Incidence and Risk Factors of Retinopathy of Prematurity in Two Neonatal Intensive Care Units in North and South China

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Abstract

Background: To investigate the incidence and risk factors of retinopathy of prematurity (ROP) in two Neonatal Intensive Care Units in North and South of China, respectively.

Methods: We studied data concerning 472 infants with gestational age (GA) ≤34 weeks or birth weight (BW) ≤2000 g who were admitted to the Zhujiang Hospital of Southern Medical University and the Fourth Hospital of Shijiazhuang between January 1, 2011 and December 31, 2011. Clinical information about perinatal neonates was collected and was confirmed by reviewing medical charts. The incidence and severity of ROP were assessed in the screened population. Main outcome measures are the incidence and severity of ROP. The relationship of clinical risk factors and the development of ROP were analyzed.

Results: The overall incidence of ROP was 12.7%, and the overall incidence of type 1 ROP was 2.3%; 9.4% of infants in Zhujiang Hospital had ROP compared to 15.0% infants in the Fourth Hospital of Shijiazhuang developed ROP, and the difference is statistically significant. ROP was significantly associated with GA (odds ratio [*OR*]: 0.77 [0.62–0.95], $P = 0.015$), BW (*OR*: 0.998 [0.996–0.999], $P = 0.008$), maternal supplemental oxygen administration before and during delivery (*OR*: 4.27 [1.21–15.10], $P = 0.024$) and preeclampsia (*OR*: 6.07 [1.73–21.36] $P = 0.005$). The risk factors for ROP are different in two hospitals. In Zhujiang Hospital, BW is the independent risk factors for ROP while GA, BW and preeclampsia in the Fourth Hospital in Shijiazhuang

Conclusions: Retinopathy of prematurity incidence is different based on area. Incidence of ROP is still high in China. More efforts need to prevent ROP.

Key words: Birth Weight; Gestational Age; Incidence; Retinopathy of Prematurity

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative eye disease, first described in 1942.[1] It is a major cause of preventable blindness of children in the developing and developed world.[2] The survival of premature infants has increased with the improvement of neonatal care.[3] Consequently, this may have been accompanied by an increase in the incidence of ROP.[4,5] However, the incidence estimates from population-based studies vary among countries with similar Neonatal Intensive Care Unit (NICU).[6] In a prospective study of Sweden,[7] ROP was detected in 73% infants with a gestational age (GA) <27 weeks at birth. In a study in Norway[8] in infants with a GA of <28 weeks at birth, ROP was reported in 33% infants. Different incidences were also reported in Belgium,[9] Australia and New Zealand,[10] Austria[11] and Finland.[12] ROP is under constant epidemiological study around the world.

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Improved neonatal care in China has increased the survival of very low birth weight (VLBW) premature infants and has consequently increased the incidence of ROP.[13] Study from Beijing, China[14] of infants with birth weight (BW) <2000 g or GA <34 weeks at birth ROP was reported in 10.8% infants. Nevertheless, there are limited studies on the incidence and risk factors of this important morbidity among preterm infants in a different area of China. Although significant advances have been made in perinatal care, ROP remains a serious complication in prematurely born individuals.

Low GA,[10,15-18] low BW[10,15-18] and prolonged exposure to supplementary oxygen[19] have been shown consistent and significant association with ROP. Other risk factor includes plasma insulin-like growth factor-1,[19] postnatal weight gain,[20,21] hyperglycemia,[22] insulin use,[22] nutrition,[23] neonatal infection,[24-26] blood transfusion,[27,28] genetic factors,[29] mechanical ventilation,[30] sepsis,[31] intraventricular hemorrhage,[19] surfactant therapy[32] and anemia[33] and apnea.[31] The precise of these factors in the

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progression of ROP has not been determined. In China, several studies elucidated that the incidence of ROP is lower in the developed regions such as Shanghai and Guangdong in the South of China than in the less developed regions in the North of China[32] despite the reason is unclear.

The aim of this prospective study was to evaluate the incidence of ROP in preterm infants at the Zhujiang Hospital in the South of China and the Fourth Hospital in Shijiazhuang in the North of China, to identify the prenatal, postnatal and regional risk factors for its development.

