RETINOPATHY OF PREMATURITY MATERNAL AND NEONATAL RISK FACTORS SCREENING FOR RETINOPATHY OF PREMATURITY

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ABSTRACT

Retinopathy of prematurity (ROP) is a disorder of the blood vessels in the developing retina of premature infants, and is one of the major causes of blindness and impaired vision among children. Screening for ROP detect infants needing treatment for ROP and decrease the risk of most severe forms Aim: To review the antenatal and postnatal risk factors, associated with ROP, evaluate the current screening guidelines in our neonatal intensive care unit and present the results of his application Materials and Methodes: Over the ten -years period from 1996-2005, 686 neonates were screened for ROP. The first examination for ROP is at four weeks of postnatal age. The criteria to include in the screening are: birth weight less than 1500g.; gestational age ≥ 32 weeks; neonates between 1500 – 2000g. and > 32 weeks, who required supplemental oxygen therapy/ mechanical ventilation for more than 7 days or those with instable clinical course. The changes of ROP are classified according to the International Classification of Retinopathy of Prematurity. Resultes: The total number of ROP cases was 143 (20, 85%), with mean birth weight 1319,5g (± 323) and gestational age 30 (± 2) weeks. We compare the outcomes of screening examinations and treatment for two study periods: from 1996 – 2000 and from 2001 – 2005. Mild ROP (stages 1 and 2) was found in 7,14% (49/686) and severe ROP (stages 3 – 5) in 13,7% (94/686) of the examined infants. Discussion: ROP is a multifactorial disease. Short gestation and low birth weight increase the risk of ROP. Other identified risk factors include sepsis, IVH, RDS and mechanical ventilation. Although supplemental oxygen is a significant risk factor for ROP. The incidence of ROP and the severity of the disease are not changed significantly in the two five-years periods, but the study's 10 years follow-up report confirmed these lasting benefits: unfavorable structural outcomes were reduced from 41,56% to 13,51%. Conclusion: The rate of severe ROP and the need for therapy decrease significantly in association with the use of adequate pulse oxymetry monitoring equipment and the implementation of a strict clinical practice of oxygen administration and management in VLBW infants Screening program and guidelines for ROP were accepted in our neonatal intensive care unit 10 years ago. We consider that our experience can be use for the elaboration of national screening guidelines for ROP.

Keywords: Retinopathy of prematurity, risk factor, screening

Increased survival of extremely low birth weight infants (ELBW), due to advances in antenatal and neonatal care has resulted in a population of infants at risk of developing retinopathy of prematurity (ROP). ROP has been recognised as an important cause of childhood visual impairment and blindness since the 1940s when improved facilities and treatment increased the survival rate of premature infants. Although its incidence and severity have been decreasing in developed countries over the past two decades, both are increasing in developing nations. (1,7)

ROP is a multifactorial, vasoproliferative disorder of the developing retina of preterm neonates and can progress to a tractional retinal detachment. In the more severe forms,

ROP results in a important visual impairment or blindness, both of which carry a high financial cost for the community, but also a high individual cost by affecting the normal motor, language, conceptual and social development of the child. (2,11,20)

The Global Initiative for the Elimination of Avoidable Blindness and the World Health Organization's Vision 2020 program targets ROP as a "avoidable disease" requiring early detection, prevention and treatment in an effort to reduce the prevalence of childhood blindness.

Screening for ROP detect infants needing treatment for ROP and decrease the risk of most severe forms. The variations in national and general health care, socioeconomic factors, criteria for treatment of ROP make necessary to adapt screening programs to each country and revise them regularly. (13,24)

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OBJECTIVE

The aim of this study is to review the antenatal and postnatal risk factors, associated with ROP, evaluate the current screening guidelines in our neonatal intensive care unit and present the results of his application.

MATERIALS AND METHODES

864 infants with a birth weight of less than 2000g. were admitted to the Neonatal Intensive Care Unit of the Hospital of Gynecology and Obstetric-Varna from 1996 to 2005. Our unit has tertiary neonatal care level with a capacity of 10 beds, and is a regional referral neonatal intensive care center for Varna region.

