Abstract

Background. Retinopathy of prematurity (ROP) is an alteration in the development of the vessels of the retina, with an incidence ranging from 12 to 78%. We undertook this study to determine risk factors associated with ROP in a group of premature infants.

Methods. This is a retrospective and comparative study in search of risk factors for ROP, reviewing the records of infants weighing <1500 g or gestational age ≤30 weeks admitted to the Neonatology Department. We carried out an ophthalmoscopy study at 4 weeks of age and then weekly until hospital discharge. We compared the group with and without retinopathy. Variables registered were birth weight, gestational age, oxygen exposure, total parenteral nutrition, antibiotics, lung disease, severe perinatal asphyxia, peri-intraventricular hemorrhage, septicemia, hyperbilirubinemia, bronchopulmonary dysplasia and red blood cell transfusion. Comparative analysis was carried out by ANOVA and logistic regression by calculating odds ratios (OR) and 95% confidence interval (95% CI).

Results. We reviewed the clinical files of 112 infants with ROP and 95 infants without ROP. According to gender ratio, birth weight, gestational age, mechanical ventilation and days with ventilation, there was no significant difference. Risk factors were antibiotics (OR 2.36, 95% CI 1.22-4.59), erythrocyte transfusion (OR 2.99, 95% CI 1.50-5.99), total parenteral nutrition (OR 3.20, 95% CI 1.63-6.25), and sepsis (OR 1.83, 95% CI 1.01-3.34).

Conclusions. ROP was present mainly in infants with very serious disease and risk factors were antibiotics, erythrocyte transfusion, total parenteral nutrition and sepsis.

Key words: retinopathy of prematurity, premature infants, ophthalmoscopy, erythrocyte transfusion.
Introduction

Retinopathy of prematurity (ROP) is an alteration in the development of retinal vessels. Overall incidence ranges from 12-78% and the condition has been reported at any stage in newborns with a birth weight <1500 g. Approximately 8-42% of patients affected with ROP progress to scarring with blindness, especially in those newborns weighing <1000 g. In a pilot study in Mexico, ROP was found in 28% of 57 infants weighing <1500 g at birth. Other hospitals have reported a rate of 23-26%. An increase in frequency has been observed because survival of preterm infants is increasing.

In Germany, ~400-600 children per year progress to blindness from ROP, which represents 20% of blindness in preschool children. In the U.S., it is estimated that out of 28,000 newborns weighing <2000 g, 16,000 will suffer some degree of retinopathy and, of these, 1500 will experience a severe form of the disease requiring surgical treatment. To stage this disease nosologically, currently the International Classification of Retinopathy of Prematurity (ICROP) is utilized.

Different risk factors have been determined that intervene in the development of this disease such as extreme prematurity, high concentrations of oxygen, mechanical ventilation, anemia, hyperemia, blood transfusions, etc. Physiologically, during the embryonic stage, the retina is avascular at up to 16 weeks of gestation, beginning with the formation of blood vessels in response to an unknown stimulus. Spindle cells of the optic nerve are the precursors of the retinal vascular system, with a fine capillary network that advances through the retina to the ora serrata, or retinal border, and ends in the nasal border at the eighth month of gestation and in the temporal border at 9 months. Once it is fully vascularized, it is not susceptible to the type of lesions that lead to ROP. In premature infants, normal growth may be altered, resulting in abnormal vessels. There are two stages in the development of ROP: 1) vasoconstriction and early obliteration of the capillary network in response to certain risk factors such as systemic exposure to high concentrations of oxygen, 2) vasoproliferation, in response to an angiogenic factor released by the hypoxic retina, producing a neovascularization that extends into the vitreous causing bleeding, fibrosis, traction and even retinal detachment. The latter change is reflected clinically in permanent blindness. Generally, the process is reversed before the occurrence of fibrosis, possibly because of reduced exposure to risk factors. A smaller number of cases result in late stages. The goal of this study was to determine, in our clinical environment, which risk factors are involved in a group of infants with ROP.

Patients and Methods

This is a retrospective and comparative study to determine risk factors for ROP. A review of the clinical records of all infants with birth weight <1500 g or gestational age ≤30 weeks was carried out. Infants were hospitalized in the Department of Neonatology of the Hospital General Dr. Manuel Gea Gonzalez during the period from January 2002 to December 2005 and underwent ophthalmoscopy at 4 weeks and then weekly until hospital discharge.

