Diode Laser Photocoagulation for Retinopathy of Prematurity: Outcomes After 7 Years of Treatment

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ABSTRACT

Purpose: This study aimed to evaluate the outcome of transpupillary diode laser photocoagulation for retinopathy of prematurity (ROP) at one institution in Romania.

Methods: This retrospective case series included all infants who received indirect diode laser photocoagulation for ROP between January 1, 2006, and December 31, 2012.

Results: The 160 eyes of 83 infants were classified into two categories: 136 eyes (85%) with classic disease (stage III ROP in zones 1 or 2) and 24 eyes (15%) with aggressive posterior ROP (AP-ROP). ROP regressed in 141 eyes (88.12%). The success rate was significantly better in the classic ROP group (94.11%) compared to the AP-ROP group (54.16%) (P < .001).

Conclusions: The ROP regression rate after the laser treatment was 88% in this series.

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding proliferative disease of the retinal vasculature. Fortunately, ROP is one of the few largely preventable causes of visual impairment in children. The standard cure for ROP is laser photocoagulation of the non-vascularized retina. The Ophthalmology and Neonatology Departments belonging to the “Iuliu Hatieganu” University of Medicine and Pharmacy from Cluj-Napoca, Romania, joined the ROP National Screening Program in 2005 and the laser treatment became available in 2006.

The purpose of this study was to evaluate the outcome of transpupillary diode laser photocoagulation for ROP performed in our hospital. We set four objectives: (1) to characterize demographically and clinically the premature infants who needed laser photocoagulation for ROP for a 7-year period; (2) to assess the timing of the laser treatment for ROP; (3) to describe the outcomes of ROP after the laser treatment; and (4) to identify the individual factors associated with the outcomes of laser therapy.

PATIENTS AND METHODS

This is a case-control, non-comparative, consecutive, interventional, retrospective case series.

Setting

This study was undertaken at the “Iuliu Hatieganu” University of Medicine and Pharmacy.
from Cluj-Napoca, Romania, involving the Ophthalmology and the Neonatology Departments. All laser therapies were performed by two ophthalmologists in the Neonatology Department. The patients were enrolled after obtaining of informed consent from the parents/tutors. The study was approved by the Ethics Committee of the “Iuliu Hatieganu” University of Medicine and Pharmacy.

Study Sample

The study sample was selected according to clinical and demographic criteria and included all premature infants with ROP who required laser treatment between January 1, 2006, and December 31, 2012. The sampling method was longitudinal retrospective.

We retrospectively analyzed the files of all consecutive infants who were treated by indirect diode laser photocoagulation for ROP for a 7-year period from January 1, 2006, through December 31, 2012. The treated premature infants came from a screening program that included preterm newborns who met the following criteria: gestational age (GA) of 33 weeks or less or birth weight (BW) of 1,500 grams or less. ROP screening also included premature infants with: GA of more than 33 weeks and BW of more than 1,500 grams, if other risk factors were associated; prolonged oxygen administration with saturation over 93%; repeated transfusions; sepsis; and necessity of more than 6 days of mechanical ventilation for cardiorespiratory support. Eyes with stage 2 zone II, 4 a, 4 b, 5 ROP and with congenital atrophy were not treated and therefore were excluded from the study sample.

ROP Classification

The ROP classification scheme includes four components: the zone, the extension, the stage, and the presence/absence of “plus” disease. Threshold ROP includes stage 3 (red, vascularized ridge at the limit between the vascularized and non-vascularized retina) with “plus” in zone I or II, extended on more than 5 contiguous or 8 cumulative clock hours. Pre-threshold ROP includes less than threshold disease in zone I, stage 2 “plus” disease in zone II, stage 3 without “plus” disease in zone II, and stage 3 “plus” disease less extended than for threshold disease. Aggressive posterior ROP (AP-ROP) is considered separate from the “classic” ROP.

