

# Intraocular Pressure Variations after Diode Laser Photocoagulation for Threshold Retinopathy of Prematurity

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**Purpose:** To investigate the intraocular pressure (IOP) variations occurring after indirect diode laser photocoagulation for threshold retinopathy of prematurity.

**Design:** Prospective, nonrandomized, comparative study.

**Participants:** A study group—21 consecutive premature babies (42 eyes) undergoing diode laser photocoagulation for retinopathy of prematurity—and control groups—32 premature babies (64 eyes) undergoing retinal examination with or without scleral indentation.

**Intervention:** Intraocular pressure was measured with a portable electronic tonometer before, immediately after, and 1, 2, and 3 days after diode laser photocoagulation in the study group; before retinal examination in control group 1; and before and after retinal examination with scleral indentation in control group 2.

**Main Outcome Measure:** Intraocular pressure after diode laser photocoagulation for threshold retinopathy of prematurity.

**Results:** Mean IOP in the study group rose from 15 mmHg (standard deviation [SD] = 4.1) before coagulation to 33.2 mmHg (SD = 7.8; range, 20–50) immediately after, and then dropped to 22.2 (SD = 5.2), 16.5 (SD = 3), and 14.5 mmHg (SD = 2.1) 1, 2, and 3 days later, respectively. All the changes were statistically significant at  $P < 0.0001$ , except for the difference between days 2 and 3 ( $P = 0.096$ ). Mean baseline IOPs were 16.3 mmHg (SD = 3.7) in control group 1 and 15.7 mmHg (SD = 2.3) in control group 2 ( $P = 0.84$  between control group 1 and study group, and  $P = 0.32$  between control group 2 and the study group). At termination of the retinal examination with scleral indentation (control group 2), IOP measured 15.1 mmHg (SD = 2.2) ( $P = 0.49$  compared with baseline).

**Conclusions:** Intraocular pressure may be significantly elevated after diode laser photocoagulation for retinopathy of prematurity. The mechanism and long-term clinical implications of this observation should be investigated. *Ophthalmology* 2004;111:1734–1738 © 2004 by the American Academy of Ophthalmology.

Diode laser photocoagulation (DLPC) of the avascular retina is the preferred treatment modality for threshold retinopathy of prematurity (ROP). Data accumulated in recent

years show that DLPC is superior to cryotherapy<sup>1–3</sup> and probably causes fewer adverse effects (such as cataract) than argon laser photocoagulation. However, there is little information concerning the effect of DLPC on the intraocular pressure (IOP) of the premature eye.

The aim of the present study was to examine variations in IOP after indirect DLPC performed for threshold ROP.

## Materials and Methods

The study group consisted of all consecutive premature infants undergoing DLPC for threshold ROP from September 2002 to December 2003 in the intensive neonatal care unit of Schneider Children's Medical Center of Israel. Both eyes were treated at the same session. The pupils were dilated by 3 instillations of tropicamide drops (Mydracyl, Alcon, Fort Worth, TX) every 15 minutes. Intravenous midazolam (100 µg/kg) and fentanyl (3 mg/kg) were administered by a neonatologist, who monitored the infants throughout the laser treatment. Just before the procedure, local anesthetic drops (oxybuprocaine) were added. Tonometry was performed with the Tono-Pen XL (Solan, Jacksonville, FL), without an eye speculum. Intraocular pressure was measured by 2 ophthalmologists: one opened the eyelids gently, without exerting

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Table 1. Demographic Data of Infants with Retinopathy of Prematurity Undergoing Diode Laser Photocoagulation and Control Groups

|                 | Gender* |        | Gestational Age (wks) [Mean (SD)]† | Birth Weight (g) [Mean (SD)]‡ | Postconceptional Age at Laser Treatment or Examination (wks) [Mean (SD)]§ |
|-----------------|---------|--------|------------------------------------|-------------------------------|---------------------------------------------------------------------------|
|                 | Male    | Female |                                    |                               |                                                                           |
| Study group     | 11      | 10     | 25.6 (1.1)                         | 817.3 (179.9)                 | 34.5 (2.1)                                                                |
| Control group 1 | 13      | 9      | 31.4 (3.3)                         | 1587.9 (553.9)                | 35.1 (2.6)                                                                |
| Control group 2 | 6       | 4      | 29.8 (6.2)                         | 1443.8 (970.7)                | 34.9 (2.8)                                                                |

SD = standard deviation.

\* $P = 0.826$ , chi-square test.

†Analysis of variance (ANOVA):  $P < 0.0001$  between study group and control group 1;  $P = 0.007$  between study group and control group 2.

‡ANOVA:  $P < 0.0001$  between study group and control group 1;  $P = 0.016$  between study group and control group 2.