Infants were screened for ROP by an ophthalmologist, using direct ophthalmoscope after dilating the pupils with Mydrum eye drops. We follow the protocol of examining the preterm infants at four weeks of postnatal age. The criteria to include in the screening are:

- birth weight less than 1500g.;
- gestational age less than 32 weeks;
- all neonates between 1500 – 2000g. and > 32weeks who required supplemental oxygen therapy +/- mechanical ventilation for more than 7 days.

If ROP was not detected at the initial examination, the infants were reevaluated once every 10 days until full retinal vascularization and then every four weeks until six months of postnatal age. If ROP was detected, the examination were performed every week until the disease started to regress.

The changes of ROP were classified according to the International Classification of Retinopathy of Prematurity.

- Stage 1. Demarcation – line separating the avascular retina anteriorly from the vascularized retina posteriorly with abnormal branching of small vessels immediately posterior to this.
- Stage 2. Intraretinal ridge: the demarcation line has increased in volume, but this proliferative tissue remains intraretinal.
- Stage 3. Ridge with extraretinal fibrovascular proliferation.
- Stage 4. Partial retinal detachment.
- Stage 5. Total retinal detachment.

Threshold ROP was defined as the presence of at least eight cumulative 30° sectors (clock hours) of stage 3, or at least five contiguous 30° sectors of stage 3 of extraretinal neovessels in the presence of disease. This is also defined as the presence of dilated tortuous vessels in the posterior pole (“plus disease”). (1,2,11)

Patients data were collected retrospectively and the following neonatal risk factors were identified: birth weight, gestational age, Apgar score of less than five at five minutes, oxygen therapy and maximum concentration of inspired oxygen, mechanical ventilation, pathology of the neonate as intraventricular hemorrhage (IVH), RDS, neonatal sepsis.

The following maternal factors were identified: antepartum haemorrhage, preeclampsia, premature rupture of membranes.

Cryotherapy for ROP was done in Hospital of Ophthalmology-Varna or in the neonatal unit. Those infants were then followed up weekly until the regression of the disease.

RESULTS

Over the ten years period from 1996 – 2005, 686 neonates were screened for the presence of ROP. The total number of ROP cases was 143 (20, 85%), there were 77 male and 66 female infants.

We compare the results of screening examinations for two study periods: from 1996 – 2000 and from 2001 – 2005.

A total of 138 infants had the disease in both eyes, two had in the left eye and three infants in the right eye only.

Mild ROP (stages 1 and 2) was found in 7,14% (49/686) and severe ROP (stages 3 – 5) in 13,7% (94/686) of the examined infants.

Table 1 shows the distribution of injured eyes, according the severity of ROP

Table 1 Distribution of injured eyes, according the severity of ROP

Severity of ROP	1996-2000		2001-2005	
	n-eyes	%	n-eyes	%
Severe ROP (stage 13-5)	77	68,75	111	65,68
Mild ROP (stage 1-2)	35	31,25	58	34,32
Total	112		169	

Chi-test -0,59

Fig.1 Incidence of ROP by birth weight specific groups neonates: 1. ≤ 1000g. 2. 1000-1250g. 3. 1250-1500g. 4. ≥ 1500g.

The frequency of the severe forms of the disease is not changed significantly in the two five-years periods.

Many authors at the last 20 years describe the birth weight and the gestational age as the most important risk factors for ROP. Low birth weight is constantly associated with the disease. (2,3,12,23)

In our study the mean birth weight of infants was 1368g ($\pm$ 343) for the first period and 1271g ($\pm$ 303) for the second and the gestational age was $30 \pm (2)$ weeks for the both periods.

The incidence of ROP by birth weight specific groups of infants is shown in fig.1.

