Retinopathy of prematurity: risk factors and clinical management in a cohort of ELBW infants

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Abstract:
The etiology of retinopathy of prematurity (ROP) is multifactorial while ROP is also frequently associated with other co-morbidity characteristics in former preterm infants. We describe the current risk factors associated with the development of pre-threshold ROP in a cohort of 267 ELBW (extreme low birth weight, i.e. < 1 000 g) infants. We hereby confirm the combined risk associated with immaturity and disease severity. When compared to earlier reported cohorts of the same unit, we document a minor reduction in incidence, with an overall high incidence in neonates at threshold of viability (≤ 26 weeks gestational age). Finally, specific observations on analgosedation and tolerance during screening for ROP or laser surgery are discussed.

Key-Words: prematurity – retinopathy of prematurity – visual impairment – risk factors – prevention

1. Introduction

Retinopathy of prematurity (ROP) remains the main cause of visual impairment in former preterm infants [1]. ROP is a multifactorial disease with numerous risk factors either based on immaturity (e.g. gestational age, birth weight) or indicators of disease severity (e.g. respiratory disease severity and duration, infection and inflammation, suboptimal perinatal growth, nutritional intolerance, need for inotropics, patent ductus arteriosus, glycaemia control, renal failure) [1-6]. Such disease related indicators to develop ROP might be used to further discriminate within the immaturity related risk to develop ROP.

The recent guidelines on the clinical management of ROP explicitly mention that there are clinical relevant differences in incidence and clinical characteristics between different units or countries [7]. Gilbert stressed that the characteristics of babies developing severe disease varies, with babies in middle and low income countries having a much wider range of birth weights and gestational ages than is currently the case in industrialized countries. Rates of disease requiring treatment also tend to be higher in middle and low income countries suggesting that babies are being exposed to risk factors which are, to a large extent, being controlled in industrialised countries. The reasons for this "third epidemic" of ROP are discussed as well as strategies for control, including the need for locally relevant, evidence based criteria which ensure that all babies at risk are examined [1].

Finally, many procedural interventions during neonatal stay remain a burden as they cause pain or discomfort to neonates. This is also true for ROP screening or surgery, but less invasive approaches can be considered [8-11].

In this paper, we aim to highlight 3 aspects ROP. Firstly, we will report on the risk factors to develop pre-threshold ROP in a recently treated cohort of 267 ELBW (i.e. extreme low birth weight, < 1 000 g) neonates in a single neonatal intensive care unit. Secondly, we aim to compare aspects of incidence and risk factors in this cohort with earlier described cohorts of the same unit to illustrate trends throughout time. Finally, we would like to drawn the attention to aspects of clinical care (ROP screening, surgery) related to the reduction of procedural pain in neonates.

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2. Incidence and most relevant risk factors

A recently reported dataset on 151 ELBW newborns admitted to the neonatal intensive care unit (NICU) of the University Hospitals Leuven (2000-2005) [12] was further extended with a similar dataset to include more recently admitted cases (2007-2010), to result in observations in 267 cases. Both datasets were initially built to evaluated aspects of perinatal creatinaemia in ELBW neonates.

Cases were included except for neonates with congenital renal anomalies and/or early neonatal death (i.e. ≤ day 7). Maternal chart review was searched for premature preterm rupture of membranes (PPROM), tocolytics, pre-eclampsia, chorio-amnionitis and prenatal betamethasone.

Neonatal chart review was searched for characteristics at birth [BW, GA, Apgar score, the need for endotracheal intubation, gender and small for gestational age (SGA)] and for characteristics of morbidity during subsequent neonatal stay [duration of ventilation (days), additional oxygen need (days), postnatal steroid or ibuprofen administration (yes/no), duration until full enteral feeding (days) and intraventricular hemorrhage (IVH, any)]. In all cases, ROP was classified according to the International Classification of ROP. For analysis, either any ROP (yes/no) or pre-threshold ROP, yes/no) were used for dichotomous classification.

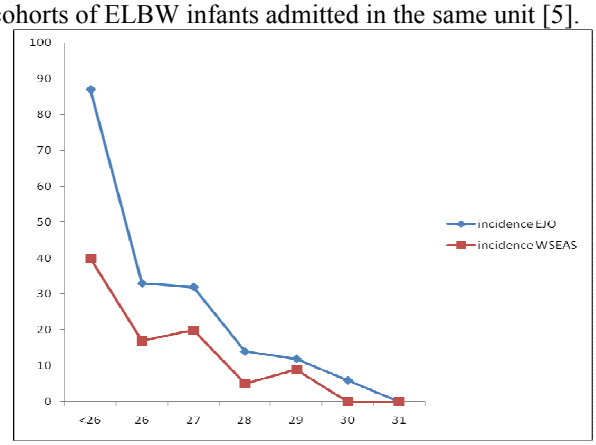
The median gestational age was 27 (range 23-33) weeks, median weight was 815 (range 370-1000) g. 50/267 (18.7 %) developed ROP ≥ grade 3. In line with other reports, indicators of *immaturity* [median GA, 25.5 *vs* 27 weeks $p < 0.001$, median weight 690 vs 847 g, $p<0.0001$] and *disease severity/co-morbidity* [inotropics, $p<0.01$ peak creatinaemia, $p<0.01$, need for intubation at birth, $p<0.01$, postnatal steroids, $p<0.0001$, duration oxygen need, $p <0.0001$, duration enteral feeding, $p<0.001$] but no growth restriction at birth, or Apgar scores at 1, 5 or minutes were indicators of an increased risk to develop pre-threshold ROP (monovariate).