Medical Intervention

We undertook the laser treatment in the following situations: zone II stage 3 ROP, zone I stage 3 ROP, and AP-ROP. Infants with AP-ROP were treated within 24 hours and those with “classic” ROP within 48 hours from the diagnosis.

All laser therapies were performed in the Neonatology Unit, under sedation. We used a portable diode laser photocoagulator, with the emission of 810 nm; the laser energy was delivered transpupillary in all cases. Prior to the intervention, the pupils were dilated with a mixture of tropicamide 0.5% and phenylephrine 2.5%. To get access to the retina, we used an eyelid speculum, a scleral depressor, and a +28 diopter lens. The parameters of the laser photocoagulation were 200 µm laser spots with 200 ms duration and 150 to 300 mW power. The post-treatment review took place 6 to 7 days after the treatment and continued every 5 to 6 days until there was evidence of ROP regression. Re-treatment was performed 7 to 10 days after the initial treatment, if ROP failed to regress. The treated eyes were monitored at a frequency dictated by the clinical condition to determine the risk of sequelae.

Statistical Analysis

Statistical analysis was performed with EpiInfo 7 software (Centers for Disease Control and Prevention, Atlanta, GA). Frequencies for the following independent variables related to the preterm infant were calculated: gender, GA, BW, type of pregnancy (single or multiple), postmenstrual age (PMA) and postnatal age (PNA) at treatment, and classification of ROP.

The results were interpreted according to the odds ratio. Statistical significance was assessed based on the P values calculated using the t test. The test of 2×2 independent samples was used. The chi-square test was used if values over 5 were expected in 80% of the table cells and Fisher exact test was used if values under 5 were expected in more than 20% of the table cells. P values less than .05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of the Study Sample

Over 7 years, we screened 836 infants for ROP. They were all white and 98 of them progressed to threshold (11.72%), requiring medical intervention. This consisted of laser photocoagulation of the retina.
in 83 premature infants or intravitreal injections with bevacizumab in the remaining 15 infants. Our study focused on the 83 cases treated by laser, of which 45 were male (54.22%) and 38 female (45.78%). Four of the 83 treated premature infants were born outside a hospital with a neonatal intensive care unit and needed to be transported (4.81%). The targeted oxygen saturation to the infants in the neonatal intensive care unit during their first weeks of life is 90% to 95%. Of the 83 treated premature infants, 18 were from Cluj (21.68%) and 65 were referred to us from neighboring departments where the laser treatment was unavailable (78.31%). The GA was between 24 and 33 weeks (mean ± standard deviation: 28.40 ± 2.91 weeks) and the BW was between 600 and 1,700 g (mean ± standard deviation: 1,122 ± 278.45 g). Of the 83 preterm infants included in the study sample, 54 were the result of single pregnancies (65.06%) and 29 of multiple pregnancies (34.93%). The PNA at treatment was between 5 and 13 weeks (mean: 8.38 ± 1.93 weeks) and the PMA at treatment was between 32 and 41 weeks (mean: 37.06 ± 1.67 weeks). The above mentioned data are summarized in Table 1.

The number of the treated premature infants differs according to the year, as presented in Table 2.

Retinal laser photocoagulation was bilateral in 77 cases and unilateral in 6 cases. The 6 eyes in which the laser treatment was not performed belonged to one of the following categories: stage 2 zone II ROP (3 eyes), stage 4a ROP (1 eye), stage 5 ROP (1 eye), and congenital atrophy (1 eye). Consequently, 160 eyes had laser treatments. The 3 eyes with stage 2 zone II ROP were followed up every 3 days and all of them regressed spontaneously with no need for laser therapy.

ROP classification of the eyes with laser treatment is as follows: stage 3 zone II = 19 eyes (71.69%), stage 3 zone I = 17 eyes (10.24%), and AP-ROP = 24 eyes (14.46%).

Timing of the Laser Treatment for ROP
We evaluated the timing of the laser treatment according to two parameters: PNA and PMA at the moment of treatment.