Some of the factors that precipitate ROP may occur before birth. Chronic hypoxia in utero, maternal infection, IUGR are prenatal conditions that seem to be related to the development of ROP. It is suspected that as many as one third cases of ROP are caused by prenatal rather than postnatal conditions.

We found some ante- and intrapartal risk factors in 53,6% of the neonates with different stages of ROP. They include: preeclampsia, maternal infection, antepartum haemorrhage, premature rupture of membranes, Apgar score ≤ 5 at 5 min.

The neonatal and maternal risk factors associated with the disease are shown in Table 2.

Many possible risk factors for the development of ROP have been postulated including: seizures, multiple spells of apnea or bradycardia, anaemia, blood transfusions. (4)

These factors may have a direct effect on the risk of ROP, or they may simply be indicators of smaller infants, who are more likely to develop many of the complications of prematurity, including ROP.

Respiratory immaturity with RDS, necessitate longer duration of mechanical ventilation and supplemental oxygen and is related significantly to the incidence and severity of ROP.

Supplemental oxygen is a significant risk factor for ROP. (10,20,22,23)

Table 3 represent the time of supplemental oxygen (h), according to oxygen concentrations and mechanical ventilation (h)

When the screening program for ROP started in our NICU in 1996, we accepted the guidelines of AAA from 1992. Because the findings of threshold ROP in babies > 1500 g. and > 30 weeks GA, we changed our criteria and in the years after 2000, there was an improvement of the outcomes after cryotherapy. Table 4 shows the outcomes after treatment with cryotherapy

Table 2 Neonatal and maternal risk factors for ROP

Risk factors	With ROP infants -number	(n=143) %	Without ROP infants -number	(n=543) %	OR
RDS	104	72,7	298	54,8	2,66
Apgar score ≤ 5 at 5min.	44	30,76	141	25,96	1,26
IVH gr.III-IV	50	34,96	109	20,07	2,14
DAP	35	24,47	156	28,7	
Maternal-fetal infections	44	30,76	176	32,41	0,93
Mecanical ventilation	74	51,74	198	36,46	1,86
Maternal preeclampsia	31	21,68	128	23,57	0,89
Premat. rupture of membranes	48	33,56	197	36,27	0,88

Table 3 Time of supplemental oxygen (h) and mechanical ventilation (h)

Fi O ₂	1996-2000 Mild ROP	Severe ROP	2001-2005 Mild ROP	Severe ROP
$\geq 70\%$	15,25	44,2	23,8	44,5
30-69%	84	96,4	64,5	102,6
$\leq 30\%$	349,5	397	219,9	380,9
Total time of suppl. oxygen	448,7 (18,6 days)	538 (22,4 days)	300 (12,5 days)	528 (22 days)
Mean time of mech. ventilation	163,4	161,4	115	173

Table 4 Outcomes after treatment with cryotherapy

Cryotherapy outcome	1996-2000		2001-2005		1996-2005	
	n-eyes	%	n-eyes	%	n-eyes	%
favourable	45	58,44	96	86,49	141	75
unfavourable	32	41,56	15	13,51	47	25
total	77		111		188	

Chi-test - 0,00001260

DISCUSSION

ROP is a multifactorial disease. Several factors increase the risk of ROP and especially those associated with short gestation and low birth weight. Other identified risk factors include sepsis, IVH, oxygen therapy and mechanical ventilation. Although supplemental oxygen is a significant risk factor for ROP. The altered regulation of vascular endothelial growth factor from repeated episodes of hyperoxia and hypoxia is one important factor in the pathogenesis of ROP. Strict oxygen management of the fraction of inspired oxygen (FiO_2) and the monitoring of O_2 saturation parameters may be associated with decreased rates of ROP. (7,9,10,12,25)

ROP begins to develop between 32 and 34 weeks after conception, regardless of gestational age at delivery, and has two distinct phases. During the acute first phase, the normal vasculogenesis of the retina is disturbed by the relative hyperoxia of the extrauterine environment. They causes vasoobliteration and nonvascularisation of some areas of the anterior retina. The subsequent hypoxia causes a second chronic phase, characterised by the proliferation of vascular and glial cells, arteriovenous shunt formation, occasionally leading to involution or cicatricial changes and visual impairment. (14)

