Risk factors and laser therapy for retinopathy of prematurity in neonatal intensive care unit

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Background: **With the increasing survival rates of preterm infants, the incidence of retinopathy of prematurity (ROP) is also increasing. This study aimed to investigate the risk factors for ROP in Neonatal Intensive Care Unit, and the effects of laser therapy.**

Methods: **Thirty-five premature infants with various other diseases were studied. Data were collected including gender, gestational age, birth weight, maternal gravidity, Apgar score, antenatal and postnatal hypoxia, anemia, jaundice, infection, pregnancy complications, and head ultrasound manifestations. All patients were subjected to fundus examinations at a postmenstrual age of 34 weeks using an indirect ophthalmoscope. The infants were divided into ROP group and non-ROP group. Infants with ROP received laser treatment. The data of the infants were analyzed using univariate analysis and the logistic regression model.**

Results: **Twenty-seven (77.1%) of the 35 infants had ROP and 21 of them also had plus diseases. The recovery rates were 74.1% and 92.6% at 2 weeks and 3 months after laser therapy, respectively. The birth weight and gestational age in the ROP group were significantly lower than those in the non-ROP group ($P<0.01$). The lower the gestational age and birth weight, the higher the incidence of ROP. There was a significant difference in the incidence of ROP with postnatal hypoxia ($P=0.013$), anemia ($P=0.012$) and gravidity two ($P<0.05$), analyzed with the Fisher's exact probability test ($P<0.05$). The gestational age was significantly lower in the plus disease group than in the non-plus disease group ($P<0.05$).**

Conclusions: **The incidence of ROP is high in premature infants with various other diseases and is correlated with birth weight, gestational age, postnatal hypoxia, anemia and maternal gravidity. Laser therapy shows good outcomes.**

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Key words: **laser therapy;**
premature infant;
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Introduction

Retinopathy of prematurity (ROP) is retrolental fibroplasia because of maldevelopment of retinal vessels, i.e., proliferation of retinal vessels and fibrous tissues, leading to traction detachment of the retina in preterm infants. With the increasing survival rates of preterm infants, the incidence of ROP is also increasing. The incidence of ROP was reported to be related to gestational age and birth weight (27.3% if <1200 g, 20.3% if <1500 g).[1] We observed 35 preterm infants with various other diseases to determine the risk factors for ROP and to investigate the effect of laser therapy on ROP.

Methods

Patients

Thirty-five premature infants with various other diseases were treated in the Neonatal Intensive Care Unit of Pediatric Department of Institute for Mother and Child Care (IOMC), Bucharest Medical University, Romania from September 2003 to August 2004. Of the 35 infants, 24 had antenatal hypoxia (12 asphyxia, 6 respiratory distress syndrome, 3 dyspnea, 1 asphyxia associated with apnea, 1 respiratory distress syndrome associated with apnea, and 1 respiratory distress syndrome associated with asphyxia), 19 had postnatal hypoxia (6 persistent postnatal dyspnea, 9 respiratory

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distress or asphyxia, and 4 treated with mechanical ventilatory assistance), 14 had anemia (9 treated with blood transfusion), 9 had jaundice, 12 had infection (3 septicemia, 5 neonatal pneumonia, 1 urinary infection, 1 necrotizing enterocolitis, 1 anemia of infection, and 1 skin infection), 3 had intracranial hemorrhage, 5 had ventriculomegaly, and 11 had intracranial hemorrhage associated with ventriculomegaly on head ultrasound. The mothers of 13 infants had complications during pregnancy (1 had decreased amniotic fluid, 3 had abnormal uterine contractions, 5 had hemorrhage, 2 had cervical transfixion, and 2 had a history of fetal death). Birth weight of the infants ranged from 700 g to 2400 g. The infants were divided into ROP and non-ROP groups, and into plus disease and non-plus disease groups.

According to the international classification of ROP, the process can be divided into 5 stages.[2]

Therapy and follow-up

Fundus examination was undertaken for all infants at the 34 weeks' corrected gestational age using an indirect ophthalmoscope in a dark room. Twenty-seven infants were diagnosed with ROP, and 25 of them were treated with the diode "Idiris" (Quantel) laser photocoagulation machine. 0.5% tropicamide (or 0.5% cyclopen) and 2.5% phenylephrine were used for mydriasis, and 2.5% proxymetacaine hydrochloride was used for local anesthesia. An average of 1287±641 light spots per eye was applied, with an exposure time of 0.1 to 0.3 second and an average power of 425 mW (200-700 mW). Data collected included changes in the eyes, and intracranial hemorrhage or ventriculomegaly on ultrasound.

