Long-Term Refractive and Biometric Outcomes Following Diode Laser Therapy for Retinopathy of Prematurity

Eibhlin M. McLoone, FRCOphth, Michael O’Keefe, FRCOphth, Sean F. McLoone, PhD, CEng, and Bernadette M. Lanigan

PURPOSE
To assess the long-term refractive and biometric outcomes of diode laser-treated eyes in threshold retinopathy of prematurity (ROP).

METHODS
Cycloplegic autorefraction and biometry (Zeiss IOLMaster) were performed, at a mean follow-up of 11 years, on 16 laser-treated eyes with threshold ROP and 9 comparison eyes with subthreshold untreated ROP.

RESULTS
The laser-treated eyes had a mean spherical equivalent of $-2.33 \pm 1.38$ D with a mean astigmatic error of $0.42 \pm 0.26$ D. This trend toward increased myopia in treated eyes did not achieve statistical significance ($p = 0.08$). The myopia in the laser group appeared to be slowly progressive in nature when compared with earlier refractive data for these patients. The laser-treated eyes had reduced anterior chamber depth (ACD) compared with the subthreshold eyes ($p = 0.02$). When physiologic accommodation was inhibited by cycloplegic drops, the anterior chamber deepened by $0.13 \pm 0.06$ mm in the laser-treated eyes and by $0.06 \pm 0.03$ mm in the comparison eyes. This effect of accommodation on ACD did not differ significantly between the two groups ($p = 0.23$). The laser-treated eyes and the comparison eyes did not differ significantly in terms of axial length, corneal power, corneal diameter, or lens power. However, both groups had steeper corneas, shallower anterior chambers, and shorter axial lengths when compared with historical full-term controls.

CONCLUSIONS
Myopia in premature infants requiring laser treatment for ROP is associated with a shallowing of the anterior chamber and a steepening of the cornea. Physiological accommodation is not impaired by laser therapy or by severe ROP. (J AAPOS 2006;10:454-459)

Prematurity and retinopathy of prematurity (ROP) are well-established independent risk factors for myopia.1-4 There have been reports that cryotherapy in threshold ROP contributes to the development of myopia and that laser photocoagulation, in comparison, produces less myopic shift.5-7 However, Quinn et al felt that the cryotherapy did not result in additional myopia but that the high myopia was related to the cicatricial retinopathy or severity of ROP.8 In recent times, laser photocoagulation has largely replaced cryotherapy as the established treatment modality for ROP. Davitt et al have shown no increase in myopia or high myopia, at 9 months, in laser-treated compared with untreated high-risk prethreshold ROP eyes in the Early Treatment of Retinopathy of Prematurity (ETROP) study.9

The clinical objective of this study was to evaluate the long-term refractive outcome of threshold ROP eyes at a mean of 11 years after diode laser treatment, with particular attention to the role of the cornea, anterior chamber depth, axial length, and effective lens power in determining the refractive status.

A comparison group with documented subthreshold ROP, which had regressed spontaneously without laser treatment, was also evaluated.

Materials and Methods
All premature babies who received diode laser photocoagulation for threshold retinopathy of prematurity (n = 41), between December 1991 and December 1995, at the neonatal unit of The National Maternity Hospital, Dublin were identified from a register of children treated for ROP. These dates were chosen because the diode laser was first introduced in this unit in December 1991 and we wished to have a minimum of 9 years of follow-up for our study population. Laser treatment was placed, under sedation, anterior to the fibrovascular ridge in accordance
with the Royal College of Ophthalmologists’ guidelines for ROP treatment.10

Four babies died before the age of 9 months (deaths not related to laser treatment). Records were not available on another four children, one of whom was known to have returned to Russia shortly after laser treatment. Thirty-three patients were eligible for entry into this study. It was not possible to trace eight of the children. Their parents were not contactable by phone, by letter, or through their general practitioners and had most likely moved without forwarding contact information. Thus 25 patients were contactable. All were recruited and reviewed with informed parental consent.

Eighteen patients, also with 9 or more years follow-up, with subthreshold ROP (at least stage 2, zone II ROP with spontaneous regression) were identified from a log book of babies screened for ROP in the neonatal unit (screening criteria of <31 weeks gestational age or ≤1500 g birth weight). These children were selected for inclusion in the study with view to having a comparison group which closely matched the study population in terms of prematurity and severity of ROP.1,2 Six of these children were not contactable, and there were three parental refusals. The remaining nine children participated in the study.