The PNA at treatment was between 5 and 13 weeks (mean ± standard deviation: 8.38 ± 1.93 weeks). The treatment was performed at PNA of 9 weeks or less in 90 eyes (56.25%) and at more than 9 weeks after birth in 70 eyes (43.75%). Within the group treated at PNA of 9 weeks or less, ROP regressed in 77 eyes (85.55%) and did not regress in 13 eyes (14.44%). If the treatment was performed at more than 8 weeks after birth, ROP regressed in 64 eyes (91.42%) and did not regress in 6 eyes (8.57%). The chi-square test proved that the difference was not statistically significant. The PMA at treatment varied between 32 and 41 weeks (mean ± standard deviation: 37.06 ± 1.67 weeks).

PMA at treatment was 37 weeks or less in 94 eyes (58.75%) and more than 37 weeks in 66 eyes (41.25%). Within the group with PMA at treatment

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### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>45 (54.22%)</td>
</tr>
<tr>
<td>Female</td>
<td>38 (45.78%)</td>
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<tr>
<td>City of origin</td>
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<tr>
<td>Cluj</td>
<td>18 (21.68%)</td>
</tr>
<tr>
<td>Outside Cluj</td>
<td>65 (78.31%)</td>
</tr>
<tr>
<td>Type of pregnancy</td>
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</tr>
<tr>
<td>Single</td>
<td>54 (65.06%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>29 (34.93%)</td>
</tr>
<tr>
<td>Mean ± SD gestational age (wk)</td>
<td>28.40 ± 2.91</td>
</tr>
<tr>
<td>Mean ± SD birth weight (g)</td>
<td>1,122 ± 278.45</td>
</tr>
<tr>
<td>Mean ± SD PNA at treatment (wk)</td>
<td>8.38 ± 1.93</td>
</tr>
<tr>
<td>Mean ± SD PMA at treatment (wk)</td>
<td>37.06 ± 1.67</td>
</tr>
</tbody>
</table>

SD = standard deviation; PNA = postnatal age; PMA = postmenstrual age

### Table 2

<table>
<thead>
<tr>
<th>Year</th>
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<th>GA (wk)</th>
<th>BW (g)</th>
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<tbody>
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<td>2005</td>
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<td>650.00 ± 70.71</td>
<td>27.00 ± 0.00</td>
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<td>2006</td>
<td>11</td>
<td>1,130.90 ± 288.45</td>
<td>28.63 ± 1.62</td>
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<td>2007</td>
<td>16</td>
<td>1,029.37 ± 277.86</td>
<td>28.06 ± 2.52</td>
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<td>2008</td>
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<td>1,246.87 ± 306.00</td>
<td>29.75 ± 2.52</td>
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<tr>
<td>2009</td>
<td>16</td>
<td>1,126.25 ± 260.53</td>
<td>28.56 ± 1.59</td>
</tr>
<tr>
<td>2010</td>
<td>16</td>
<td>1,124.37 ± 242.48</td>
<td>28.43 ± 1.86</td>
</tr>
<tr>
<td>2011</td>
<td>5</td>
<td>1,238.00 ± 114.97</td>
<td>29.00 ± 1.87</td>
</tr>
<tr>
<td>2012</td>
<td>1</td>
<td>800.00</td>
<td>27.00</td>
</tr>
</tbody>
</table>

GA = gestational age; BW = birth weight

*Values are mean ± standard deviation.
37 weeks or less, ROP regressed after the laser treatment in 82 eyes (87.23%) and failed to regress in 12 eyes (12.76%). In the cases with PMA at treatment of more than 37 weeks (66 eyes), the laser treatment induced ROP regression in 59 eyes (89.39%), whereas in 7 eyes (10.60%) ROP progressed toward retinal detachment. The difference was not statistically significant.

**Outcomes of ROP After Laser Therapy**

We defined the outcomes after laser treatment of ROP by the following parameters: ROP regression rate, frequency of re-treatment, structural outcomes, and complication rate.