In a logistic forward regression model, with pre-threshold ROP as dependent variable, gestational age (OR 0.63, 0.45-0.88 95 % CI) together with the duration of oxygen need (OR 1.02, 1.01-1.03 95 CI) correctly classified 84 % of the individuals in this cohort.

3. Trends in incidence and risk factors within a single neonatal unit

In this ELBW cohort (2000-5 and 2007-2010), the incidence of ROP ≥ grade 3 was 50/267 (18.7 %). When analysed for both 'subgroups' in the cohort, the incidence of pre-threshold ROP was (28/151) 18 % and (22/116) 19 % respectively. When compared with earlier publications from the same unit, [(1996-2000) 31/155 + (2000-2001) 28/90, 24 %], there seems to be only a modest improvement in the overall incidence [5,13]. This absence of overall significant changes does however reflect also in part a shift within the ELBW cases to even more immature cases. The gestational age dependent incidence in consecutive cohorts is provided in figure 1 and shows another, more relevant trend with a significant reduction in cases of 26 weeks onwards and a still high incidence in cases < 26 weeks.

Figure 1: incidence (%) of pre-threshold ROP for increasing gestational age categories in two consecutive cohorts of ELBW infants admitted in the same unit [5].



4. Prevention of discomfort

Analgosedation and tolerance of topical ophthalmic drug administration during ROP screening:

We would like to report on our observations on the impact of topical ophthalmic drug administration during screening for retinopathy of prematurity (ROP) [10,11]. These observations were prospectively collected as part of a broader study on the assessment of the stress response during and following ROP screening in preterm neonates, using a Fabry

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lens. Besides clinical characteristics, vital signs (heart rate, mean blood pressure, saturation) and CRIES score were recorded before, and 10, 30 and 60 min after administration of the eye drops. Following ROP screening, vital signs (heart rate, blood pressure, oxygen saturation) and CRIES score were recorded 5, 10, 15, 30, 60 min and 3, 6 and 12 h afterwards. Every infant was only included once. Outcome variables (CRIES score, vital signs) before and after screening were compared using a paired analysis (Wilcoxon, Mc Nemar's test).

Clinical characteristics at birth and at inclusion of 42 neonates in whom the stress response was evaluated were prospectively collected. Based on these observations, we documented that the administration of eye drops was not associated with any significant effect on heart rate, mean arterial pressure or CRIES score. Following eye examination, median mean arterial blood pressure (47 versus 46 mmHg), heart rate (158 versus 154/min) and CRIES score (0 versus 0) normalised within 5 min with no additional differences during further evaluation up to 12 h after the procedure.

We therefore conclude that the administration of topical ophthalmic dilatatory drugs (tropicamide 0.5% and phenylephrine 2.5%) one hour before ROP screening examination was not associated with any measurable effect on vital signs or signs of discomfort in a prospective study on 42 procedures in 42 preterm neonates. Secondly, and in contrast to the observations of Belda *et al.* [10], there was no clinical relevant stress response when a Fabry lens was used instead of the more routinely used eyelid distractor.

Perioperative management:

In contrast to data on the ophthalmologic outcome following treatment for ROP, non-ophthalmologic short outcomes variables are almost absent, resulting in variation in practice of anaesthetic management mostly based on personal opinions, habits and perceived eminence [7,8,9]. At present, laser treatment is the preferred treatment modality, based on the ophthalmologic advantages of laser treatment, but this switch was also of relevance for some non-ophthalmologic outcome variables since we recently documented that laser treatment resulted in a more limited postoperative inflammatory response and a faster clinical recovery [11,13]. Laser photocoagulation was associated with a modest increase in C-reactive protein (CRP) compared with a marked increase after cryoablation, reflecting reduced tissue damage and inflammation of laser photocoagulation compared to cryoablation. Using standardized evaluation and treatment of pain after surgery in a single neonatal unit [16-18], a significant decrease in duration of postoperative ventilation, in postoperative administration of analgesics and in time until regain of full enteral feeding was documented in infants who received laser photocoagulation compared with cryo-treated neonates [9,11].

5. Discussion and conclusion

Retinopathy of prematurity (ROP) still remains the main cause of visual impairment in former preterm infants. ROP is a multifactorial disease, but both between as well as within units, there might be shifts in the incidence and risk factors, related to the type of patients taken care for in a specific unit [7]. In line with the UK guidelines on the management of retinopathy, we hereby re-illustrated the need to document the regional incidence and the clinical characteristics of ROP to ensure effective screening and treatment of this disease. However, new concepts should focus on the ROP-immaturity association and might unveil new risk factors like glycaemia control or other indicators [14,15].

Secondly, neonatal care has also changed with among other issues, more emphasize on analgesia [16]. Since the eighties, survival rates at threshold of viability have increased dramatically resulting in an even more vulnerable group of preterm neonates who need laser treatment. There is a trend to treat retinopathy in an earlier phase in an attempt to ameliorate long term visual outcome [7]. Such strategy likely will further increase the number of infants who will undergo screening or retinal surgery. Caregivers of various disciplines (ophthalmologists, anaesthesiologists, neonatologists) should therefore collaborate to at least document the non-ophthalmologic outcome variables of screening or laser surgery [8,9,16].

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