INCIDENCE, PERINATAL RISK FACTORS, VISUAL OUTCOME AND MANAGEMENT OF THRESHOLD RETINOPATHY

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ABSTRACT

The incidence of threshold retinopathy, clinical characteristics and risk factors to develop threshold retinopathy are described in a group of preterm infants admitted between 1996 and 2000 in a single tertiary neonatal intensive care unit.
A subset of these infants (n=31) developed threshold retinopathy (ROP). Incidence of threshold ROP in survivors with a birth weight below 1500g is 6,4%. Pre-, peri- and postnatal characteristics of these infants are described and compared with matched controls of the same gestational age (GA) and admitted in the same unit in an attempt to focus on relevant risk factors of threshold ROP. We also report on visual outcome data in infants who developed threshold retinopathy. Finally, we describe our experience with perioperative management in this cohort.

RÉSUMÉ

Nous décrivons l'incidence de rétinopathie-seuil, les caractéristiques cliniques et les facteurs de risque dans un groupe d'enfants nés prématurément et hospitalisés dans un seul centre néonatal tertiaire de soins intensifs. Certains de ses enfants (n=31) ont développé une rétinopathie-seuil. L'incidence de rétinopathie-seuil parmi les survivants d' un âge gestationnel inférieur à 1500 g atteint 6.4%. Afin de mettre en évidence les facteurs de risque de la rétinopathie-seuil du prématuré, les caractéristiques pré-, péri- et postnatales de ces enfants sont décrites et comparées avec une population d'enfants contrôle d'âge gestationnel équivalent admis dans la même unité. Nous rapportons également les données concernant l'évolution clinique ultérieure sur le plan visuel des enfants traités par cryothérapie. Finalement, nous décrivons notre expérience concernant la prise en charge periopératoire dans notre unité de ce groupe d'enfants prématurés traités pour rétinopathie-seuil

SAMENVATTING

De incidentie van threshold retinopathie, de klinische karakteristieken en de risicofactoren worden beschreven in een groep prematuur geboren borelingen die allen in één tertiair centrum voor neonatale intensieve zorgen gehospitaliseerd werden. Een deel (n=31) van deze borelingen ontwikkelden threshold ROP. De incidentie van threshold ROP bij overlevende kinderen met een geboortegewicht lager dan 1500g is 6.4%. Om de geassocieerde risicofactoren in het licht te stellen worden de pre-, peri- en postnatale karakteristieken van deze kinderen beschreven en vergeleken met een controlegroep van éénzelfde postmenstruele leeftijd bij de geboorte en opgenomen op dezelfde afdeling. We documenteerden ook de visuele resultaten op langere termijn. Tenslotte beschrijven we eveneens het perioperatief beleid bij deze groep.

KEY-WORDS

Threshold retinopathy, risk factors, outcome, neonatal

MOTS-CLÉS

rétinopathie-seuil, facteurs de risque, évolution ultérieure - néonatal

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INTRODUCTION

Retinopathy of prematurity (ROP) is a significant outcome variable of morbidity in preterm infants and still is an important cause of visual impairment, especially in extreme low birth weight infants (ELBW infants, i.e. <1000 g at birth). There is striking variability in incidence of retinopathy, only partially explained by differences in survival or patient characteristics (i.e. gestational age, birth weight, genetic aspects) (21). With improving survival, preventive strategies to avoid morbidity become even more relevant. Until strategies are available to prevent preterm birth (primary prevention), we have to focus on other risk factors involved (secondary prevention) (21).

In an attempt to compare our results and risk factors to the data available in the literature, a retrospective evaluation was made with special emphasis on incidence and co-morbidity characteristics, risk factors involved and visual outcome. On addition, we report on the perioperative management in this cohort.