Methods

The prospective study was carried out at the Zhujiang Hospital of Southern Medical University in South of China and the Fourth Hospital of Shijiazhuang in North of China between January 1, 2011 and December 31, 2011. The Neonatal Department of Zhujiang Hospital in Guangzhou and the Fourth Hospital of Shijiazhuang in Shijiazhuang are both high-risk perinatal centers. About 500 preterm infants are admitted to the NICUs in Zhujiang Hospital every year, about 200 of them need to be screened for ROP. While about 300 preterm infants need to be screened in the Fourth Hospital of Shijiazhuang every year. All preterm infants admitted to the NICU between January 1, 2011 and December 31, 2011, who received eye examination for ROP, were eligible for the study. Ethical Committee clearance from the institution was obtained.

Eye examination schedules

The screening examinations were performed on all infants who met the criteria bellowed:

- All preterms with GA ≤34 weeks and/or BW ≤2000 g
- Selected preterm infants who had prolonged exposure to oxygen who were at risk for ROP.

Infants were examined according to the 2004 Chinese Ministry of Health guidelines on oxygenation policies and prevention and treatment of ROP.[33] The first examination was at 4 weeks after birth.

Eye examination methods

Ophthalmologists who had sufficient knowledge and experience to identify the location and sequential retinal changes of ROP performed all examinations. Pupils were dilated with 0.5% tropicamide and 0.5% phenyleprine drops 2 h before examination. Indirect ophthalmoscopy was routinely performed used a lid speculum and scleral indentation after topical anesthesia. Digital retinal images were also obtained using Retcam for objective documentation of retinal findings.

Monitoring and management

Examination was performed on a weekly or biweekly basis, depending on the retinal findings and continued until vascularization had reached zone 3, or the disease progressed to type 1 ROP defined as early treatment for ROP (ET-ROP) or established ROP was definitely regressing. The retinal findings were classified according to the International Classification of ROP including the stage, extent, zone, and presence or absence of plus disease.[34] Indication for treatment is the type 1 ROP according to ET-ROP study.

Data collection

Genders of newborn and delivery pattern were recorded. The perinatal variables documented included preeclampsia (defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg with proteinuria) and presence of fetal distress, maternal supplemental oxygen administration before and during delivery. The following risk factors occurring during the first 4 weeks after birth were recorded: GA, BW, respiratory distress syndrome, surfactant administration, intraventricular hemorrhage, hyperbilirubinemia, blood transfusion, sepsis, duration of oxygen and duration of continuous positive airway pressure.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS version 16, SPSS Inc, Chicago, IL, USA) program. GA and BW in different groups were compared using *t*-test. Chi-square tests were used to compare the rate of ROP in different groups. Univarate analysis was used to explore variables associated with ROP with the appropriate significance of $P < 0.05$, and those found to be significant were included in a logistic regression model using a backward stepwise method. In the model, comparison was made between the groups without ROP and with ROP. The odds ratio (*OR*) and 95% confidence interval (*CI*) for each possible risk factor were also calculated.

Results

During the study period, 472 infants who met the inclusion criterion were admitted to the two hospitals. Totally, 202 infants were admitted to the Zhujiang Hospital of Southern Medical University and the rest to the Fourth Hospital in Shijiazhuang. Totally, 4 of the 472 babies were lost to follow-up.

Data were available on 468 babies, and 61.5% of whom were male. Only 6 had a GA of <28 weeks and 3 weighed <1000 g. GA ranged from 26.0 to 36.9 (mean 32.3 [2.0]) weeks and BW from 850 to 2450 (mean 1646.6 [292.4.8] g). Any stage of ROP was detected in 58/468 babies (12.4%) and distribution of ROP by GA and BW is shown in Table 1a and Table 1b. The rate of type 1 ROP was high in very premature babies that is <30 weeks (6/43, 14.0%) [Table 1a]. Only 0.9% of infants with gestational weeks ≥30 weeks developed type 1 ROP ($P < 0.001$). Low BW infants were more at risk than bigger babies, as 16.4% (21/128) with BW <1500 g developed any stage ROP compared with 10.9% (37/340) among babies with BW ≥1500 g [Table 1b].

The GA showed no significant difference between the two hospitals ($P = 0.839$), while babies admitted to Zhujiang Hospital had bigger BW ($P = 0.029$) and more male gender babies were admitted to the Zhujiang Hospital ($P = 0.015$) [Table 2]. The incidence of ROP is higher in

Shijiazhuang Fourth Hospital than that in the Zhujiang Hospital with significant statistical difference ($P = 0.048$) and the incidence of type 1 ROP is higher in Shijiazhuang Fourth Hospital without significant difference ($P = 0.199$) [Table 2].