ROP regressed after the laser photocoagulation in 141 eyes (88.12%). The regression was achieved after one laser session in 133 eyes (94.32%) and after two laser sessions in 8 eyes (5.67%). The regression of ROP was achieved after one laser session in all 112 eyes with stage 3 zone II ROP, in 14 of the 16 eyes with stage 3 zone I ROP (87.50%), and in 7 of the 13 eyes with AP-ROP (53.84%). Two laser sessions were required in 2 eyes with stage 3 zone I ROP (12.50%) and in 6 eyes with AP-ROP (46.15%).

Macular dragging was identified in 3 of the 141 eyes with the retina attached after the laser therapy. They all belonged to the AP-ROP type. Complications related to the laser therapy were represented by two cases of mild anterior uveitis, both in the AP-ROP group. They responded promptly to mydriatic and anti-inflammatory eye drops.

**Individual Factors Associated With the Outcomes of Laser Therapy**

We analyzed the following individual factors in relation to the outcomes of the laser therapy: ROP type, gender, type of pregnancy, BW, and GA.

Within the stage 3 zone II ROP group (119 eyes), the laser photocoagulation of the non-vascularized retina was followed by ROP involution in 112 eyes (94.12%) and ROP progression in 7 eyes (5.88%). Among the 17 eyes with stage 3 zone I ROP, regression of ROP was noted in 16 eyes (94.12%) and worsening of ROP in 1 eye (5.88%) after laser treatment. In the group of 24 eyes with AP-ROP, the laser treatment induced the ROP regression in 13 eyes (54.16%) and ROP progression toward retinal detachment in 11 eyes (45.83%).

The statistical tests proved that the outcome of the laser treatment was significantly worse in AP-ROP compared to stage 3 zone II ROP and stage 3 zone I ROP (odds ratio = 13.53, relative risk = 7.79, \( P < .001 \)). Statistically, the difference was significant.

ROP failed to regress after the laser treatment in 11 of the 84 eyes belonging to the male gender (13.09%) and in 8 of the 76 eyes belonging to the female gender (10.52%). The difference was not statistically significant.

The type of pregnancy did not influence significantly the result of the laser treatment. Of the 103 eyes belonging to infants coming from single pregnancies, the laser treatment was followed by ROP regression in 91 eyes (88.34%) and of the 57 eyes within the multiple pregnancies group, ROP regressed after the laser treatment in 50 eyes (87.71%).

Within the 160 treated eyes, 64 belonged to premature infants having a BW of 1,000 g or less (40%) and 96 to premature infants having a BW of more than 1,000 g (60%). ROP failed to regress after the laser therapy in 4 eyes (6.25%) from the first group and in 15 eyes (15.62%) from the second group. The difference was not statistically significant.

Among the 160 treated eyes, the GA was 28 weeks or less in 88 eyes (55%) and more than 28 weeks in 72 eyes (45%). Within the GA of 28 weeks or less group, ROP regressed after the laser treatment in 82 eyes (93.18%) and did not regress in 6 eyes (6.81%). Within the group of premature infants born after more than 28 weeks of gestation, ROP regressed following laser photocoagulation in 59 eyes (81.94%) and did not regress in 13 eyes (18.05%). The \( P \) value (.02) indicates that the difference is statistically significant: the premature infants born after more than 28 weeks of gestation had a significantly lower regression rate of ROP after the laser treatment compared to those born after gestation of 28 weeks or less.