PATIENTS AND METHODS

The Neonatal Intensive Care Unit at University Hospitals, Gasthuisberg, is a tertiary neonatal intensive and high care unit within a structured regional perinatal referral centre. Besides inborn infants who developed threshold retinopathy during their neonatal stay, infants were specifically referred for retinal surgery. During the period (1996-2000) studied, 3406 infants were admitted. Five hundred seventy-one (571) infants had a birth weight below 1500g. Eighty-five % (485/571) of these infants survived until discharge, with an increase in survival with higher gestational age (GA) (54% <25 weeks to 92% at 30 weeks). Screening for retinopathy was performed by the same ophthalmologist (IC) in all infants born earlier than 33 weeks GA. Observations were classified according to the International Classification of Retinopathy of Prematurity (8). First examination was performed at the postnatal age of 4 weeks. In case of normal fundoscopy, a two weeks interval examination was performed until the GA of 40 weeks (full term). If ROP stage 1 or 2 was diagnosed, the baby was examined on a weekly basis. In case of ROP stage 3, fundoscopy was performed twice a week. If Plus-disease was documented, cryotherapy was planned if according to Cryo-ROP criteria (9,15). All infants fulfilled Cryo-ROP criteria at time of surgery, i.e. threshold disease (at least five contiguous or eight cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of Plus-disease (9,15). Incidence and perinatal risk factors were only studied in infants admitted at the Gasthuisberg unit within 24 hours after birth. Perinatal data of all admitted infants are available in a prospectively collected EpiInfo database. Potential risk factors as reported in the literature to develop threshold retinopathy were extracted from this database. Other relevant data were collected from the available nursing reports. A full list of perinatal risk factors investigated is available in figure 1. A case-control approach (cases = infants who developed threshold retinopathy) with matched control infants of the same GA was used to bypass GA as dominant risk factor. Long term ophthalmologic evaluation was in line with the CRYO-ROP study (9,15). Visual outcome data collected in infants who developed threshold ROP were fundoscopy, visual acuity and refraction. One eye of each subject was the unit of analysis in this study. This eye was chosen at random for the analysis. Data were collected by retrospective chart review.

To evaluate peroperative management, all inborn infants who received cryotherapy for threshold retinopathy (96-00) were included. Cryotherapy was performed in the neonatal ward under general anaesthesia. After dilatation with atropine and phenylephrine, an incision of the conjunctiva was performed and the avascular retina anterior to the edge of the ridge was treated over 360° with a contiguous single or double row of cryo-points. In the postoperative period, all infants were treated with topical steroids and atropine tapered over a week. After surgery, the infants were ventilated by conventional ventilation to enable postoperative analgesia. Perinatal and preoperative characteristics were studied by data extraction from the EpiInfo database and by retrospective chart review.

Fig 1. Prenatal, perinatal and neonatal characteristics in threshold retinopathy cases and GA-matched controls. Results reported by mean and interquartile range. When significant differences are documented, confidence intervals are calculated. (Abbreviations explained in full text)

	Threshold ROP	Controls	p value	confidence interval
Prenatal				
Any maternal	23/31	19/31	NS	
Hypertension	10/31	8/31	NS	
Pre-eclampsia	9/31	9/31	NS	
Chorioamnionitis	13/31	11/31	NS	
Multiple birth	14/31	6/31	p<0.05	3.5-48.1 %
Assisted conception	4/31	2/31	NS	
Vaginal delivery	10/31	11/31	NS	
Celestone	20/31	16/31	NS	
At birth				
Apgar score 1 min	6 (4-8)	6(4-7)	NS	
Apgar score 10 min	8 (8-9)	8 (8-9)	NS	
CRIB score	7.6 (5-10)	4.9 (2-7)	p<0.01	1-4.4
Birth weight	760 (615-907)	906 (797-967)	p<0.02	37-255 g
< 10^{th} percentile	11/31	4/31	p<0.04	1.5-42.5 %
< 25^{th} percentile	19/31	8/31	p<0.005	16-62 %
During neonatal stay				
Ventilation (days)	27 (10-39)	13.5 (5-16)	p<0.004	4.9-22.1 d
Respiratory support (d)	55.3 (41-64)	39.8 (29-54)	p<0.006	4.9-26.1 d
Oxygen provided (d)	63.8 (42-77)	49.3 (36-58)	p<0.04	1.8-27.2 d
BPD 28 days (number)	29/31	26/31	NS	
BPD 36 weeks (n)	18/31	5/31	p<0.0005	20.3-63.5 %
Infection documented (n)	27/31	20/31	p<0.04	1.9-43.1%
Blood culture proven	41	23	p<0.001	9-29
postnatal growth (g/kg/d)	13,1 (10-16,2)	13,3 (10,2-15,9)	NS	
Respiratory characteristics				
MAP 0-24	13 (12-15)	10.3 (8-13)	p<0.02	0.4-5
MAP 24-48	10.3 (8-12)	7.9 (6-10)	p<0.03	0.6-4.2
MAP 48-72	9.4 (7-10)	7 (3-8)	p<0.03	0.3-4.5
MAP 72-96	8.6 (7-10)	5.6 (3-8)	p<0.05	1.3-4.7
OI 0-24	14.2 (9-18)	7.2 (3-12)	p<0.0004	3.5-10.5
OI 24-48	9.2 (5-13)	4.4 (3-6)	p<0.0004	2.4-7.2
OI 48-72	6.7 (4-9)	3.8 (3-6)	p<0.02	0.9-4.9
FiO2 0-24	59.6 (46-70)	48 (36-60)	p<0.03	2.5-20.7 %
FiO2 24-48	44.6 (31-50)	33.3 (28-40)	p<0.003	4.7-17.9 %
FiO2 48-72	41.1 (32-48)	32.8 (23-40)	p<0.02	2.4-14.2 %
FiO2 72-96	35 (25-47)	25 (21-30)	p<0.03	1.2-13.8 %