Those infants who had ROP to any degree constituted the case group. Those infants with stage 3 or threshold were treated with cryotherapy, and those infants in stage 1 or 2 were managed with weekly ophthalmological monitoring until discharge. The control group consisted of infants without ROP. The two groups were exposed to one or more risk factors. Ophthalmoscopy was performed by an ophthalmologist who was an expert in retinal examination and was performed with an indirect binocular ophthalmoscope with scleral indentation. We excluded infants who died before ophthalmoscopy or those who were transferred to another hospital for any reasons. Variables analyzed were birth weight, gestational age, exposure to oxygen, parenteral nutrition, antibiotics, lung disease, severe perinatal asphyxia, intraventricular hemorrhage, sepsis, hyperbilirubinemia, bronchopulmonary dysplasia and blood transfusion. A comparative analysis was performed using Student’s t-test for normally distributed continuous variables and χ² test for categorical variables. For all variables we calculated the risk for ROP, obtaining odds ratio (OR) and confidence intervals at 95% (95% CI) by logistic regression analysis and ANOVA; p ≤0.05 was considered statistically significant.

Results

During the study period, 352 infants were born with birth weight <1500 g; 145 were excluded due to death prior to their ophthalmoscopy or due to having been transferred to another hospital. The total sample was 207 infants and, of these, 112 infants presented ROP compared with the remaining 95 infants who did not
develop the condition. Prevalence of ROP during that time period was 54.1% in the 207 infants studied. In the ROP group, 46 were males and 66 females (ratio 1:1.4.), whereas in the control group 39 were male and 56 female (ratio 1:1.4). No statistical difference was reported for either group. As for other parameters, there were no differences in weight and gestational age, demonstrating the homogeneity of both groups (1246 ± 203 vs. 1244 ± 179 g, p = 0.90 and gestational age 29 ± 0.6 vs. 29 ± 0.6 weeks, p = 0.44). All patients received oxygen in different forms. There was no difference between those who required mechanical ventilation or those who had 10 days or more of endotracheal intubation for ventilatory support. It was not possible to determine the highest concentrations of arterial pressures of oxygen. In comparative analysis, variables with significant difference and which, therefore, can be considered as risk factors were antibiotics, transfusion of packed red blood cells, parenteral nutrition and sepsis. Intracranial hemorrhage also showed a significant difference but was more frequent in the control group (Table 1). When performing a stratified analysis of the number of RBC transfusions, we found that a greater number of transfusions did not increase the risk of ROP. In contrast, fewer transfusions increased the risk, although not significantly (Table 2). Other variables analyzed had no significant difference.

### Discussion

ROP is a disease whose prevalence is increasing due to the increasing greater survival of premature infants. In this study, prevalence was higher in relation to other studies (54.1%). However, it should be noted that all stages of RP were included and that screening was performed by ophthalmologists with expertise in retinal examination. We found several risk factors that reflect a multifactorial etiology.

### Table 1. Statistical analysis of the risk factors for ROP

<table>
<thead>
<tr>
<th>Variable</th>
<th>ROP No. (%)</th>
<th>Without ROP No. (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean</td>
<td>90 (80.3)</td>
<td>76 (80)</td>
<td>1.02</td>
<td>0.49-2.14</td>
<td>0.94</td>
</tr>
<tr>
<td>Partum</td>
<td>22 (19.6)</td>
<td>19 (20)</td>
<td>0.98</td>
<td>0.47-2.05</td>
<td>0.98</td>
</tr>
<tr>
<td>Gestation</td>
<td>95 (84.8)</td>
<td>82 (86.3)</td>
<td>0.89</td>
<td>0.38-2.06</td>
<td>0.76</td>
</tr>
<tr>
<td>FiO₂, 100%</td>
<td>67 (59.8)</td>
<td>49 (59.5)</td>
<td>1.40</td>
<td>0.78-2.52</td>
<td>0.23</td>
</tr>
<tr>
<td>&gt;10 days intubation</td>
<td>66 (58.9)</td>
<td>57 (60)</td>
<td>0.96</td>
<td>0.53-1.73</td>
<td>0.87</td>
</tr>
<tr>
<td>PIP &gt;17 cm H₂O</td>
<td>68 (60.7)</td>
<td>67 (70.5)</td>
<td>0.65</td>
<td>0.35-1.20</td>
<td>0.14</td>
</tr>
<tr>
<td>Cycles &gt;60 x min</td>
<td>78 (69.6)</td>
<td>64 (67.3)</td>
<td>1.11</td>
<td>0.59-2.09</td>
<td>0.72</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>16 (14.2)</td>
<td>18 (18.9)</td>
<td>0.71</td>
<td>0.32-1.58</td>
<td>0.36</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>89 (79.4)</td>
<td>59 (62.1)</td>
<td>2.36</td>
<td>1.22-4.59</td>
<td>0.005</td>
</tr>
</tbody>
</table>