The patients were recalled to the eye clinic at the Children’s Hospital for assessment. Best-corrected distance visual acuity was recorded using a back-illuminated Distance Early Treatment of Diabetic Retinopathy Study (ETDRS) chart (Lighthouse Inc., New York, NY) at a test distance of 4 m. Visual acuity was estimated as the logMAR value of the last line on which the child could correctly identify three of the five available letters. Biometry was performed in the accommodative dynamic state (without dilating drops) using the IOLMaster (Carl Zeiss, Jena). Corneal diameter, corneal power, anterior chamber depth (ACD), and axial length (AL) were all measured. The average of the K1 and K2 readings was defined as the mean K reading (corneal power) of that eye. The SRK-T formula was used to calculate the effective lens power (LP) for each eye. Cyclopentolate 1% was subsequently instilled in both eyes and, after 30 minutes, the biometry was repeated (nonaccommodative static state). A desktop autorefractometer (Model AR-630A, Nidek Co., Ltd., Japan) was then used to evaluate the cycloplegic refraction. The sphere, positive cylinder, and axis were measured for each eye and the spherical equivalent (SE) was recorded (sphere + half cylinder value). Demographic information was obtained from hospital records and details regarding the laser treatment were ascertained from the register of treated children.

### Statistical Analysis

For statistical purposes, only one eye per patient in both the laser and comparison groups was included in the comparative analysis of the effect of diode laser on refractive and biometric outcomes. The right eye was chosen in all cases where data were available for both eyes. Analysis was performed using MATLAB® 6.5 (Statistics Toolbox 4.0). As the demographic and refractive data were normally distributed, the parametric Student’s t-test was used to compare continuous outcomes. The biometric data were not normally distributed; consequently, continuous outcomes were compared using the nonparametric Wilcoxon rank-sum test. Fisher’s Exact test was used to compare categorical outcomes. A p-value of less than 0.05 was considered significant.

### Results

Of the 25 laser-treated children recruited for this study, three had cerebral palsy, three had marked manifest nystagmus, and one had limited mobility. These patients were excluded as they were unable to cooperate with the IOLMaster examination. As all 9 children in the subthreshold ROP comparison group had normal retinal appearance with a history of regressed Zone II ROP, a further 2 patients were excluded from the laser group—one with bilateral retinal detachments due to Zone I ROP and one with a macular fold. Therefore, 16 laser-treated eyes with normal retinal appearance were included in the study analysis.

The baseline characteristics of both the laser and the subthreshold ROP groups are outlined in Table 1. The gestational age for the study population as a whole ranged from 24 to 30 weeks and the birth weight ranged from 620 to 1398 g. The duration of follow-up for these children ranged from 9.0 to 12.8 years. There were no statistically significant differences in the means between the laser group and comparison group with respect to gestational age, birth weight, follow-up, and best-corrected distance visual acuity. Neither was there a significant difference in sex distribution between the 2 groups.

### Laser Treatment Details

The number of laser burns per eye ranged from 303 to 1261, with a mean of 716 ± 287 burns. The power ranged from 300 to 750 mW (median 325 mW) and the duration of each burn ranged from 200 to 500 ms (median 200 ms).

### Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser group (16 eyes)</th>
<th>Comparison group (9 eyes)</th>
<th>Laser versus comparison (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA in weeks (mean ± SD)</td>
<td>26.6 ± 1.7</td>
<td>27.4 ± 1.5</td>
<td>0.21</td>
</tr>
<tr>
<td>BW in grams (mean ± SD)</td>
<td>890.0 ± 207.7</td>
<td>972.6 ± 230.6</td>
<td>0.37</td>
</tr>
<tr>
<td>Follow-up in years (mean ± SD)</td>
<td>11.1 ± 0.9</td>
<td>11.2 ± 1.4</td>
<td>0.83</td>
</tr>
<tr>
<td>BCDVA (mean ± SD)</td>
<td>0.17 ± 0.31</td>
<td>−0.04 ± 0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender (number/%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (63)</td>
<td>7 (71)</td>
<td>0.37</td>
</tr>
<tr>
<td>Female</td>
<td>6 (37)</td>
<td>2 (29)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

GA: gestational age; BW: birth weight; SD: standard deviation; BCDVA: Best-corrected distance visual acuity.
A mean of 2.1 laser treatment sessions was required per eye to achieve regression of ROP.

**Refractive Outcome**

Figure 1 illustrates the refractive outcome of the study population. Although the laser-treated eyes were more myopic than the subthreshold ROP eyes (mean spherical equivalents of \(-2.33\) and \(+1.07\) D, respectively), this difference did not reach statistical significance \((p = 0.08)\). However, there was a significant difference in terms of mean astigmatic error \((+1.38\) and \(+0.42\) D, respectively, \(p = 0.007)\). The mean plus cylinder axis was \(91^\circ\) for the laser-treated eyes and \(65^\circ\) for the subthreshold ROP eyes with both groups having predominantly against-the-rule astigmatism.

