Screening for Retinopathy of Prematurity in a Tertiary Hospital in Istanbul: Incidence and Risk Factors

Aylin Ardagil Akçakaya, MD; Sevil Ari Yaylali, MD; Hasan Hasbi Erbil, MD; Fariz Sadigov, MD; Asiyé Aybar, MD; Nihat Aydin, MD; Güzide Akçay, MD; Hüseyin Acar, MD; Cem Mesçi, MD; Hüseyin Yetik, MD

ABSTRACT

Purpose: To study the incidence and risk factors of retinopathy of prematurity (ROP) in premature infants examined in a tertiary hospital in Istanbul.

Methods: Data of infants screened for ROP from April 2007 to September 2009 were retrospectively reviewed. Possible risk factors and eye examinations were record and analyzed using the chi-square test and univariate and multivariate regressions.

Results: ROP was detected in 177 (34.3%) of the 517 infants enrolled in the study; 64 had mild ROP (77.4%) and 38 had severe ROP (22.6%). The mean gestational age and birth weight of patients who were treated for ROP were 28.6 ± 2.3 and 1,143.5 ± 337.4, respectively. Two of these infants had a gestational age of 32 g or greater and three had a birth weight of 1,500 g or greater. The multivariate regression analyses showed gestational age, birth weight, sepsis, respiratory distress syndrome, and length of oxygen therapy as independent predictors of ROP.

Conclusion: The incidence of ROP observed in this study was higher than that in developed countries and relatively more mature infants were affected. Criteria including gestational age of less than 34 weeks or birth weight of less than 2,000 g would have identified all infants who were at risk.

INTRODUCTION

Retinopathy of prematurity (ROP) is the primary cause of visual impairment in premature infants. The proportion of blindness as a result of ROP varies greatly among countries, being influenced by both levels of neonatal care and the availability of effective screening and treatment programs. It was demonstrated that larger and more mature infants are developing severe ROP in countries with low or moderate levels of development compared with highly developed countries.

Increased awareness of the risk of blindness among premature infants has led to expansion of ROP programs in Turkey. No official screening guidelines have been established in our country and most ophthalmologists use broad criteria to include all premature infants who are at risk.

Factors demonstrated to be associated with an increased risk of the development of ROP are short gestational period and low birth weight, sepsis, intraventricular hemorrhage, blood transfusions, and...
The current study was undertaken to explore the possible risk factors associated with ROP, to estimate the number of premature infants at risk, and to ascertain the current screening practices for ROP and the findings of screening in our population.

**PATIENTS AND METHODS**

This study was conducted in the Eye Clinic of Göztepe Training and Research Hospital from April 2007 to September 2009 on premature infants who were screened for ROP here. The study included both infants born in the neonatal intensive care unit (NICU) of the same hospital and also infants referred for screening from other centers in Istanbul.

We included all infants with a gestational age of less than 37 weeks so as not to miss any infants who were at risk. Neonates who had insufficiently documented records and those who did not complete the follow-up were excluded.

All examinations were performed by two retina specialists. The first examination was performed at 31 weeks’ postmenstrual age or 4 weeks after birth, whichever was later. Pupils were dilated with tropicamide 0.5% and phenylephrine 1% half an hour before the examination. Indirect ophthalmoscopy was performed using a speculum and scleral indentation after topical anesthesia. Follow-up examinations were done every 1 to 2 weeks after the first evaluation and continued until ROP regressed, the retina was fully vascularized, or the disease progressed to threshold ROP requiring laser therapy.

The staging of ROP was recorded according to the revised International Classification of ROP, including the extent, zone, and presence or absence of “plus” disease.

Data on birth weight, gestational age, gender, phototherapy, blood transfusion, sepsis (culture proven), mechanical ventilation, total number of days receiving oxygen therapy, necrotizing enterocolitis, respiratory distress, and hyperbilirubinemia (defined as total serum bilirubin concentration > 15 mg/dL) were extracted from the patients’ records.

Univariate analysis was used to explore variables associated with ROP, and those found to be significant were included in a logistic regression model using a backward stepwise model.

