Is retinopathy of prematurity decreasing? - Comparison of two different periods in the same NICU

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Retinopathy of prematurity is a retinal vascular disorder seen frequently in very premature infants, and is associated with poor clinical outcomes. The aim of the present study was to assess the association between the incidence of retinopathy of prematurity and mechanical ventilation, oxygen therapy, gestational age, and antenatal steroids in extremely low birth weight infants as well as to retrospectively analyze changes in the incidence and risk factors of retinopathy of prematurity over two study periods.

Key words: neonate, retinopathy of prematurity, risk factors.

Retinopathy of prematurity (ROP) is a retinal vascular disorder seen frequently in very premature infants, and is associated with poor clinical outcomes. Increased survival of extremely low birth weight infants due to advances in antenatal and neonatal care has resulted in a population of infants at high risk of developing ROP.

In the last four decades, ROP has emerged as one of the leading causes of blindness in children in the developed world. Heath[1] first used the term ROP in 1951. In 2002, a Swedish study reported that of those infants weighing less than 750 g, 95.3% developed ROP, while 5.4% of those with a birth weight (BW) >1,500 g developed the disease[2]. In study of Yang et al.[3], the overall incidence of ROP in very low birth weight (VLBW) infants was 45.8%.

Many risk factors for the development of ROP in VLBW infants have been identified, including low BW, low gestational age (GA), supplemental oxygen therapy following delivery, and multiple births[4-7].

The aim of the present study was to assess the association between the incidence of ROP and mechanical ventilation, oxygen therapy, GA, and antenatal steroids in premature infants as well as to retrospectively analyze changes in the incidence and risk factors of ROP over two study periods in the Neonatal Intensive Care Unit (NICU) of a university hospital in the Çukurova region.

Material and Methods

The data of 97 infants (194 eyes) admitted between 1995 and 1997, screened for ROP according to the guidelines of the American Academy of Pediatrics (AAP) and the American Academy of Ophthalmology[8], were compared to those of 122 infants (244 eyes) admitted between 2009 and 2010.

Premature infants born in the Çukurova region and admitted to the NICU of the Çukurova University Balcalı Hospital, Adana, between 1 January 1995 and 31 December 1997 (1st period) and between 1 January 2009 and 31 December 2010 (2nd period), who underwent complete ROP screening, were included in this retrospective study.

Indirect ophthalmoscopy with a 20- to 30-dpt lens was performed. If the border between the vascularized and unvascularized retina could not be visualized, we used a lid speculum and indentation. In eyes in which ROP was observed, the location and severity were recorded, and the stage of ROP was also diagnosed according to the International Classification of Retinopathy of Prematurity (ICROP)[9]. Examinations were conducted at least every two weeks after ROP was first seen, and those with normal findings were

observed monthly. ROP was graded according to the classification system developed by the International Committee for the Classification of ROP[10]. The following clinical data were collected: GA, BW, Apgar scores at the 5th minute, duration of mechanical ventilation, duration of oxygen therapy, intraventricular/periventricular hemorrhage (IVH/PVH), prenatal steroid therapy, surfactant therapy and respiratory distress syndrome (RDS), sepsis, duration of parenteral nutrition, transfusions, and patent ductus arteriosus (PDA).

Respiratory distress syndrome (RDS) was classified following the grading system of Giedion et al[11]. IVH was classified according to the classification of Levene et al.[12] GA was defined by the neonatologist caring for the patient, and was based on obstetric data including early ultrasound findings and menstrual history, when available, or New Ballard Score based on physical-neurological examination findings[13]. Apnea was defined as cessation of respiratory flow for one 20 seconds (s) or associated with bradycardia. Oxygen therapy was defined as either no oxygen administered or the use of supplemental oxygen, whether continuous or intermittent oxygen therapy.

Eye drops to dilate the pupils [0.5% cyclopentolate and 2.5% phenyl epinephrine, 1 drop to both eyes - 3 instilled 5 minutes (min) apart] were administered by the bedside nurse 1 hour before the examination. Examinations were performed by experienced ophthalmologists following international classification and AAP recommendations.

Accepted values in blood oxygen saturation (SpO_2) were 85-95% for infants >32 weeks' gestation and 85-93% for those ≤32 weeks' gestation. Prenatal glucocorticoid was used when preterm birth was expected for the infants with GA of 25-34 weeks.

The Medical Ethics Committee of the Çukurova University Medical Faculty, Adana, approved the study.

Results

Ninety-seven infants who were admitted to the NICU and underwent complete ROP screening between 1 January 1995 - 31 December 1997 and 122 infants who were admitted to the NICU and underwent complete ROP screening between 1 January 2009 - 31 December 2010 were retrospectively included. Demographic characteristics of the infants in the 1st and 2nd periods are shown in Table I.