§ANOVA:  $P = 0.3$ .

pressure on the eye, and the other took the measurements. Repeatable IOP values within the limits of 2 mmHg were recorded. The measurements were repeated at least 3 times, and the average of the 3 repeatable values (within 2 mmHg) was recorded for analysis. This procedure was done immediately before DLPC (when the child was already sedated), directly at its conclusion (when the neonate was still sedated), and 1, 2, and 3 days after treatment. Slit-lamp examination was performed before and after DLPC using a portable slit lamp to exclude angle-closure glaucoma, blood in the anterior chamber, and severe corneal edema obscuring the anterior chamber.

Findings were compared with 2 control groups. Control group 1 consisted of premature babies undergoing screening retinal examination, and control group 2 consisted of premature babies undergoing retinal examination with scleral indentation, which is performed during laser treatment as well. The IOP in all 3 groups was measured when the babies were relaxed and quiet. Intraocular pressure was measured in the same manner, before the retinal examination in control group 1 and before and immediately after the examination (including scleral indentation) in control group 2. Both control groups received the same eye drop regimen as the study group. Although IOP measurements before and after DLPC have become a routine examination in our practice, the study was approved by the institutional review board in Rabin Medical Center, allowing for IOP measurements in the DLPC and control groups. Informed consent was obtained from the neonates' parents for the IOP measurements, as well as for the laser treatments. Statistical analysis was performed with SPSS.<sup>4</sup> Student's *t* test, general linear model repeated-measures test, chi-square test, analysis of variance (ANOVA) and Pearson correlation were performed. Because the IOP measurements in both eyes of the same baby were positively correlated (ranging from 0.6 to 0.85 in the different groups), the above analyses were first performed using one eye only from each baby to assess the significance of the differences in a valid way. The analyses were then repeated using the other eye from each baby, thereby getting 2 *P* values for assessing the significance of each tested difference. Each pair of *P* values was then combined using the Simes test,<sup>5</sup> by taking the minimum of (1) the largest *P* value of the pair and (2) twice the smallest *P* value of the pair. This procedure yields a valid *P* value (even though conservative) when the test statistics are positively correlated.<sup>6</sup>

## Results

The study group included 21 babies (42 eyes) with threshold ROP, and control groups 1 and 2 consisted of 22 neonates (44 eyes) and

10 neonates (20 eyes), respectively. Their demographic data are presented in Table 1. There was a statistically significant difference (ANOVA) between the study group and control group 1 in gestational age ( $P < 0.0001$ ) and birth weight ( $P < 0.0001$ ) and between the study group and control group 2 in gestational age ( $P = 0.007$ ) and birth weight ( $P = 0.016$ ). Treatment was performed at the mean postconceptional age of 34.5 weeks (standard deviation [SD] = 2.1). Postconceptional ages at the time of IOP measurement were similar in all 3 groups ( $P = 0.3$ ).

Forty eyes (95.2%) had stage 3 ROP, and 2 eyes (4.8%) had stage 2 ROP. There were 19 eyes (45.2%) with zone 1 disease and 23 eyes with zone 2 disease (54.8%). All the eyes had plus disease. A near-confluent laser pattern was delivered, with the power setting ranging from 300 to 530 mW, with a mean of 405.5 (SD = 66) and duration of 0.2 to 0.3 seconds. The number of laser spots per eye ranged from 1000 to 4000, with a mean of 2700 (SD = 776.7) (reflecting the severity of the ROP at its posterior location).

The IOP measurements in the study and control groups are presented in Table 2. Mean IOP in the study group was 15 mmHg (SD = 4.1) before photocoagulation and rose to 33.2 mmHg (SD = 7.8; range, 20–50) immediately after. It dropped to 22.2 (SD = 5.2), 16.5 (SD = 3), and 14.5 mmHg (SD = 2.1) at 1, 2, and 3 days later (Fig 1). There was a statistically significant difference in mean IOP between the baseline value and the value directly after laser treatment (increase of 18.2 mmHg [SD = 7],  $P < 0.0001$ , general linear model repeated-measures test combined with the Simes test), between the immediate postprocedural value and the values on days 1 to 3 ( $P < 0.0001$ ), and between the values on days 1 and 2 (drop of 5.7 mmHg,  $P < 0.0001$ ) and days 1 and 3 (drop of 7.7 mmHg,  $P < 0.0001$ ). The difference in IOP between days 2 and 3 after treatment was smaller, and not significant ( $p = 0.096$ ).

Comparison with control measurements yielded no statistically significant difference in baseline values between the study group and control groups 1 and 2 ( $P = 0.32$  and  $0.84$ , respectively). In the second control group, mean IOP changed from 15.7 mmHg (SD = 2.3) before examination to 15.1 mmHg (SD = 2.2) after ( $P = 0.49$ ). No correlation was found between the increase in IOP and gestational age, birth weight, postconceptional age at the time of DLPC, number of laser burns, and laser power ( $P = 0.55, 0.31, 0.81, 0.45$ , and  $0.085$ , respectively, Pearson correlation).