Fifty percent of laser-treated eyes were myopic (mean SE of these eyes, \(-6.45\) D) compared with 22.2% of eyes in the comparison group (mean SE, \(-0.75\) D). The distribution of myopia in both groups is given in Figure 2.

**Biometric Outcome**

Analysis of the biometric data was performed on the results obtained after cycloplegia to eliminate any variation in the biometric parameters which may have occurred due to accommodation. These findings are given in Table 2. There was a statistically significant difference in ACD \((p = 0.02)\) between the laser-treated and subthreshold ROP eyes. However there was no difference in terms of axial length, corneal power, corneal diameter, or lens power between the 2 groups. In other words, the eyes that received diode laser treatment had shallower anterior chambers than the comparison eyes in which the subthreshold ROP had spontaneously regressed.

When paired sample testing was performed on the biometric data for the study eyes in the dilated nonaccommodative state and the undilated accommodative state, the only study parameter that demonstrated a statistically significant change was the ACD. When physiological accommodation was inhibited by the cycloplegic drops, the ACD deepened in the laser eyes by a median difference of 0.13 mm \((p < 0.001)\) and in the comparison eyes by a median difference of 0.06 mm \((p = 0.039)\) as illustrated in Figure 3. However, the effect of accommodation on ACD did not differ significantly between the two groups \((p = 0.23)\).

**Discussion**

It is now recognized that ROP and prematurity-induced myopia cannot be fully explained by increased axial length and that anterior segment arrest contributes to the increased myopia seen in these conditions.11-13 This is the first study to use the Zeiss IOLMaster to analyze the various biometric elements that collectively determine the refractive status of an eye in a cohort of premature children treated with diode laser photocoagulation for threshold ROP. The IOLMaster is based on an optical measurement technique known as partial coherence interferometry and produces results for axial length measurement that have been shown to be as accurate as immersion ultrasound findings and superior to applanation ultrasound biometry.14-16 It has the added advantage of being a non-contact technique, rendering it particularly useful in the assessment of children. Kriechbaum et al demonstrated that the IOLMaster is also a reliable method of ACD measurement in phakic eyes.17 The ACD values are significantly higher with this noncontact technique compared with the more frequently reported applanation ultrasound values.15,17,18

An ideal control group for this study would consist of patients with threshold ROP randomized to observation without laser treatment. However, in light of the unequivocal benefit of treatment demonstrated in the CRYO-ROP study, this is obviously unethical.19 In view of this, we selected age-matched comparison eyes with significant ROP (stage 2 or more ROP in zone II), which failed to reach threshold level and which regressed spontaneously.

Our refractive outcome results showed that the laser group was more myopic than the comparison group with mean spherical equivalents of \(-2.33\) D (SD 5.21) and \(+1.07\) D (SD 2.72), respectively. However, this difference
did not reach statistical significance (p = 0.08). As illustrated in Figure 1, there is a much wider variation of refractive error among the laser-treated patients compared with the subthreshold ROP patients. Of the laser-treated eyes 37.5% had more than 4 D of myopia, whereas none of the comparison eyes had more than 4 D of myopia. Kent et al assessed the refractive error in premature babies across the spectrum of ROP stages, including subthreshold and laser-treated stage 3 ROP. Comparison of refractive error between stage 0 and stage 3 subthreshold eyes in their study showed no difference but there was a marked difference between stage 0 and stage 3 laser-treated eyes. As our comparison eyes had subthreshold ROP, we are unable to determine whether this observed difference in refractive error is attributable to the fact that the laser-treated eyes had more severe (threshold) ROP from the outset or whether the laser treatment itself contributed to the increased myopia. Recent ETROP findings would indicate that the increased myopia in laser-treated patients is in fact due to the more severe ROP in these patients rather than any direct effect of the laser treatment. There was a significant difference in terms of mean astigmatic error between our laser-treated and untreated subthreshold ROP eyes (+1.38 and +0.42 D, respectively, p = 0.007). Kent et al and Laws et al have also reported increasing astigmatism with increasing stage of ROP.

