Clinical features of infants treated for severe retinopathy of prematurity: 8-year study from a large tertiary neonatal intensive care unit in Turkey

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Background/aim: The aim of this study was to report the gestational age (GA) and birth weight (BW) distribution of premature babies who needed treatment for retinopathy of prematurity (ROP) and to assess the timing of the treatment.

Materials and methods: The records of 9008 infants who were screened for ROP were examined and 556 infants who underwent laser therapy for ROP were reviewed. Sex, GA, BW, postnatal age, and postmenstrual (PM) age at the time of laser therapy were recorded. The babies were classified as in-born (Group 1) and out-born infants (Group 2).

Results: The mean GA was 27.3 weeks (range: 22–33 weeks) and the mean BW was 991.1 g (range: 520–2160 g). Of the treated infants, 7.0% were born later than 32 weeks and 8.3% were born over 1500 g. The mean postnatal age was 9.48 weeks (range: 5–22 weeks) and the mean PM age was 36.72 weeks (range: 29–48 weeks) at the time of treatment. Mean BWs and GAs were significantly higher and the mean postnatal age at the time of laser therapy was significantly earlier in Group 2.

Conclusion: Infants with severe ROP had a wider range of BWs and GAs compared to those from developed countries and earlier treatment was needed for out-born infants.

Key words: Laser photocoagulation, retinopathy of prematurity, screening

1. Introduction
Advances in neonatal care and increasing survival rates have been associated with an increasing number of prematurely born infants. Retinopathy of prematurity (ROP) continues to be an important cause of childhood blindness all over the world. The clinical features of infants developing severe ROP vary among developed and developing countries (1–4).

Revised ROP screening guidelines by the American Academy of Ophthalmology, the American Academy of Pediatrics, and the American Association for Pediatric Ophthalmology and Strabismus suggest screening all infants with a birth weight (BW) of 1500 g or less and/or a gestational age (GA) of 30 weeks or less and selected infants with a BW between 1500 and 2000 g or a GA of over 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending neonatologist or pediatrician to be at high risk for ROP (5). The UK guideline recommends screening all infants with a GA of less than 30 weeks or with a BW of less than 1251 g (6). The recommended age for the initial ROP examination is 4–6 postnatal weeks or 31 PM weeks (5–7). These guidelines are based on studies that showed that the development of severe ROP requiring treatment is rare in infants with a BW over 1250 g and/or a GA greater than 31 weeks (5–8). In developing low- and middle-income countries, ROP has been reported in older and/or larger infants (9).

In this study, we had four objectives: to report the BW and GA distribution of premature infants who were treated with laser photocoagulation for severe ROP and to determine the population at risk for severe ROP in our country; to assess the timing of the treatment; to evaluate the appropriateness of the ROP screening criteria for our clinic, which is a referral center for ROP in our country; and to contribute to a subsequent metaanalysis.

2. Materials and methods
A hospital-based retrospective study of premature neonates who were screened for ROP between January 2006 and
December 2013 was conducted. The data were collected from prospectively completed ROP screening forms and retrospectively analyzed by the authors. All infants with a BW of 1500 g or less and/or a GA of 32 weeks or less, and selected infants with a BW of over 1500 g or a GA of more than 32 weeks with an unstable clinical course (as defined by the attending neonatologist or pediatrician), were screened. Infants with systemic anomalies and/or with ocular anomalies, such as microphthalmia, anophthalmia, coloboma, or congenital cataracts in one or both eyes, or those who died during the follow-up period or were unavailable for follow-up were excluded from the study.

The first examination was performed at 4 postnatal weeks for all infants and the infants continued to be monitored until complete retinal vascularization was reached.

The medical records of 9008 infants who underwent screening examination for ROP were reviewed and 556 patients who underwent laser photocoagulation therapy for severe ROP were examined in this study. Sex, BW, GA, postnatal age, and PM age at the time of treatment were analyzed. The need for treatment was based on the Early Treatment of ROP (ETROP) criteria and all infants underwent transpupillary laser photocoagulation therapy with an 810-nm diode laser delivered through the indirect ophthalmoscopic system under general anesthesia (8). The annual distribution of the patients was examined and changes according to years were evaluated. The treated patients were classified as in-born infants (Group 1: infants who were born in our hospital and who received treatment for ROP in our hospital) and out-born infants (Group 2: infants who were born at different centers and referred to our hospital for ROP treatment). The variables regarding BW, GA, PM, and postnatal age at the time of laser therapy were compared independently between these groups.