Threshold ROP was defined as stage 3+ in zone I and zone II involving 5 contiguous hours or 8 noncontiguous hours. If plus disease still existed in the untreated area 7-14 days after the first treatment, and progressive proliferation of the outer retinal fibrous vessels was found near the untreated area, the therapy was repeated.

The first examination was undertaken 7 days after laser therapy; the second treatment (if necessary) was undertaken 14 days after laser therapy, and the infants were followed up for another 3 months. Eye condition of the infants and head ultrasound results were reassessed at the second week and the third month after treatment. Characteristics such as gender, gestational age, birth weight, laser therapy procedures, and associated diseases were recorded.

Statistical analysis

All the data were analyzed with SPSS13.0 and STATA8.0, using the Chi-square test, rank-order test, Fisher's exact test and logistic regression (α=0.05).

Results

Risk factors for ROP

Twenty-seven (77.1%) of the 35 infants had ROP. Among them, no infants were diagnosed in stage 1, 4 (14.8%) in stage 2, 23 (85.2%) in stage 3, and 0 in stage 4 and 5. The postmenstrual age at diagnosis ranged from 32 weeks to 52 weeks. Tables 1 and 2 show the relationship between ROP and risk factors including gender, birth weight, gestational age, Apgar score (1 and 5 minutes), infection, jaundice, anemia, antenatal and postnatal hypoxia, head ultrasound results, labor, pregnancy complications, and maternal gravidity. Abnormal findings on head ultrasound included eye changes, ventriculomegaly and intracranial hemorrhage.

The data analyzed with Student's *t* test showed that birth weight was significantly lower in the ROP group than in the non-ROP group (t=4.658, P<0.01), and gestational age was significantly lower in the ROP group than in the non-ROP group (t=3.386, P<0.01). The Chi-square test showed that the lower the gestational age and birth weight, the higher the incidence of ROP (Table 3).

Anemia and postnatal hypoxia were the other two risk factors associated with ROP. In our study, all 14 infants (100%) with different levels of anemia had ROP. Of the other 21 infants without anemia, 13 (61.9%) had ROP. Of the 19 infants with postnatal hypoxia, 18 (94.7%) had ROP, while 9 (56.3%) of 16 infants without postnatal hypoxia had ROP. The data which were analyzed using Fisher's exact test (P<0.05) indicated a significant relationship between ROP and anemia (P=0.012) and postnatal hypoxia (P=0.013).

Multiple factor logistic regression was used to analyze the risk factors. Birth weight and postnatal hypoxia were found to be closely correlated with ROP (birth weight: β=-3.212, OR=0.995, P=0.039; postnatal hypoxia: β=4.209, OR=7.162, P=0.090).

The incidence of ROP in the gravidity two group was significantly higher than in the other groups (Fisher's exact test, P<0.05). There was no significant difference in gender, pregnancy complications, jaundice, hypoxia (Chi-square test, P>0.05) or Apgar score (rank-sum test, P>0.05) between the ROP group and the non-ROP group.

Risk factors for plus disease

The risk factors for plus disease were the same as those for ROP. Twenty-one (60%) of the 35 premature infants had plus diseases. Student's *t* test showed that the gestational age was significantly lower in the plus disease group (29.00±2.57 weeks) than in the non-plus disease group (31.00±3.03 weeks, t=2.177, P<0.05).

Head ultrasound

B-ultrasound showed the infants with ROP had no abnormality of eyes. Head ultrasound through the anterior fontanelle detected intracranial hemorrhage in 3 infants (8.6%), ventriculomegaly in 5 (14.3%), and intracranial hemorrhage associated with ventriculomegaly in 11 (31.4%). These results were not statistically correlated with ROP (P>0.05).

Complications and follow-up

Complications of treatment included palpebral edema in most infants, corneal opacity in 1 infant, preretinal hemorrhages in 2, and vitreous hemorrhage in 1 infant. The ROP infants were followed up at the second week and third month after therapy, with the recovery rates of 74.1% and 92.6% respectively. One infant died of severe pneumonia at one month after therapy, 2 had a bit of scar tissue on their eyeground at the second follow-up, and 4 had a retreatment. Of these infants, 1 had ROP of stage 3, 2 stage 3+, and 1 stage 3+ with purulent conjunctivitis. All of them recovered completely after the second treatment.

Table 1. Retinopathy of prematurity (ROP) and risk factors

Group (mean±SD)	Birth weight (g)*	Gestational age (wk)	Apgar score	
			1 min	5 min
Non-ROP (n=8)	1743.75±423.79	32.50±1.85	5.88±3.31	8.75±2.31
ROP (n=27)	1144.81±284.83	29.04±2.70	5.89±2.61	8.52±2.21

*: P<0.01.