Slit-lamp examination did not show a flat anterior chamber or blood in the anterior chamber. Corneal edema, which did not obscure the details of the anterior chamber, was observed in 4 eyes with an IOP of  $\geq 38$  mmHg at the conclusion of DLPC.

Table 2. Intraocular Pressure Variations

|                                    | Pretreatment IOP<br>(mmHg) (SD) | Immediate<br>Post-treatment/<br>postexamination<br>IOP (mmHg)<br>(SD)* | Day 1 (mmHg)<br>(SD) | Day 2 (mmHg)<br>(SD) | Day 3 (mmHg)<br>(SD) |
|------------------------------------|---------------------------------|------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| Study group (42 eyes) <sup>†</sup> | 15 (4.1)                        | 33.2 (7.8)                                                             | 22.2 (5.2)           | 16.5 (3)             | 14.5 (2.1)           |
| Control group 1 (44 eyes)          | 16.3 (3.7)                      | —                                                                      | —                    | —                    | —                    |
| Control group 2 (20 eyes)          | 15.7 (2.3)                      | 15.1 (2.2)                                                             | —                    | —                    | —                    |

SD = standard deviation.

\*Immediate post-treatment in the study group, and immediate postexamination with scleral indentation in control group.

<sup>†</sup> $P < 0.0001$  (general linear model repeated-measures test combined with the Simes test) for all IOP variations in the study group.

## Discussion

The normal IOP in premature infants was reported by several authors. Brockhurst,<sup>7</sup> using a McLean tonometer, obtained values from 6.5 to 33 mmHg (average, 24.5) in 59 premature infants at a postconceptional age of 27 to 34 weeks, and Musarella and Morin,<sup>8</sup> using a handheld Perkins applanation tonometer, obtained average values of 18 and 18.6 mmHg (SD = 2.3), in the right and left eyes, respectively, in 37 quiet infants at 29 to 38 weeks' gestation. The latter authors found no correlation between IOP and postconceptional age or birth weight. Tucker et al<sup>9</sup> measured IOP in premature infants at 25 to 37 weeks' postconceptional age with the Tonopen and noted a mean value of 10.3 mmHg (SD = 3.5), with no significant correlation between the IOP and gestational age or birth weight. They concluded that 97.5% of premature babies should have an IOP of  $\leq 18$  mmHg. In a study of 38 premature neonates undergoing retinal examination, Kumar et al<sup>10</sup> reported that mean IOPs (taken by a pneumatonometer) were 20.5 mmHg (SD = 7.6) before introduction of the eye speculum, 35.0 mmHg (SD = 9.4) on introduction of the speculum to retract the eyelids, and 31.4 mmHg (SD = 8.2) immediately

after indentation. Tucker et al<sup>9</sup> suggested that the differences in IOP among the various series may be due to the influence of the high scleral rigidity in infants, making indentation tonometry less reliable in this population, as well as to problems inherent in IOP measurements in premature infants. Specifically, the IOP fluctuates with the rise in venous pressure caused by crying and straining and with the increase in extraocular muscle tonus caused by squeezing the eyelids. Therefore, to ensure accuracy, they recommended that IOP be measured when the infant is not crying, preferably with applanation tonometry.

In our series, IOP was measured with the Tonopen, without a lid speculum, which has been shown to increase the IOP,<sup>10</sup> and when the babies were calm. Mean baseline values were 15 mmHg (SD = 4.1) in the study group and 16.3 mmHg (SD = 3.7) and 15.7 mmHg (SD = 2.3) in the control groups, all higher than the IOP reported by Tucker et al.<sup>9</sup> The baseline IOP of our treated babies was not measured before sedation, and therefore a possible effect of the IV sedation on the IOP cannot be ruled out. Furthermore, although the post-DLPC IOP measurements were taken when the babies were still sedated, it may be argued that the anesthetic effect was wearing off, with possible