SPSS 16.0 was used for statistical analysis. Descriptive statistics were given as mean ± standard deviation (SD) and percentages. An independent sample t-test was used for comparisons between groups. P < 0.05 was considered significant.

The study was approved by the hospital ethics committee and informed written consent was obtained from the parents or guardians before enrollment. All works were conducted in accordance with the Declaration of Helsinki and with the approval of the institutional review board.

3. Results

Of the 9008 infants screened, 556 (6.2%) were treated with laser photocoagulation according to ETROP criteria. Of the 556 infants representing the original cohort, 396 (71%) infants were in Group 1 and 160 (29%) were in Group 2. The number of treatment-requiring severe ROP cases decreased from 6.2% to 4.5% when the infants in Group 2 were excluded.

Two hundred and sixty (46.8%) infants were female and 296 (53.2%) were male. The mean GA was 27.3 ± 2.5 weeks (range: 22–33 weeks) and the median GA was 27 weeks. The mean BW was 991.1 ± 314.7 g (range: 520–2160 g). Of the treated infants, 39 (7.0%) were born at a GA of 32 weeks and no infant was born later than 33 weeks. Forty-six infants (8.3%) were born over 1500 g and 20 (3.6%) over 1750 g. Only three infants had BWs over 2000 g and the highest BW was 2160 g. Tables 1 and 2 display the distribution of the treated infants according to BW and GA. The annual distributions of the examined and the treated infants are analyzed by the means of BW and GA in Table 3.

The mean postnatal age at the time of laser treatment was 9.48 ± 2.82 weeks (range: 5–22 weeks) and the mean PM age at the time of treatment was 36.72 ± 2.83 weeks (range: 29–48 weeks). Treatment was needed at 5 postnatal weeks for 14 infants (2.5%) and at 6 postnatal weeks for 66 (11.9%) infants. When we analyzed PM ages at the time of treatment, treatments were needed before 31 PM weeks for four infants. Eleven (2.0%) infants were over 42 PM weeks.

Table 1. The distribution of treated infants in relation to birth weight.

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>Number of treated infants</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;750</td>
<td>144</td>
<td>25.9</td>
</tr>
<tr>
<td>751–1000</td>
<td>202</td>
<td>36.3</td>
</tr>
<tr>
<td>1001–1250</td>
<td>120</td>
<td>21.6</td>
</tr>
<tr>
<td>1251–1500</td>
<td>44</td>
<td>7.9</td>
</tr>
<tr>
<td>1501–1750</td>
<td>26</td>
<td>4.7</td>
</tr>
<tr>
<td>&gt;1750</td>
<td>20</td>
<td>3.6</td>
</tr>
<tr>
<td>Total</td>
<td>556</td>
<td>100.0</td>
</tr>
</tbody>
</table>
old at the time of laser therapy and all except one were in Group 2. Ten of these later-treated babies were treated at 43 PM weeks and only 1 infant in Group 2 was treated at 48 PM weeks.

The mean BW and the mean GA were significantly higher in Group 2 and the mean postnatal age at the time of laser therapy was significantly earlier in Group 2. The PM age at the time of laser therapy did not differ between the two groups (Table 4).

4. Discussion

A third epidemic of ROP is now being experienced in developing countries with high preterm birth rates, where babies are exposed to risk factors that are largely well controlled in developed countries. Affected babies have a wider range of BWs and GAs compared to those from developed countries. There are great differences in the standard of care even in different neonatal intensive care units in the same country. Population-specific or even institution-specific criteria should be established for ROP screening to minimize the number of infants screened while missing no patient with ROP who requires treatment (1,9–15). Recent studies from Turkey indicated that first we need a national guideline for ROP screening and then we should discuss institution-specific screening criteria (1,9,15–17).

Our hospital, which has the largest neonatal intensive care unit in Turkey, is the referral center for central, east, and north Anatolia for high-risk pregnancies and preterm births, and our clinic is the ROP referral center for high-risk babies.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Number of treated infants</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26</td>
<td>134</td>
<td>24.1</td>
</tr>
<tr>
<td>26–28</td>
<td>269</td>
<td>48.4</td>
</tr>
<tr>
<td>29–31</td>
<td>112</td>
<td>20.1</td>
</tr>
<tr>
<td>≥32</td>
<td>41</td>
<td>7.4</td>
</tr>
<tr>
<td>Total</td>
<td>556</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2. The distribution of treated infants in relation to GA.