**DISCUSSION**

**Rationale of the Laser Treatment for ROP**

The retina of the preterm infants is immature and when exposed to high levels of oxygen, which is necessary for the infant’s life support, the pro-angiogenic growth factors (such as vascular endothelial growth factor [VEGF]) decrease, inducing the cessation of vessel growth. The subsequent relative hypoxia leads to higher VEGF levels and the formation of new vessels. Therefore, ROP is understood as a two-phase process: an acute phase, generated by the relative hyperoxia of the extra-uterine environment, characterized by vaso-obliteration and non-
vascularization of the anterior retina, and a chronic phase, defined by vasoproliferation. The rationale for ROP treatment by laser photocoagulation is to destroy the non-vascularized retina to remove the source of the angiogenic factors, thus interrupting the pathogenic mechanism of the vasoproliferation and subsequent retinal detachment. This was achieved for the first time in 1988 by cryotherapy, which proved its efficacy in preventing blindness caused by ROP. In 1994, the Laser ROP study group demonstrated that laser photocoagulation of the retina is as effective as cryotherapy in ROP and has the advantage of causing less severe side effects. Laser therapy is also more effective than cryotherapy in treating posterior zone 2 and zone 1 disease and causes less manipulation and trauma to the eye.

**Indications for the Laser Treatment in ROP**

We performed laser photocoagulation in the following situations: zone II stage 3 ROP, zone I stage 3 ROP, and AP-ROP. According to the Early Treatment for Retinopathy of Prematurity Randomized Trial study, the threshold ROP as defined in the Multicenter Trial of Cryotherapy for ROP may no longer be the ideal indication for treatment. Therefore, treatment may also be initiated in the following circumstances: zone I any stage ROP with “plus” disease, zone I stage 3 ROP without “plus” disease, and zone II stage 2 ROP with “plus” disease. All of our treated zone I cases were already in stage 3 by the time we first examined them, because they were referred by other neonatal intensive care units where the laser therapy was not available. For the same reason, the majority of zone II cases were in stage 3 by the time they were referred to us. Regarding the cases with zone II stage 2 with “plus” disease coming from our own screening, we followed them closely (every 3 days) and performed the laser treatment immediately (within 24 hours) if progression toward stage 3 disease was noticed. We identified stage 2 zone II ROP with “plus” disease in 40 eyes, of which 23 reached stage 3 and required laser therapy. ROP regression was noticed in 21 of the 23 eyes receiving laser treatment (91.3%). Therefore, taking into account the significant proportion of zone II stage 2 ROP with spontaneous regression (42.5%) and the good outcome after laser therapy performed in stage 3, our protocol in stage 2 zone II ROP with “plus” disease is close observation and prompt treatment if stage 3 is reached.

We did not identify any case of stage 3 zone I ROP without “plus” disease.

**Demographic and Clinical Characteristics of the Study Sample**

The treated infants in our series had higher BW (1,122 g) and older gestational ages (28 weeks) than their counterparts in the United States (830 g BW average and 26 weeks GA average). The oldest treated infant was born at 33 weeks and the heaviest treated infant was 1,700 g, both beyond the screening criteria in United States.

The number of premature infants who needed laser treatment for ROP increased after the first year of the interval and maintained a relatively constant level for the next 5 years, followed by a significant decrease. There are two explanations for this observation: the laser treatment became available in three more centers and intravitreal injections with anti-VEGF were introduced into clinical practice and replaced the laser photocoagulation in AP-ROP.

**Timing of the Laser Treatment for ROP**

Because of the short window of opportunity during which the laser is effective, timely recognition of the disease is crucial for the positive result of the treatment. This was detected early and to follow it closely, so that treatment could be established at the appropriate time, if indicated. It has to be performed at a point in the natural history where vasoproliferation can be reversed, because once the vitreoretinal traction commences it is difficult to control the disease and prevent the retinal detachment with subsequent visual loss. Knowing the progression of ROP in correlation with time is crucial for a correct screening. ROP usually does not develop within the first 2 weeks after birth. The median age for detection of stage 1 ROP is 34 weeks PMA, pre-threshold ROP appears at approximately 36 weeks PMA, and threshold ROP appears at approximately 37 weeks PMA. The vascularization of the retina is complete by 40 to 44 weeks PMA. Therefore, the interval for ROP detection is between 32 and 40 weeks PMA. The critical phase, during which ROP progresses and may have to be treated, is between 34 and 37 weeks PMA. The mean PMA at treatment in our study was 37.06 weeks. The statistical analysis on our series proved that the ROP regression rate was not influenced significantly by the PMA at treatment.
Outcomes of the Laser Therapy