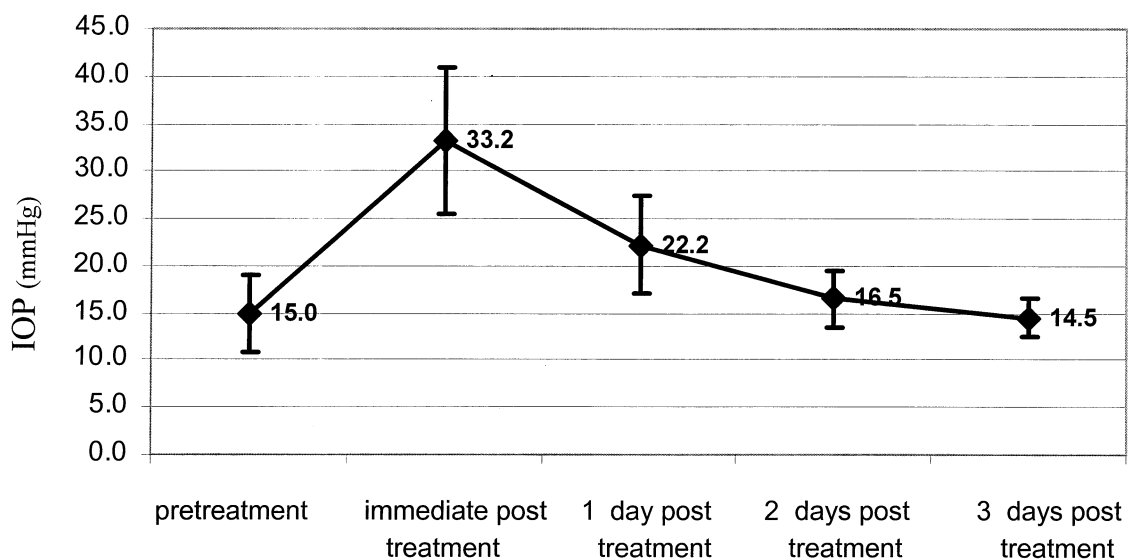


Figure 1. Intraocular pressure (IOP) variations after diode laser photocoagulation for threshold retinopathy of prematurity.

influence on IOP variations. However, although the babies in the study group were sedated, their baseline IOP was similar to that in the control groups, as well as to the IOP values reported in previous series.<sup>8,9</sup> Moreover, the IOP remained elevated on the first post-DLPC day and gradually declined to the pretreatment values by the third postoperative day.

In our study, although postconceptional ages at the time of IOP measurements were similar in the study and control groups, there were statistically significant differences between the study and control groups in gestational age and birth weight. These differences could have introduced bias when comparing IOP values between study and control groups. However, comparison between study and control measurements yielded no statistically significant difference in baseline IOP values, and no correlation was found within the DLPC group between the change in IOP, birth weight, and gestational age. Our findings confirm data reported in previous studies, showing that the IOP is not influenced by birth weight and gestational age.

Diode laser photocoagulation has been found to be a safe and effective means of retinal ablation,<sup>1-3</sup> and it has become the standard treatment for ROP. However, rare treatment complications have been described. These include cataract,<sup>1,11,12</sup> corneal edema, anterior segment ischemia, posterior synechiae, and vitreous hemorrhage.<sup>12-15</sup> Angle-closure glaucoma was reported in one baby after DLPC for ROP, requiring bilateral surgical peripheral iridectomies.<sup>16</sup> An elevation in IOP after panretinal photocoagulation may be caused by angle closure from choroidal effusion or a transient decrease in outflow with an open anterior chamber angle. The effusion is caused by fluid leakage from damaged choroidal vessels.<sup>17-19</sup>

To the best of our knowledge, this is the first study to report IOP variations in premature infants after DLPC. We found that IOP increased acutely after treatment (from a mean of 15 mmHg, with a range of 5–20, to a mean of 33.2 mmHg, with a range of 20–50) and then dropped back to pretreatment levels during the next 2 days. No correlation was found between the IOP increase and the number of laser burns or laser power. The mechanism underlying the pressure elevation is unknown. None of the babies had post-treatment shallowing of the anterior chamber or hyphema, and only 4 eyes had transient corneal edema, which did not obscure the details of the anterior chamber. The photocoagulation burns produced by a transpupillary diode laser (810 nm) lead to retinal and choroidal changes. Compared with the argon laser, the diode laser has a greater effect on the choroid.<sup>20,21</sup> We delivered near-confluent laser burns, with a mean of 2700 spots (SD = 776.7) per eye. Although we did not observe clinical choroidal effusion, it is possible that some of the increase in IOP was caused by subclinical choroidal congestion. Another mechanism could be postoperative inflammation with inflammatory cells and secondary aqueous in the anterior chamber, compromising the outflow facility of the premature neonate's eye. The IOP elevations occurring after DLPC should be differentiated from acute closed-angle glaucoma that may require surgical intervention.<sup>16</sup> The differential diagnosis should be made by slit-

lamp examination, to determine the proper course of treatment.

We think that clinicians should be aware of possible IOP elevation after DLPC for ROP, which declines (according to our experience) to pretreatment levels within 2 to 3 days. However, because IOP may increase to levels of up to 50 mmHg, physicians might consider topical antiglaucomatous treatment in selected cases.

Further studies are needed to identify the mechanism and long-term clinical implications of the IOP variations after DLPC.

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