The mean GA of infants with ROP was significantly lower than those without ROP (mean 31.2 [2.0] weeks vs. 32.5 [1.9] weeks, $P < 0.001$). Furthermore, the means GA of type 1 ROP were also significantly lower than those without ROP and mild ROP (mean 29.6 [2.4] weeks vs. 32.4 [1.9] weeks, $P < 0.001$). The mean BW of infants without ROP was 1674.0.1 ± 294.5 g, while it was 1440.0 ± 172.1 g with ROP ($P < 0.001$). When it comes to infants with no ROP plus mild ROP and type 1 ROP, the mean BW was 1649.6 ± 293.1 and 1426.0 ± 147.3 g ($P = 0.020$), respectively.

Results of univariate analysis of maternal and postnatal factors for ROP are shown in Table 3. In the multivariate logistic regression analysis, four variables were identified as significant, independent risk factors for ROP [Table 4]:

Table 1a: Rates of ROP by GA

GA (weeks)	*n* (%)			
	No ROP	ROP	Mild ROP	Type 1 ROP
<28	3 (50)	3 (50)	1 (33.3)	2 (66.6)
28-30	25 (67.6)	12 (32.4)	8 (29.6)	4 (10.8)
30-32	116 (87.2)	17 (12.8)	15 (11.3)	2 (1.5)
32-34	161 (89.0)	20 (11.0)	19 (7.2)	1 (5.5)
≥34	105 (94.6)	6 (5.4)	5 (4.5)	1 (0.9)

ROP: Retinopathy of prematurity; GA: Gestational age.

Table 1b: Rates of ROP by BW

BW (g)	*n* (%)			
	No ROP	ROP	Mild ROP	Type 1 ROP
<1000	3 (100)	0 (0)	0 (0)	0 (0)
1000-1250	15 (71.4)	6 (28.6)	5 (23.8)	1 (4.8)
1250-1500	89 (85.6)	15 (14.4)	13 (11.5)	3 (2.9)
1500-2000	231 (88.8)	29 (11.2)	25 (16.3)	4 (1.5)
≥2000	72 (90.0)	8 (10.0)	6 (7.5)	2 (2.5)

BW: Birth weight; ROP: Retinopathy of prematurity.

Table 2: Comparison of characteristics and incidence of ROP between two hospitals

	Zhujiang Hospital *n* (%)	The Fourth Hospital in Shijiazhuang *n* (%)	*P*
Number of patients (%)	202 (43.2)	266 (56.8)	
GA in weeks: range, (mean) (SD)	26.0-36.9 (32.3) (2.0)	26.0-36.9 (32.3) (1.9)	0.839
BW in grams: range (mean) (SD)	975-2400 (1678.5) (300.1)	850-2450 (1620.0.1) (284.8.1)	0.029
Male gender	137 (67.8)	151 (56.8	0.015
Without ROP	184 (91.1)	226 (85.0)	
ROP	18 (8.9)	40 (15.0)	0.048*
Type 1 ROP	2 (1.0)	8 (3.0)	0.199

SD: Standard deviation; BW: Birth weight; ROP: Retinopathy of prematurity; GA: Gestational age.

GA, BW, preeclampsia and maternal oxygen administration. The risk factors for ROP are different in two hospitals. In Zhujiang Hospital, BW is the independent risk factors for ROP, while GA, BW and preeclampsia in the Fourth Hospital in Shijiazhuang [Table 5].

Discussion

Our study indicates that the incidence of any ROP and type 1 ROP was 12.7% and 2.3% respectively. It is corresponded to the incidence reported in six NICUs in Beijing, China[14] but very different from the studied in developed countries.[30,35] This variation might be partly accounted for by differences in the proportions of infants at high risk of ROP who survive when born at an early GA. In addition, the screening criteria for inclusion were BW ≤2000 g or GA ≤34 weeks, being much wider than those used in other studies. For example, the cry therapy of retinopathy of prematurity (CRTO-ROP)[36] included infants with weights of <1250 g and showed an incidence of 65.8%. We used the criteria recommended by the Chinese Medical Association, which was based on a review of criteria used in other countries[7,10] and on clinical experience of China.[14] Our study showed the mean BW of babies developing ROP to be 1440.0 (172.1) g and the mean GA was 31.2 (2.0) weeks suggesting that current screening criteria are suitable for these two hospitals.