Indirect diode laser photocoagulation of the retina proved its efficacy in the treatment of ROP on our series: 88.12% of all the treated eyes had a good outcome based on the complete remission of ROP and attached retina. Our ROP regression rate is comparable to those quoted in the literature. We applied the laser spots on the surface of the avascular retina, from the anterior margin of the ridge to the ora serrata, in a confluent manner, with no space between the laser burns, using a continuous laser mode. In 4 eyes we also placed laser burns posterior to the ridge with a double purpose: to create focal chorioretinal adhesions to limit the spread of tractional retinal detachment and to destroy the ischemic areas known to occur in this location. All of the 4 eyes in which we used this technique had a good anatomical outcome. Other authors do not recommend the application of laser burns posterior to the ridge, arguing that it potentially reduces the peripheral visual field with no proven benefit.

Macular dragging was identified in 3 cases of AP-ROP. This condition prevents the normal development of the visual acuity by displacing the macula.

In all of our cases, the laser energy delivery was transpupillary. Laser energy can also be delivered through the sclera. The two delivery methods have the same efficacy, but the transscleral approach is more traumatic, although it has the advantage of decreasing the risk of cataract formation (by circumventing the lens). We had no case of cataract formation with the transpupillary laser delivery system in our series. If argon green light is used, the risk of burns to the tunica vasculosa lentis and the adjacent lens is higher than with the infrared diode laser because it is absorbed by blood vessels. The only complication related to the laser treatment in our series was the mild anterior uveitis noted in two cases of AP-ROP, provoked by the high degree of energy that was delivered into the eyes.

Individual Factors Associated With the Outcomes After Laser Therapy

Regression was noted in 128 of the 136 eyes treated by laser (94.11%) in stage 3 zones I and II ROP and 13 of the 24 eyes treated by laser (54.16%) in AP-ROP. The chi-square test proved that the outcome of the laser treatment was significantly worse in AP-ROP compared to the classic form of ROP. This observation was statistically significant.

Regression was achieved after one laser session in 126 of the 128 eyes (98.43%) with classic ROP, but in only 7 eyes (53.84%) with AP-ROP. Two laser sessions were required in 6 of the 13 eyes with regressed AP-ROP. In the AP-ROP cases, the difficulty comes from the fact that the laser treatment has to be performed immediately, before any ridge develops. Therefore, the absence of any landmark makes the laser photocoagulation difficult. The lack of macular development at this age adds more challenge to these cases.

It was reported that the male gender is associated with a higher morbidity and mortality rate related to prematurity. In this context, published data prove a higher rate of the visual impairment by ROP in males than in females. The basis for this finding is not decoded yet, but it is presumed to be related to the relative maturation of the lungs and central nervous system in boys. In our study, the male gender was not associated with a poorer outcome after the laser treatment for ROP.

Although low BW was reported to be a poor prognosis factor for ROP evolution, according to our results, the BW did not significantly influence the ROP regression rate.

Our results show that a gestation of more than 28 weeks was significantly associated with a lower ROP regression rate after the laser treatment (P = .02). Therefore, we cannot conclude that lower BW was associated with poorer outcomes after laser photocoagulation for ROP on our series.

Our results prove that the only factor that significantly influenced the results of the laser treatment was the ROP type. The results were significantly worse in AP-ROP compared to classic ROP. The overall ROP regression rate after transscleral photocoagulation was good in our series: 88.12%. However, the disappointing results of the laser ablation of the non-vascularized retina in AP-ROP motivated us to replace it by intravitreal injections with anti-VEGF agents. As such, during the past 4 years, we have performed intravitreal injections with anti-VEGF instead of the laser retinal ablation in AP-ROP.

REFERENCES


