \\
 \end{array}
\]

or $(+2/+2_{90}) + (+1/+1_{180}) \neq +4/+4_{90}$, which is the correct result.\textsuperscript{22} It is evident that the space of cylinders is not closed under addition or subtraction (i.e., a cylinder plus a cylinder does not necessarily equal a cylinder). Clearly, in any analysis of changes in refractive powers, the components need to be treated as co-variates.\textsuperscript{15,17-21,27,28} As shown in the Methods section, using Long’s formalism\textsuperscript{16} and the methods of Harris\textsuperscript{9,10,17-19} and Kaye and Harris\textsuperscript{21} allows one to calculate the total and mean standard deviation, upper and lower confidence intervals, and standard error of the mean among other statistical parameters.

In the analysis of refractive power, a commonly used term is astigmatism. Astigmatism refers to the absence of stigmatism (a point focus). Therefore, aberrations are types of astigmatism. However, if one considers only paraxial powers, then astigmatism is limited to that found within a cylinder. However, a cylinder is not the same as astigmatism. Indeed, if one accepts the concept of there being a spherical equivalent, then it follows that a cylinder has a spherical component. It is then possible to subtract the spherical component from a cylinder, leaving a Jackson crossed cylinder, which is the actual astigmatic component.\textsuperscript{12} For example, a cylinder of $0/+1_{90}$ yields a spherical equivalent of $+0.5$ and, as the astigmatic component, a Jackson crossed cylinder of $-0.5/+1_{90}$.

### Table 4: Refractive Data of Anisometropia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sphere</td>
<td>Cylinder</td>
</tr>
<tr>
<td>Mean difference</td>
<td>-0.39</td>
<td>+0.28 × 13</td>
</tr>
<tr>
<td>SD</td>
<td>0.28</td>
<td>+2.89 × 145</td>
</tr>
<tr>
<td>$P$</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>0.31</td>
<td>+5.63 × 146</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>-6.47</td>
<td>+5.70 × 53</td>
</tr>
</tbody>
</table>

$SD =$ standard deviation; $CI =$ confidence interval

\textsuperscript{a}Difference in the mean refractive error between affect and fellow eye prior to and at 6 months following treatment.

\textsuperscript{b}Note the significant reduction in the variability of the anisometropia at 6 months ($P < .001$).
In this study, we found a significant reduction in both the magnitude and variability of the refractive error in the affected eye following treatment. Although this is likely to be a treatment effect, the initial high variability of the refractive error prior to treatment is also likely to reflect the different sizes and locations of the hemangioma. It is also important to view the change in refractive error in relation to the unaffected eye. In the unaffected eye, there was also a myopic and astigmatic change of -1.01/+0.31 × 3.16 but with much lower variability (eg, a standard deviation of 1.01/+0.51 × 107.82 and correspondingly smaller lower 95% confidence interval and upper 95% confidence interval of -4.02/+1.12 × 0.00 and +1.49/+0.51 × 90.00, respectively). The change in refraction in the unaffected eye might be explained by the natural process of emmetropization that occurs during infancy and childhood, although the treatment may also have had an effect on the unaffected eye. Anisometropia is a risk factor for amblyopia and a reduction in both the amount and variability following treatment with propranolol is therefore of important clinical significance.

This study does have some important limitations. The size, duration, and location of the hemangiomas differed between patients. In addition, we did not have an untreated control group to determine the actual benefit of propranolol. Given that there have been reports in the literature supporting its use, it would be difficult to undertake a comparative study to an untreated control group. The length of follow-up is an important factor in assessing the effect of propranolol and other treatments. Although it is evident clinically that the onset of effect from propranolol is almost immediate, the changes in refractive effect might continue for several weeks or months. The optimum duration of treatment is yet to be established, but this comparison of our data with the published alternatives would suggest that propranolol is required in the medium term. It might also be wise to consider that the proliferative phase of hemangiomas usually finishes between 6 and 12 months of age, so continued therapy, or at least close follow-up, would be wise during this time.

REFERENCES