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of examined infants</th>
<th>Number of treated infants</th>
<th>% of treated infants</th>
<th>Mean GA ± SD (min–max) (weeks)</th>
<th>Mean BW ± SD (min–max) (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>927</td>
<td>32</td>
<td>3.5</td>
<td>28.8 ± 1.9 (26–32)</td>
<td>1231.2 ± 277.9 (900–1900)</td>
</tr>
<tr>
<td>2007</td>
<td>1056</td>
<td>26</td>
<td>2.5</td>
<td>28.8 ± 2.4 (26–33)</td>
<td>1265.0 ± 306.9 (850–1850)</td>
</tr>
<tr>
<td>2008</td>
<td>1027</td>
<td>34</td>
<td>3.3</td>
<td>27.8 ± 1.6 (26–31)</td>
<td>1047.6 ± 289.2 (760–1770)</td>
</tr>
<tr>
<td>2009</td>
<td>1117</td>
<td>132</td>
<td>11.8</td>
<td>27.5 ± 2.1 (24–32)</td>
<td>980.4 ± 263.7 (510–2030)</td>
</tr>
<tr>
<td>2010</td>
<td>1132</td>
<td>100</td>
<td>8.8</td>
<td>27.1 ± 2.6 (22–32)</td>
<td>926.5 ± 254.0 (550–1600)</td>
</tr>
<tr>
<td>2011</td>
<td>1237</td>
<td>74</td>
<td>6.0</td>
<td>26.5 ± 2.4 (23–33)</td>
<td>912.3 ± 245.1 (630–1700)</td>
</tr>
<tr>
<td>2012</td>
<td>1241</td>
<td>64</td>
<td>5.2</td>
<td>26.6 ± 2.3 (24–33)</td>
<td>978.7 ± 349.4 (520–1900)</td>
</tr>
<tr>
<td>2013</td>
<td>1271</td>
<td>94</td>
<td>7.4</td>
<td>26.9 ± 2.9 (22–33)</td>
<td>973.4 ± 409.8 (560–2160)</td>
</tr>
<tr>
<td>Total</td>
<td>9008</td>
<td>556</td>
<td>6.2</td>
<td>27.3 ± 2.5 (22–33)</td>
<td>991.1 ± 314.7 (510–2160)</td>
</tr>
</tbody>
</table>

Table 3. The annual distribution of infants in relation to GA and BW.
premature infants. In our study group, treatment-requiring severe ROP was determined in 6.2% of the overall infants and 4.5% in Group 1. In the previous studies from our country, the rates of severe ROP were 3.1%–11.5% (1,13–22). Our present study has the largest sample size among them and the study period was much longer. When we compared percentages with the data from other countries, we observed that our results were more compatible with the data from developed countries, but the BWs and GAs of screened infants were not the same in each study group. The incidence of treatment-requiring severe ROP has been reported as 1.8%–8.3% in the Netherlands, 1.3%–7.8% in the United States, 6.8% in China, 9.5% in Iran, 4.9% in Taiwan, 11.7% in Romania, 5.8% in Brazil, 6.4% in Saudi Arabia, and 6.7% in India (9–12,23–27).

We saw more infants requiring laser treatment in 2009 and 2010. Because our clinic was labeled a ROP referral and training center by the Ministry of Health in 2009, the numbers of Group 2 infants were higher in 2009 and 2010. Approximately two-thirds of the treated infants were referred from other hospitals in these years. After 2010, the number of ROP referral and training centers in Turkey increased, so the number of infants referred to our clinic began to decline.

It has been presented that the mean BW of infants with severe ROP is 750 g in developed countries and 1500 g in developing countries. Recent data from the United States, the United Kingdom, and Canada show that infants requiring treatment for ROP have a mean BW of 736 g (415–1255 g), 737 g (450–1260 g), and 759 g (440–1785 g) and a mean GA of 25.4 (23–29), 25.3 (23–32), and 25.6 weeks (22–32), respectively (28). Populations of babies with ROP in low- and middle-income countries are quite different from populations studied in high-income countries. Karkhaneh et al. from Iran reported that the frequency of severe ROP was 22.5% among babies who were born before 37 weeks’ GA and that babies with severe ROP had a mean GA of 28.8 ± 2.2 weeks and a mean BW of 1257 ± 348 g (29). In a multicenter study from China, the incidence of treatment-requiring ROP was 3.6% among babies with BWs less than 2000 g or GAs younger than 35 weeks; mean GAs and BWs of those babies were 30.2 ± 2.1 weeks and 1273.9 ± 263.5 g, respectively (30). In another study from Hong Kong, the incidence of Type 1 ROP in extremely low birth weight infants was 14.5% (31). In the present study, the mean GA of treated infants was 27.3 ± 2.5 weeks (22–33 weeks) and the mean BW was 991.1 ± 314.7 g (520–2160 g). These values were between the values of the industrialized countries and the developing countries and slightly better than the other developing countries (23–27).