**RESULTS**

A total of 620 premature infants were examined in the Ophthalmology Clinic of Göztepe Training and Research Hospital during the study period. Of these, 103 neonates did not satisfy the inclusion criteria and 517 infants were enrolled in the current study, 51.3% of whom were male.

The mean gestational age at birth was 32.5 weeks (range: 22 to 38 weeks), and the mean birth weight was 1,886.3 g (range: 560 to 4,100 g) (Tables 1 and 2). Any stage of ROP was detected in 177 (34.2%) of the infants. The mean gestational age of patients with ROP was 30.9 ± 2.9 weeks and the mean birth weight was 1,549.4 ± 512.9 g.

Of the neonates with retinopathy of prematurity, 77.4% had mild ROP (64 in stage I, 31 in stage II) and 22.6% had severe ROP (35 in stage III, 3 in stage IV).

Of the 35 patients in stage III, 8 improved without treatment, 20 improved with argon laser photocoagulation, and 7 progressed to stage IV despite treatment. Only 4 of the infants who developed severe ROP were observed in the NICU of our hospital. All of them were treated with argon laser photocoagulation and improved after the treatment.

The mean gestational age and birth weight of patients who were treated for ROP were 28.6 ± 2.3 weeks and 1,143.5 ± 337.4 g, respectively. Two of these infants had a gestational age of 32 weeks or
greater and 3 had a birth weight of 1,500 g or greater. Of the 3 infants treated for ROP with a birth weight of 1,500 g or greater, 2 had a history of respiratory distress syndrome and mechanical ventilation, but the third infant was determined to be clinically stable by the attending neonatologist.

Threshold disease was diagnosed at a median of 35.9 ± 1.6 weeks (range: 33 to 39 weeks).

The difference between infants with ROP and infants without ROP for gestational age, birth weight, and length of oxygen therapy were statistically significant (P < .0001 for all). The roles of gender, phototherapy, blood transfusion, sepsis, mechanical ventilation, necrotizing enterocolitis, respiratory distress, and hyperbilirubinemia as risk factors for ROP were assessed by chi-square test. The analyses showed a significant relationship between ROP and blood transfusion, sepsis, respiratory distress, and mechanical ventilation. These risk factors together with gestational age, birth weight, and length of oxygen therapy were entered into multivariate logistic regression analyses in which five variables were identified as significant independent risk factors for development of retinopathy of prematurity (P < .05).

**DISCUSSION**

ROP is emerging as a major cause of blindness in moderately developed countries. More information on the population of infants who develop treatable ROP is required from these regions to develop screening programs that include all premature infants who are at risk.

The incidence of ROP in our study population was 34%. This is within the range of the incidences reported in previous studies from Turkey (33.4% to 37.1%). In the infants with a gestational age of 32 weeks or less, the ROP incidence in our study was 52.7%, which was close to the reported incidence from another center in Turkey (50.9%). When compared to other developing countries, this incidence was similar to Iran (47.3%) but higher than India (31.2%), and also higher than the incidences of developed countries such as the United Kingdom (31.2%), France (22.3%), and Sweden (25.5%). In the infants with a birth weight of 1,000 g or less, the ROP incidence in our study population was 75.6%, whereas it was 49.4% in Iran and 48.9% in Brazil. In the infants with a birth weight of 1,500 g or less, the ROP incidence in our study population was 61.8%, whereas it was 33.3% in Iran and 29.2% in Singapore.

The percentage of the infants with a gestational age of 32 weeks or less who required treatment or progressed to stages 4 and 5 was 11.1%, which was higher than the 7.4% in India, 8.2% in Sweden, 5.9% in Brazil, and 4.9% in Singapore. It was similar to the 11.8% reported in 2010 from another tertiary center in Turkey. Three of the infants who required treatment exceeded the screening criteria for ROP currently recommended by the American Academy of Pediatrics (gestational age < 32 weeks and birth weight < 1,500 g). Criteria of gestational age less than 34 weeks or birth weight less than 2,000 g would have identified all infants who required treatment in our study. Broadening of the criteria will increase the number of infants who need