It is encouraging to note that the mean spherical equivalent and mean astigmatic error outcomes for our laser-treated eyes compare favorably with the findings of other investigators, as presented in Table 3. The short-term refractive outcome at 1, 2, and 3 years has previously been reported for the laser-treated patients in our study. In the earlier reports, as in this study, all unilateral cases and only the right eyes of cases where treatment was bilateral were selected for inclusion in the refractive analysis. We see from Table 4 that the overall percentage of patients with myopia does not seem to increase significantly with time. However, the refractive error, in those patients who develop myopia at an early age, appears to be slowly progressive. This is consistent with previously published reports describing a trend of increasing myopia in laser-treated patients.

The Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study Group has demonstrated a significant effect of age on refractive error and ocular biometric parameters between the ages of 6 and 14 years. We have therefore chosen to compare our biometric findings with those in the literature for similarly aged full-term children and similarly aged preterm children with and without threshold ROP (Table 5). There is no evidence of an association between increasing AL and either prematurity or severity of ROP in this historical data. In fact, mean AL appears to be shorter in the subthreshold ROP and threshold ROP eyes compared with those with no ROP, indicating that the myopia in these patients is nonaxial in nature.

Our laser-treated eyes had significantly shorter ACDs (p = 0.02) than our subthreshold ROP eyes. The historical data in Table 5 also show a trend of reducing ACD with increasing severity of ROP. Shallowing of the anterior chamber would give rise to a more anteriorly placed lens and could account for the increased myopia seen in the laser-treated eyes. Although Kent et al also observed a trend toward a shallower anterior chamber in stage 3 treated eyes compared with stage 3 subthreshold eyes, this did not reach statistical significance. In their study, biometric assessment was performed by a “through-the-lid”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser group (16 eyes)</th>
<th>Comparison group (9 eyes)</th>
<th>Laser versus comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spherical equivalent (D)</td>
<td>−2.33 ± 5.21</td>
<td>−0.50 ± 1.07</td>
<td>0.38 ± 0.08</td>
</tr>
<tr>
<td>Axial length (mm)</td>
<td>22.81 ± 1.88</td>
<td>22.05 ± 22.47</td>
<td>22.90 ± 0.97</td>
</tr>
<tr>
<td>Anterior chamber depth (mm)</td>
<td>3.38 ± 0.25</td>
<td>3.46 ± 3.70</td>
<td>3.87 ± 0.02</td>
</tr>
<tr>
<td>Corneal power (D)</td>
<td>45.24 ± 1.30</td>
<td>45.00 ± 44.82</td>
<td>45.00 ± 0.52</td>
</tr>
<tr>
<td>Corneal diameter (mm)</td>
<td>11.85 ± 0.30</td>
<td>11.80 ± 12.06</td>
<td>12.15 ± 0.24</td>
</tr>
<tr>
<td>Lens Power / SRK-T (D)</td>
<td>21.80 ± 6.19</td>
<td>24.00 ± 23.50</td>
<td>21.25 ± 0.97</td>
</tr>
</tbody>
</table>

SD: standard deviation.
Connolly et al reported a mean LP of 22.8 D for children (mean LP for girls of 22.7 D and for boys of 23.5 D, respectively, versus 23.5 D, respectively, p = 0.23), indicating that the apparent failure of emmetropization in these eyes and resultant failure of reduction in lens power with aging was not significant between the laser-treated eyes and the control eyes (mean LP of 21.8 D vs. 23.5 D, respectively, p = 0.039) in the untreated subthreshold eyes with active accommodation (Figure 3). The effect of accommodation on ACD did not differ significantly between the laser-treated eyes and the control eyes (p = 0.23), indicating that neither laser therapy nor severe ROP had any adverse effect on the mechanism of accommodation.

Our study has several limitations: the numbers are relatively small; our comparison group had less severe ROP from the outset; and, due to cognitive impairment, several patients were unable to cooperate with biometric assessment. While we recognize these limitations, we nevertheless feel that this study provides valuable information regarding the long-term refractive and biometric outcomes of laser therapy for ROP.

Table 3. Summary of studies on long-term refractive outcome of laser therapy for ROP