As the years go by, we encounter smaller and more prematurely born infants with severe ROP, but we still continue to see treatment-requiring ROP in infants with BWs over 1500 g. Of the 556 treated babies, 7.4% had GAs over 31 weeks, but no infant had a GA greater than 33 weeks. Out of the treated infants, 8.3% had BWs over 1500 g; the highest BW of an infant with severe ROP was 2160 g. Mutlu et al. reported that the percentage of infants with BWs greater than 1500 g treated for ROP was 9.1% (15). In other studies from Turkey, while Sarikabadayi et al. and Alpay et al. reported that no infant born at a GA of older than 32 weeks needed treatment for ROP, Ugurbas et al. and Başmak et al. reported that the percentage of treated babies among infants born at a GA of 32 weeks or older was 9.6% and 9.3%, respectively (1,14,20,21). Similar findings were reported in studies from China, India, Iran, Saudi Arabia, Taiwan, Brazil, and Turkey, and it was recommended that larger infants be included in screening programs to avoid missing cases (9,10,17,24–27).

Globally, 6.2% (4.3%–8.9%) of all ROP visually impaired infants were born at a GA of 32 weeks (9). Several studies have shown that the screening criteria of developed countries are not adequate to identify all infants at risk of severe ROP requiring treatment in low- and middle-income countries (24–27). Gilbert et al. found that, overall,
13% of infants from several low- and middle-income countries would not have been examined if UK criteria had been applied (28). In China, Chen et al. showed that 16% of infants who needed treatment exceeded the UK criteria and 30% exceeded the US criteria (30). Jalali et al. from India reported that 13% of treated infants exceeded the US criteria (32). A study from Brazil confirmed that wider criteria were needed as well; 11% of treated infants exceeded the Western screening criteria (27).

In previous studies, it was reported that treatment for severe ROP was rarely required before 31 PM weeks. Mean PM age for treatment in high-income settings is 35.2 weeks (30.6–42.1 weeks) (8). Treatment might be carried out up to 51 PM weeks in some low-income settings because of delayed case detection (9). In the present study, the mean PM age at the time of treatment was 36.72 ± 2.83 weeks and it ranged between 29 and 48 weeks. This mean value is compatible with high-income settings, but the range of PM ages in our study group were as wide as in low-income settings.

The recommended time for the initial ROP examination is 4–6 postnatal weeks or 31 PM weeks in high-income settings (5–7). In this study, the treatments for ROP were required at 5 postnatal weeks in 14 infants (2.5%) and at 6 postnatal weeks in 66 (11.9%) infants. For four infants, treatments were needed before 31 PM weeks. We suggest that ROP screening programs should start at 4 postnatal weeks and not later than 5 postnatal weeks. It should not be postponed until 31 PM weeks because of infants who need treatment at an earlier age.

When we compared the infants in Group 1 and Group 2, we determined that the mean BW and the mean GA were significantly higher in Group 2 and the mean postnatal ages at the time of laser therapy were significantly younger in Group 2. These results may be related to unstandardized conditions of the neonatal intensive care units, such as unstandardized oxygen supplementation levels and the number of babies per nurse and per doctor (1,4,8,33–36). To evaluate these differences, future studies with expanded risk factors should be planned.

A major limitation of this long-term study was being based in a single center, but approximately 30% of the babies were infants referred from different neonatal intensive care units all over our country. We need multicenter trials to create a national ROP screening guideline. We believe that our long-term study, with its large number of infants, can contribute to this guideline.

This study has shown that larger infants in our country may need treatment for ROP. When we analyzed GA independently from other risk factors, no treatment was required for babies born at a GA of over 33 weeks. Treatment for ROP may be needed before 31 PM weeks and before 6 postnatal weeks for some premature babies. The screening criteria must be individualized for our country and a national guideline must be created for ROP screening with the guidance of large series and multicenter trials. A future prospective study with expanded screening criteria was planned to help create the national screening criteria. Screening the infants most at risk and timely treatment for ROP that progresses to a sight-threatening level must be the standard care to prevent serious visual disability.

References