Mean and interquartile range were used to describe the clinical characteristics in threshold retinopathy cases. For statistical analysis of risk factors (case-control), student t was used in continuous variables and chi-square in categorical variables in a monovariate analysis. A p-value less than 0.05 was significant.

RESULTS

Incidence and relative risk (figure 2)

From 1996 to 2000, 31 infants (admitted within 24 hours after birth in the unit) developed threshold retinopathy during neonatal stay. Incidence of threshold retinopathy is 6.4 % in

survivors with a birth weight below 1500g. Incidence is 38 % in survivors with a birth weight <750g, 12,5 % in infants between 751-1000g and still 1,7% in infants with a birth weight between 1001 and 1250g. There were no threshold retinopathy cases in infants with a birth weight above 1250g. Absolute numbers of threshold cases for each birth weight and each GA-category are given in figure 2.
Co-morbidity characteristics are either respiratory (bronchopulmonary dysplasia) or neurologic (intracranial haemorrhage). Eighteen out of thirty-one (58%) infants had associated bronchopulmonary dysplasia. An intracranial haemorrhage was documented by ultrasound in 9/31 (29%) infants. Threshold retinopathy was an isolated morbidity characteristic in 10/31 (32%) infants.

Risk factors (figure 1)

Prenatal: Maternal complications (hypertension, pre-eclampsia or chorio-amnionitis) were not associated with an increased risk to develop threshold retinopathy, nor were medically assisted conception, way of delivery and prenatal lung maturation. Being part of a multiple pregnancy was associated with an increased risk to develop threshold ROP ($p<0.05$).

At birth: There were no significant differences in Apgar score at 1 and 5 minutes. CRIB score (Clinical Risk Index for Babies) was significantly higher in cases when compared to controls ($p<0.01$) and the incidence of growth retardation (low birth weight for a given GA, i.e. dysmaturity) was significantly higher in cases ($p<0.04$). Mean relative postnatal growth (g/kg/day) was not significantly different between threshold retinopathy cases and controls.

Respiratory characteristics: Duration of ventilation, respiratory support and days on supplemental oxygen were significantly longer in cases (all at least $p<0.04$). Besides length of respiratory disease, intensity of neonatal respiratory disease also correlates with an increased risk to develop threshold ROP. Oxygenation Index (marker for respiratory disease severity), oxygen provided and Mean Airway Pressure were significantly higher in cases in the first 24 hours of life and remained significantly higher in the first 96 hours of life (figure 1)

Fig 2. relative risk to develop threshold retinopathy for each birth weight category and for each gestational age (threshold infants/survivors)

BW category	threshold ROP	survivors	procentual risk
<750g	14	35	38 %
751-1000 g	15	120	12.5 %
1001-1250 g	2	116	1.7 %
1251-1500 g	0	214	0 %
<1250 g	**31**	**271**	**11.5 %**
<1500 g	**31**	**485**	**6.4 %**

GA category	threshold ROP	survivors	procentual risk
<25 weeks	15	36	41 %
26 weeks	5	33	15 %
27 weeks	4	56	7 %
28 weeks	5	59	8 %
29 weeks	2	71	2.8 %
30 weeks	0	171	0 %
<31 weeks	**31**	**426**	**7.2 %**

Fig 3. preoperative characteristics (n=31) (ref 4)

Postnatal age at surgery	65	60-71 days
Gestational age at surgery	34	34-36 weeks
Weight at time of surgery	1622	1519-1862 g
BPD 28 days	93 %	29/31
BPD 36 postmenstrual weeks	58 %	18/31
Receiving respiratory support	32 %	10/31
Receiving extra oxygen	52 %	16/31
Receiving methylxanthins	83 %	26/31
Receiving corticoids (topical or systemic)	55 %	17/31
History of previous surgery	25 %	8/31

Infections: Incidence and number of documented (blood-culture proven) infections were significantly higher in cases ($p<0.001$), due to the higher number of nosocomial infections (staphylococcus epidermidis) ($p<0.01$).