Table 2. Retinopathy of prematurity (ROP) and risk factors

Characteristics	Non-ROP group	ROP group	Total
Gender			
Male	6	15	21
Female	4	10	14
Anemia*	0	14	14
Antenatal hypoxia	6	18	24
Postnatal hypoxia*	1	18	19
Jaundice	0	9	9
Infection	3	9	12
Abnormal ultrasound	6	13	19
Pregnancy complications	2	11	13
Delivery			
Eutocia	7	16	23
Dystocia	1	3	4
Operative delivery (forceps, vacuum, cesarean)	0	8	8
Gravidity			
One	1	9	10
Two*	2	11	13

*: P<0.05.

Table 3. The relations of retinopathy of prematurity (ROP) with birth weight and gestational age

	All infants (n=35)	Infants with ROP	ROP incidence (%)
Birth weight (g)*			
<1000	9	9	100.0
1000-1499	17	15	88.2
≥1500	9	3	33.3
Gestational age (wk)†			
23-28	10	10	100.0
29-31	14	12	85.7
32-36	11	5	45.5

*: χ^2=11.019, P=0.001; †: χ^2=10.987, P=0.004.

Discussion

ROP is a severe oculopathy which can result in blindness and other complications including strabismus, myopia, amblyopia and glaucoma.

The data of this study showed that the incidence of ROP in premature infants was 77.1%, notably higher than the general incidence rate of 11%-60%.[1,3-6] This may be related to an unstable blood environment including temperature and blood pressure fluctuations, glycopenia, acidosis, electrolyte disturbances and deficiency of anti-oxidants. The high incidence rate might be due to that the hospital is the national center for diagnosis and treatment of ROP, where an international ROP cooperation project has been going on. Most of high-risk premature infants with ROP came to this hospital.

Besides birth weight and gestational age, postnatal hypoxia, frequent oxygen administration (including improper use) and anemia were also closely related to ROP. The lower the birth weight and gestational age, the more severe the postnatal hypoxia and the more frequent the use of oxygen, the higher the incidence of ROP, which further confirms the findings reported.[3-9] Our study shows that anemia is correlated with ROP because anemia may increase the tissue hypoxia and oxygen consumption of patients, and because frequent blood transfusions for severe anemia may cause fluctuations in oxygen concentration. Few reports described the relationship between ROP and anemia. Some researchers thought that anemia would not result in ROP, but long-term severe anemia (hemoglobin ≤8 g/dl, hematocrit ≤ 25%) could increase the incidence of mild ROP.[10] In our study, the Hb of anemic patients with ROP ranged from 6 g/L to 9 g/L, and all the infants had other abnormalities such as jaundice, infection, respiratory distress syndrome, intracranial hemorrhage or ventriculomegaly, which may have some relations with ROP.

We also found that maternal gravidity is correlated with ROP, but there are no reports giving the reason for the higher incidence of ROP in the gravidity two group. Other factors, such as gender, jaundice, infection,

maternal age and pregnancy complications, which did not show a significant correlation with ROP, may be unimportant for pathogenesis.

In our study, all ROP infants were investigated with head ultrasound to observe the correlation between intracranial hemorrhage and ROP, but no significant correlation was observed. We observed the structure of the eyeball and changes of the eyeground, with no positive results. This may be due to the small eyeballs of premature infants, lack of experience of operators, or vessel proliferation without retinal detachment of stage 4 and 5.

Apgar score at 1 minute may be related to ROP.[11] This was not true in our study, presumably because of the small number of infants with abnormal Apgar scores.

Plus disease, also called additional changes, often rapidly accelerates ROP.[12] In this study we found that plus disease is closely related to gestational age, and that the lower the gestational age, the more likely plus disease is to occur. Severe stages of ROP were not seen above 30 weeks of gestational age.[13]

We did not identify any patients in stage 4 or 5, possibly because of the early screening, early diagnosis and early therapy of ROP at this hospital. Laser therapy has been widely used to treat ROP worldwide. The effectiveness of laser therapy is thought to be the same as or better than cryotherapy with fewer complications, including postoperative hemorrhage.[14,15] The major complications of laser therapy in our study are palpebral edema, corneal opacity, preretinal hemorrhage and vitreous hemorrhage, which were cured during the follow-up.

In conclusion, besides birth weight and gestational age, postnatal hypoxia, oxygen use, anemia and blood transfusion are correlated with ROP. When premature infants have other severe diseases, the incidence of ROP will increase noticeably. Further study is needed to determine whether ROP has other causative factors except for oxygen use and fluctuation of blood oxygen concentration. Because ROP may cause blindness at an early age, early screening and therapy, especially control of ROP within stage 3, can improve the outcomes of patients.[8,16-20]

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