A number of other risk factors have been suggested as contributors to ROP although it is unclear whether these are truly independent risk factors or simply indicators of the compromised health of the neonate. These factors include bronchopulmonary dysplasia, number of blood transfusions, parenteral nutrition, hypo/hypercarbia, early intubation, hypotension, patent ductus arteriosus, necrotising enterocolitis, administration of β blockers to mothers before delivery, intraventricular haemorrhage, poor postnatal weight gain. (4,5,10,22)

The incidence of ROP and the severity of the disease are not changed significantly in the two five-years periods, but the study's 10 years follow-up report confirmed these lasting benefits: unfavorable structural outcomes were reduced from 41, 56% to 13,51%.

We note that the long duration of the study period during which significant advances have been made in the treatment protocol of VLBW could have influenced our results. The main goal was to minimize repeated episodes of alternating hypoxia/hyperoxia by modifying the practice of wide fraction of inspired oxygen (FiO_2) and to avoid undesired episodes of high oxygen saturation levels as measured by pulse oximetry (SpO_2). (11,14,15)

Accepted values in SpO_2 were 95 – 100% for all babies in the first period during 1996 – 2000. Those saturation goal

Table 5 Screening criteria for ROP

Screening criteria	Supplemental oxygen +/- Gest.age (weeks)	Birth weight t(g)	Supplemental oxygen Birth weight(g)	I examination/w
AAP, 1992	≤ 30	≤ 1250	≤ 1800	5-7
AAP, 2001	≤ 28	≤ 1500	1500-2000/ ≥ 32 with instable clinical course	4-6/31-33PMA
AAP, 2005	≤ 32	≤ 1500	1500-2000/ ≥ 32 with instable clinical course	4-9
Canada	≤ 29	≤ 1250	$\geq 1250/\geq 29$ with instable clinical course	5-7/31-33PMA
Varna, 1996	≤ 34	≤ 2000	≤ 2500	5-7
Varna, 2001	≤ 32	≤ 1500	$\leq 2000/\geq 32$ with instable clinical course	4

AAP - American Academy of Pediatrics

PMA - postmenstrual age

limits were changed and after 2001 supplemental oxygen was given to maintain pulse oximetry SpO₂ between 90 and 95%.

As our understanding of ROP increases, screening guidelines are altered. Table 5 present the screening criteria for ROP accordingly different guidelines

In the last years some guidelines recommend that examinations be limited to neonates, born more prematurely but expands the criteria to include infants with higher birth weight regardless of clinical course. (3,8,13,16,17)

Treatment of ROP is associated with a 41% decrease in the occurrence of posterior retinal traction or detachments and a 19% to 24% decrease in the incidence of blindness. Because of the sequential nature of the progression of the disease, the proven benefits of cryotherapy demand carefully timed retinal examinations of at-risk preterm neonates for ROP to minimize the risk of visual loss by those infants. (14,18,19)

CONCLUSION

The rate of severe ROP and the need for therapy decrease significantly in association with the use of adequate pulse oxymetry monitoring equipment and the implementation of a strict clinical practice of oxygen administration and management in infants with birth weight of less than 1500g.

Screening program and guidelines for ROP were applied in our neonatal intensive care unit 10 years ago. They were based on an epidemiological study on the incidence of ROP and other international studies. We consider that our experience can be use for the elaboration of national screening guidelines

The goal of an effective screening program must be to identify the relatively few preterm infants who require treatment for ROP from among the much number born, while minimizing the number of stressful examination required for these infants.

Examination for ROP should be performed by an ophthalmologist with sufficient regular experience and knowledge in the examination of preterm infants for ROP.

Unit – specific criteria for examination for ROP should be established for each neonatal intensive care unit by consultation and agreement between neonatology and ophthalmology services.

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