Birth weight (BW) and duration of oxygen were significantly different between infants without [ROP (-)] and with [ROP (+)] ROP in the 1st and 2nd periods ($p<0.05$). Gestational week was significantly lower in ROP (+) patients in the 2nd period ($p<0.01$) (Table I).

Eighty-three (85.6%) infants were ROP (-), while 14 (14.4%) were ROP (+) in the 1st period. Six infants had Grade 1 ROP, 4 infants had Grade 2 ROP, and 4 infants had Grade 3 ROP (totally 14 infants [14/97, 14.4%] and 20 eyes [20/194 eyes, 10.3%]). In the 1st period, 4 infants in Grade 3 and 2 infants who progressed to Grade 3 from Grade 2 in the follow-up received cryotherapy.

Ninety-nine (81.1%) infants were ROP (-), while 23 (18.9%) were ROP (+) in the 2nd period. Fourteen infants had Grade 1 ROP, 3 infants had Grade 2 ROP, and 6 infants had Grade 3 ROP (totally 23 infants [23/122, 18.9%] and 28 eyes [28/244 eyes, 11.5%]). 45.5% of the infants in the study received antenatal steroids. In the 2nd period, 3 of the 6 infants in Grade 3 had laser therapy (2 had cryotherapy, 1 was transported to another hospital for ROP treatment). Only 2 infants had anti-vascular endothelial growth factor (VEGF, Bevacizumab) treatment in the 2nd period.

When the two periods were compared according to risk factors, BW was smaller, oxygen duration was longer, number of infants with 5th minute Apgar score <7 was lower, number of infants who received surfactant therapy was higher, acidosis was lower, and intracranial hemorrhage was higher in the 2nd period (Table II).

Discussion

In our study, we found that ROP incidence did not change over time in our unit - ROP was detected in 14.4% of the infants in 10.5% of eyes from 1995-1997 and in 18.6% of the infants in 11.5% of eyes from 2009-2010.

Retinopathy of prematurity (ROP) is associated with excessive oxygen use shortly after the initial description of the disease. The altered regulation of VEGF from repeated episodes of hyperoxia and hypoxia is an important factor in the pathogenesis of ROP. Duration of oxygen was longer in ROP (+) patients in both the 1st and 2nd periods in our study. In addition,

apnea and number of infants exposed to oxygen were also higher in ROP (+) infants in both periods, although there were no significant differences between the periods.

Even with monitored oxygen use, the number of infants with ROP has been increasing, most likely due to the increased survival of VLBW infants. Controlled supplemental oxygen is now delivered to premature infants to maintain adequate blood levels of oxygen. In our unit, strict oxygen saturation limits are also performed.

It is widely acknowledged that ROP is a multi-factorial disorder, with low GA, low birth weight, oxygen exposure, and neonatal sepsis[14-20]. Prematurity is the main causal factor, as demonstrated by the widely proven correlation between the incidence and severity of ROP and GA, and GA was also reported to be the dominant risk factor for severe ROP[19,21,22]. In our study, although GA in the 1st period was not different between patients with and without ROP, GA was significantly lower in the 2nd period.

In a study conducted by Gallo et al.[23], it was reported that BW rather than GA is associated with development of ROP. In our study, BW was statistically significantly lower in ROP (+) infants than in ROP (-) infants in both periods.

A recent study reported short gestation, prolonged ventilation, frequent apnea, and surfactant use as risk factors for developing severe ROP; however, these factors again may be the marker for the severity of illness[24]. Bassiouny et al.[25] reported that lower BW, GA, apnea, blood transfusion, mechanical ventilation, metabolic acidosis, total parenteral nutrition (TPN), IVH, and sepsis were associated with development of ROP. Blood transfusion was not significantly different between the two periods of our study, at 71% versus 78%, respectively. Hypotension and fluctuation of oxygen saturation following sepsis might affect retinal perfusion and lead to retinal ischemia[26]. Nevertheless, in our study, sepsis was not significantly different between the two periods.

Shohat et al.[27] reported apnea requiring bag and mask ventilation, prolonged TPN, blood transfusion, and episodes of hypoxemia and hypercarbia as risk factors for the development of ROP. Apgar score at the 5th minute was significantly different between the two periods of our study. In the 1st period, some infants progressed to grade 3 ROP, but none of the infants in the 2nd period worsened. Experienced personnel attending in delivery is very important in smaller babies. Neonatal resuscitation programmers (NRP) were much more common after 2003 in Turkey, so the number of experienced NRP certified personnel was higher in the 2nd period. Metabolic acidosis and apnea were lower in the 2nd period, most probably due to better ventilation strategies, better equipment and the higher number of experienced personnel working in the NICU in the 2nd period.