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of eyes</th>
<th>Type of laser</th>
<th>Mean follow-up (yr)</th>
<th>Mean spherical equivalent (D)</th>
<th>Myopic patients (%)</th>
<th>Mean SE of the myopic eyes (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahni et al²²</td>
<td>81*</td>
<td>Argon and diode</td>
<td>3.0</td>
<td>-2.40</td>
<td>38.5</td>
<td>-1.79</td>
</tr>
<tr>
<td>Kent et al²⁰</td>
<td>21*</td>
<td>Unspecified</td>
<td>3.4</td>
<td>-2.35</td>
<td>42.9</td>
<td>-2.83</td>
</tr>
<tr>
<td>Ospina et al²³</td>
<td>42*</td>
<td>Argon</td>
<td>6.2</td>
<td>-4.95</td>
<td>45.5</td>
<td>-3.03</td>
</tr>
<tr>
<td>Shalev et al²⁴</td>
<td>10†</td>
<td>Diode</td>
<td>7.0</td>
<td>-6.50</td>
<td>44.82</td>
<td>2.00</td>
</tr>
<tr>
<td>Connolly et al⁷</td>
<td>20†</td>
<td>Argon and diode</td>
<td>9.9</td>
<td>-4.56</td>
<td>44.00</td>
<td>1.28</td>
</tr>
<tr>
<td>Our study</td>
<td>16†</td>
<td>Diode</td>
<td>11.1</td>
<td>-2.33</td>
<td>50.0</td>
<td>-6.45</td>
</tr>
</tbody>
</table>

*Both eyes of same patient included in analysis.
†Only one eye per patient included in analysis.

There was also no significant difference in lens power between our laser-treated eyes and our comparison eyes in terms of corneal power (mean Ks of 45.24 D versus 44.82 D, respectively, p = 0.52). However, both groups had steeper corneas than expected when compared with data for historical full-term normal eyes (mean K of 42.99 D), supporting the concept of anterior segment arrest in premature eyes with ROP.¹³

There was also no significant difference in lens power with aging (mean Ks of 45.24 D versus 44.82 D, respectively, p = 0.039) in the untreated subthreshold eyes with active accommodation, the ACD was seen to have shortened by 0.13 mm (p < 0.001) in the laser-treated eyes and by 0.06 mm (p = 0.039) in the untreated subthreshold eyes with active accommodation (Figure 3). The effect of accommodation on ACD did not differ significantly between the laser-treated eyes and the control eyes (p = 0.23), indicating that neither laser therapy nor severe ROP had any adverse effect on the mechanism of accommodation.

Our study has several limitations: the numbers are relatively small; our comparison group had less severe ROP from the outset; and, due to cognitive impairment, several patients were unable to cooperate with biometric assessment. While we recognize these limitations, we nevertheless feel that this study provides valuable information regarding the long-term refractive and biometric outcomes of laser therapy for ROP.

Table 5. Comparison of our mean biometric outcomes with data from the literature for similarly-aged children

<table>
<thead>
<tr>
<th>Study population</th>
<th>Follow-up (yr)</th>
<th>No. of eyes</th>
<th>SE (D)</th>
<th>AL (mm)</th>
<th>ACD (mm)</th>
<th>Corneal power (D)</th>
<th>Lens power (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-term, no ROP (Fledelius, 1976)</td>
<td>10.2</td>
<td>67</td>
<td>+0.61</td>
<td>23.50</td>
<td>3.90</td>
<td>42.99</td>
<td>23.50</td>
</tr>
<tr>
<td>Pre-term, no ROP (Fledelius, 1996)</td>
<td>8.9</td>
<td>28</td>
<td>+0.93</td>
<td>22.98</td>
<td>3.98</td>
<td>44.00</td>
<td>23.50</td>
</tr>
<tr>
<td>Pre-term, subthreshold ROP (Our comparison group, 2005)</td>
<td>11.2</td>
<td>9</td>
<td>+1.07</td>
<td>22.47</td>
<td>3.70</td>
<td>44.82</td>
<td>23.50</td>
</tr>
<tr>
<td>Pre-term, laser-treated, threshold ROP (Our laser group, 2005)</td>
<td>11.1</td>
<td>16</td>
<td>-2.33</td>
<td>22.81</td>
<td>3.38</td>
<td>45.24</td>
<td>21.80</td>
</tr>
<tr>
<td>Pre-term, laser-treated, threshold ROP (Connolly et al, 2002)</td>
<td>9.9</td>
<td>20</td>
<td>-4.56</td>
<td>22.89</td>
<td>3.44</td>
<td>46.68</td>
<td>22.80</td>
</tr>
</tbody>
</table>

SE: spherical equivalent; D: diopters; AL: axial length; ACD: anterior chamber depth.
of diode laser photocoagulation in threshold ROP eyes. At a mean follow-up of 11 years, our laser group had a mean spherical equivalent of −2.33 D with a mean astigmatic error of 1.38 D. The myopia appeared to be slowly progressive in nature when compared with earlier refractive data for these patients. The laser-treated eyes had shallower anterior chambers than the comparison eyes in which the subthreshold ROP spontaneously regressed. However, the two groups did not differ significantly in terms of axial length, corneal power, corneal diameter, or lens power. Physiological accommodation was not impaired in the laser-treated eyes.

References