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>0.904</td>
<td>0.816 - 1.001</td>
<td>.049</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>0.999</td>
<td>0.998 - 0.999</td>
<td>.0001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.285</td>
<td>0.135 - 0.603</td>
<td>.001</td>
</tr>
<tr>
<td>O₂ therapy (d)</td>
<td>1.015</td>
<td>0.999 - 1.031</td>
<td>.05</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>0.497</td>
<td>0.326 - 0.759</td>
<td>.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.159</td>
<td>0.729 - 1.843</td>
<td>.533</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0.651</td>
<td>0.333 - 1.274</td>
<td>.211</td>
</tr>
</tbody>
</table>

*a Gestational age, birth weight, sepsis, length of oxygen therapy, and respiratory distress syndrome were identified as independent risk factors for development of retinopathy of prematurity (P < .05).
examination, but more mature infants frequently need fewer examinations and most infants with a gestational age of more than 32 weeks are likely to need only one examination.\(^2\)

One reason for the high ROP incidence and higher treatment rates may be the variation in case mix. We included not only the infants from our NICU but also infants referred from other centers and other cities for ROP screening; some of the infants were already diagnosed as having ROP and referred for follow-up and treatment to our center.

Another possibility is that Turkey is experiencing an epidemic of ROP. Turkey is a country with a high birth rate. Approximately 1.3 million infants are born each year, 86,000 of whom are premature. The neonatal care in Turkey is expanding and improving, which has resulted in increased survival of premature infants with a more complicated course. The survival rate of very low birth weight infants (birth weight < 1,500 g) was estimated to be 73% in 2008 in a study conducted in 32 NICUs throughout Turkey.\(^18\) Unfortunately, national guidelines on oxygenation policies have not yet been developed. More conservative use of supplemental oxygen and meticulous monitoring of blood oxygen levels are probably the most important factors that are responsible for the lower risk in more mature infants in developed countries.\(^2\) The characteristics of infants with ROP requiring treatment may vary considerably from unit to unit. Chen et al. reported that infants in China referred for ROP treatment from level 2 NICUs are more mature than infants cared for in level 3 NICUs.\(^17\) We also had a similar impression for our study population.

Our data suggest that this epidemic is similar to the epidemic of ROP described in the middle-income countries of Latin America. In these countries, the epidemic has been described as the “third epidemic” because the population of infants affected has the characteristics of both the “first epidemic” (inadequately monitored oxygen) and “second epidemic” (extreme prematurity). Of the infants who developed severe ROP in our study, 72% were infants with very low birth weight (birth weight < 1,500 g) and 29% had a birth weight of less than 1,000 g. The mean gestational age and birth weight of the infants who were treated for ROP were 28.6 ± 2.3 weeks and 1,143.5 ± 337.4 g, respectively. These data are also within the range of the mean gestational age and birth weight of infants with severe ROP from the countries affected by the “third ROP epidemic” (gestational age: 26.3 to 33.5 and birth weight: 903 to 1,527 g, respectively).

Multivariate logistic regression analyses demonstrated that birth weight, gestational age, sepsis, respiratory distress, and length of oxygen therapy were independent risk factors associated with ROP. Another study in Turkey additionally defined bronchopulmonary dysplasia as a risk factor, but the authors did not perform multivariate analyses.\(^9\) The measure of immaturity as a predictor for ROP and the role of oxygen therapy have been reported many times in the literature.\(^3,5,8,9,19\) In addition, a study demonstrated that neonatal sepsis, oxygen exposure, and low gestational age are not only independently associated with a significantly increased risk of ROP, but also interact beyond additive and even multiplicative patterns.\(^20\)

ROP accounts for up to 60% of blindness in moderately developed countries. The high incidence of infants with severe ROP in our study calls for aggressive measures for prevention and control of the disease. Ophthalmologists and neonatologists should work together so that comprehensive screening programs can be instituted in all units that admit high-risk infants. Guidelines for infant care in NICUs also need to be addressed, including tighter control and monitoring of supplemental oxygen to reduce the number of infants developing severe ROP. Increasing the awareness of the disease among the general population will also increase the compliance of the parents when treatment or prolonged follow-up are required.

---

REFERENCES

7. The International Committee for the Classification of the Late