Visual outcome data

During the period 1996-00, visual outcome data are available in 32 infants (31 inborns and 1 referred). A normal fundus was diagnosed in 21 (66%) eyes, dragging of the posterior pole in 3, optic atrophy in 8 eyes. Five (15%) retinal detachments were documented. Mean refractive error in this cohort was -0.88 D.

Perioperative management (figure 3)

Cryotherapy for threshold ROP was performed in 31 (32 procedures) inborn infants. Mean

weight at surgery was 1270 (SD 484) g. Mean duration of postoperative ventilation was 30 (SD 19) hours. Mean duration of postoperative analgesia was 65 (SD 45) hours. Mean duration of postoperative opioids was 39 (35). The other clinical variables are available in figure 3.

DISCUSSION

Incidence of threshold retinopathy in this cohort is high when compared to American populations and is more in line with European cohorts (6,10,13,15-18,20,21). A shift to younger infants with lower birth weight is documented when compared to the original CRYO-ROP study. Clinical variables of these threshold ROP infants are more in line with the STOP-ROP trial (15,17).

When compared to reported data in literature, there is a lower incidence of co-morbidity in this cohort (15,17). Therefore, the overall high incidence in this cohort is explained by a higher incidence of isolated threshold retinopathy, i.e. infants who only had threshold ROP at discharge.

We already reported on the visual outcome variables by comparing this cohort with an earlier treated (89-95) cohort of threshold retinopathy infants without changes in surgical technique between both periods. We could illustrate an improved visual outcome in the more recently treated infants, in line with other reports (7,18).

Although there are reports in literature on the effect of maternal disease on the risk to develop threshold retinopathy, we could not document any maternal risk factor in this study, besides being part of a multiple pregnancy (12). This risk factor can be explained by the associated lower birth weight after multiple pregnancy. Growth retardation (i.e. a birth weight below the 10^{th} percentile for a given GA) is a strong risk factor to develop threshold ROP (20). This risk factor remains relevant, even if these infants display normal postnatal growth (4).

CRIB (Clinical Risk Index for Babies) score is a marker of disease severity at birth. A higher CRIB score is associated with an increased risk of mortality and therefore, most likely, also with an increased risk of morbidity (19). A higher CRIB score was documented in infants who developed threshold retinopathy during neonatal stay. Other markers of intensity of disease already available in the first week of life (oxygenation index, oxygen need, mean airway pressure) are also associated with an increased risk to develop threshold retinopathy (2).

In contrast to length of oxygen need or ventilation, these risk factors are already available in the first week of life and therefore, might be more useful to further delineate the relative risk associated with a given GA or birth weight.

A documented nosocomial infection is also a risk factor to develop threshold retinopathy. Preventive strategies to avoid these infections might therefore very likely also reduce the incidence of threshold ROP (1).

In the design of the CRYO-ROP study, uniformity on ophthalmologic management was emphasized but caregivers were given freeway on perioperative management. There is still variability on perioperative management (12). We recently described our experience with performing cryotherapy on the neonatal ward using general anaesthesia. We could illustrate that this approach is a feasible and save option (3). The recent switch in surgical technique (laser treatment instead of cryotherapy) might very likely enable us to shorten postoperative need for analgesics and postoperative length of ventilation, in line with the reports on the reduction of systemic side-effects after introduction of laser treatment for threshold ROP (14).

In conclusion, incidence of threshold retinopathy in our cohort is in line with other European cohorts while incidence of co-morbidity is lower. Visual outcome variables improved when compared to an earlier treated cohort without changes in surgical technique. Growth retardation is associated with an increased risk to develop threshold retinopathy, even when these infants display normal postnatal growth. Markers of severity of disease, already available in the first week of life might be used to further delineate the relative risk to develop threshold retinopathy associated with a given GA or birth weight while reduction of nosocomial infections seems to be a promising strategy to reduce threshold ROP.

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