Intraventricular hemorrhage (IVH) was shown to be a significant factor related to the incidence of ROP in reported studies[27]. Brown et al.[26] implicated the similarity in circulation of the

Table I. Demographic and Clinical Properties of the Infants in the 1st and 2nd Study Periods

	1st period 97 infants			2nd period 122 infants		
	ROP (-) n=83 infants	ROP (+) n=14 infants	p	ROP (-) n=99 infants	ROP (+) n=23 infants	p
Gestational week (wk) Mean±SD (Min-max)	30.7±2.61 (25-35)	29.6±2.7 (27-36)	> 0.05	30.7±2.5 (25-37)	29.3±1.8 (26-32)	<0.01
Birth weight (g) Mean±SD (Min-max)	1537.6±356.6 (1000-2500)	1309.5±237.5 (910-1670)	<0.05	1472.34±483.9 (790- 2820)	1157.4±276.4 (780-1780)	<0.05

Table II. Comparison of Risk Factors between the Two Periods of the Study

	1995-1997 97 infants	2009-2010 122 infants	p
ROP (+) infants (%)	14 infants (14.4)	23 infants (18.6)	>0.05
ROP (+) eyes (%)	20 eyes (10.3)	28 eyes (11.5)	>0.05
Gestational week (weeks) mean±SD, (min-max)	29.6± 2.7 (27-36)	29.3±1.8 (26-32)	>0.05
Birth weight (g) mean±SD, (min-max)	1309.5±237.5 (910-1670)	1157.4±276.4 (780-1780)	>0.05
Duration of O_2 (days) mean±SD, (min-max)	13.9±7.9 (0-34)	26.2 ± 18.0 (3-62)	>0.05
Exposed to O_2 (%)	14 (100)	23 (100)	>0.05
Apgar score <7 at 5th min n (%)	10 (71)	2 (8.7)	0.0001
RDS (%)	8 (57)	17 (74)	>0.05
Surfactant (%)	3 (21)	14 (60)	0.02
Acidosis (%)	10 (71)	10 (43)	>0.05
Sepsis (%)	9 (64)	18 (78)	>0.05
Apnea (%)	11 (78)	14 (61)	>0.05
*Intracranial Hemorrhage (%)	1 (7.1)	14 (61)	0.001
PDA (%)	0 (0)	3 (13)	>0.05
Erythrocyte Transfusion (%)	10 (71)	18 (78)	>0.05

*No ultrasonography was available in the unit in the 1st period. In the 2nd period, there was a portable ultrasonography in the unit; cranial ultrasonography was routinely performed in the 2nd period.
PDA: Patent ductus arteriosus. RDS: Respiratory distress syndrome.

central nervous system (CNS) with the retina, which yields simultaneous influence on the retina and CNS when circulation is impaired. Liu et al.[19] revealed the significant correlation of IVH with ROP. However, other researchers have proposed conflicting results. No significant association between ROP and IVH was obtained in their studies[28,29]. Our study demonstrated that the rate of IVH was higher in 2009-2010, and the difference was statistically significant. This higher ratio may be due to the lower number of ultrasonographies performed in neonates with IVH in the 1st period, since during that period cranial ultrasonography could not be performed at the bedside in the NICU.

Kim et al.[24] reported that surfactant therapy showed a statistically significant influence on ROP incidence, even after controlling for GA and BW. These results may indicate that infants suffering from RDS are at higher risk for ROP. Since the number of patients treated with surfactant is increasing, close monitoring is necessary for those high-risk infants. In our study, although not statistically significant, RDS and surfactant use were higher in the 2009-2010 period. However, the higher surfactant use may be due to our health policy, since in the 1st period, parents had to obtain/bring their own surfactant, while it was available in the hospital pharmacy in the 2nd period.

There was no infant with stage 4 or 5 ROP in this study. This emphasizes the importance of a screening program, timely referral and early treatment, which can prevent blindness due to ROP.

In conclusion, 10 years after the 1st study period, we found similar rates of ROP in our unit (2009-2010). Although GA, BW and oxygen use are all risk factors for ROP development, in our study, none of these parameters was different between the groups. ROP incidence was slightly increased in the

2nd period, though not statistically significant. However, the number of patients with grade 1 ROP was high and of grades 2-3 ROP low. From this point of view, we may speculate that there may be some other undefined factors affecting ROP development that must be investigated.

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