ROP, retinopathy of prematurity; OR, odds ratio; 95% CI, 95% confidence interval; FiO₂, inspired fraction of oxygen; PIP, inspiratory peak pressure; TPN, total parenteral nutrition.

*ANOVA.

### Table 2. ROP: comparative table of the number of transfusions of erythrocytes

<table>
<thead>
<tr>
<th>No. of transfusions</th>
<th>ROP</th>
<th>W/ROP</th>
<th>OR</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4</td>
<td>22</td>
<td>10</td>
<td>2.08</td>
<td>0.88-5.20</td>
<td>0.07</td>
</tr>
<tr>
<td>5-7</td>
<td>58</td>
<td>42</td>
<td>1.36</td>
<td>0.75-2.44</td>
<td>0.27</td>
</tr>
<tr>
<td>&gt;8</td>
<td>13</td>
<td>7</td>
<td>1.65</td>
<td>0.58-4.82</td>
<td>0.30</td>
</tr>
<tr>
<td>Without transfusions</td>
<td>19</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ROP, retinopathy of prematurity; OR, odds ratio; 95% CI, 95% confidence interval. *ANOVA.
In the current study, antibiotics, red blood cell transfusion, parenteral nutrition and sepsis were risk factors.

RBC transfusion is evident as a risk factor; however, on performing a stratified analysis by number of transfusions, it was found that the risk disappears with a greater number of transfusions. It is possible that only one transfusion may have caused the damage.

Currently, research has shown that fetal hemoglobin, unlike in the adult, has a higher affinity for oxygen. Red cell transfusions in neonates are from adult donors, which increases the circulating free oxygen. In addition, free iron in plasma not bound to transferrin is significantly increased after transfusion and remains partially in the ferrous form due to low ferroxidase activity with a reduction of ferric iron by ascorbic acid action. Free iron can catalyze the generation of reactive-oxygen species, which may be responsible for retinal damage. Also, an increase in the levels of serum growth factor has been found, similar to insulin, because the amount that exists in the transfused blood is too high for the infant who receives it. Sepsis, as a risk factor, generates a systemic inflammatory response and possibly an alteration in the production of vascular endothelial growth factor that alters the neovascularization of the retina. This has not been completely proven. In regard to total parenteral nutrition, it has been mentioned that early administration of lipids may exacerbate the production of a growth factor precursor, similar to insulin, but this is still under investigation. Because several factors were involved, this may reflect that the newborns with ROP were sicker and, therefore, required more therapeutic procedures. It has been found that hemodynamic instability is also a risk factor, a variable not analyzed in this study. Results were inconclusive in this regard. Risk factors revealed in this study are similar to what has been previously reported in a pilot study. Intracranial hemorrhage was also associated with ROP in previous studies, although in the current study it predominated in the group without ROP. Some of the risk factors found are part of the therapeutic arsenal of the neonatologist for the full management of these patients and cannot be avoided, but their proper use should be emphasized in order to prevent abuse. An example is red blood cell transfusions when an arbitrary parameter becomes “routine” as an indication for this procedure, for example, hematocrit <40%. It is necessary to individualize each case and evaluate the risk/benefit associated with each therapeutic action.

Some of these actions are not well founded. Evidence-based medicine has tried to modify but has not been entirely successful. At times, “minimum” management benefits the premature infant more than “therapeutic modes” or “extraordinary treatments.”

Finally, neonatologists or pediatricians who manage preterm infants must be aware of this condition. They must ensure evaluation by an ophthalmologist, and a review of the retina should be done at the end of the first month of life in order to detect and provide timely ROP treatment when necessary.

However, not all ophthalmologists are trained to assess the retina of premature infants. For this reason, a national training program is being organized in Mexico aimed at these specialists as well as for neonatologists. ROP screening should be performed for all at-risk infants.

In conclusion, ROP in premature infants is a serious condition and is associated with various risk factors. The study of each of these factors separately will determine which are more important for its pathogenesis.

References