In 1993, a study in the first Affiliated Hospital of Peking University reported the incidence of any stage of ROP was 20.3%.[37] In 2005, six NICUs in Beijing screened 639 babies (using the same criteria as the current study) and 10.8% of babies developed ROP and 3.6% developed threshold ROP[14] compared with 12.7% and 2.3% respectively in current study ($P = 0.33$, $P = 0.21$). It is disappointed that the data suggested that the incidence had no changed substantially over time since efforts had been done. Perhaps increased survival of very immature infants at high risk for the disease balanced against improved neonatal intensive care for ROP can account for this finding. Although no individual study has been conclusive as to the best SpO_2 target, strict management of oxygen to minimize alternating hypoxia and hyperoxia and avoidance of undesired high oxygen saturations seem to be the most promising strategies to prevent ROP.[6]

In this study, GA and BW were independently associated with ROP that were consistent with many other studies.[17,30,38] We also found preeclampsia, and maternal oxygen administration to be significant risk factors of any stage of ROP. Few studies have been published to determine the association of preeclampsia with ROP and the results reported are conflicting.[18,36,39,40] Fortes Filho *et al*.[40] reported that preesclapmsia reduced the risk for any stage of ROP by 60% in early preterm infants (<32 weeks). Holmström *et al*., in a population-based study, reported that preeclampsia was less common in the non-ROP group, but the difference was not statistically significant.[41] Another retrospective study of 252 VLBW infants in Taiwan[42] found that maternal preeclampsia (*OR*: 2.52, 95% *CI*: [1.32, 4.7]) predicted the development of

Table 3: Univariate analysis of maternal and postnatal risk factor for retinopathy of prematurity

Indices	No ROP *n* (%)	ROP *n* (%)	*OR* (95% *CI*)	*P*
Hospital (Zhujiang)	173 (43.4)	18 (31.0)	0.62 (0.34-1.12)	0.111
Gender (male)	256 (95.2)	32 (55.2)	0.76 (0.43-1.35)	0.350
GA (weeks) (mean ± SD)	32.5 ± 1.9	31.2 ± 2.0	0.70 (0.60-0.81)	<0.001*
BW (g) (mean ± SD)	1674.0674 ± 0.5	1440.0 ± 172	0.997 (0.996-0.998)	<0.001*
Fetus number (mean ± SD)	1.3 ± 0.5	1.4 ± 0.6	1.53 (0.96-2.43)	0.071
Delivery pattern (natural labor)	108 (82.2)	20 (34.5)	1.27 (0.65-2.48)	0.485
Preeclampsia	29 (7.3)	12 (20.7)	2.92 (1.37-6.21)	0.004*
Presence of fetal distress	20 (5.0)	2 (3.4)	0.59 (0.13-2.62)	0.484
Maternal supplemental oxygen administration	9 (2.3)	8 (13.8)	6.09 (2.20-16.88)	0.0001*
Respiratory distress	192 (48.1)	26 (44.8)	0.89 (0.51-1.57)	0.692
Surfactant administration	196 (49.1)	28 (48.3)	1.00 (0.56-1.74)	0.971
Intraventricular hemorrhage	28 (7.0)	3 (5.2)	0.77 (0.23-2.63)	0.678
Hyperbilirubinemia	173 (43.4)	25 (43.1)	0.96 (0.55-1.68)	0.879
Sepsis	35 (8.8)	5 (8.6)	0.97 (0.36-2.58)	0.945
Steroid usage	4 (1.0)	2 (3.4)	3.47 (0.62-19.4)	0.132
Blood transfusion	90 (22.6)	16 (27.6)	1.03 (0.52-2.04)	0.942
Duration of CPAP (days) (mean ± SD)	4.9 ± 4.1	5.3 ± 5.2	1.02 (0.91-1.14)	0.710
Duration of oxygen (days) (mean ± SD)	16.0 ± 12.8	17.8 ± 19.0	1.01 (0.98-1.04)	0.567

SD: Standard deviation; BW: Birth weight; *OR*: Odds ratio; CL: Confidence level; ROP: Retinopathy of prematurity; GA: Gestational age; CPAP: Continuous positive airway pressure.

Table 4: Independent risk factors for retinopathy of prematurity

ROP	*OR*	95% *CI*		*P*
Gestational age	0.75	0.61	0.93	0.008
BW	0.94	0.86	0.98	0.049
Maternal supplemental oxygen administration	4.66	1.39	15.63	0.013
Preeclampsia	8.26	2.36	28.9	0.001
Fetus number	1.67	0.93	2.98	0.083

BW: Birth weight; *OR*: Odds ratio; *CI*: Confidence interval; ROP: Retinopathy of prematurity.

Table 5: Independent maternal and postnatal risk factors for the retinopathy of prematurity in Zhujiang Hospital and the Fourth Hospital in Shijiazhuang

	Zhujiang Hospital		The Fourth Hospital in Shijiazhuang	
	OR (0.95% *CI*)	*P*	*OR* (0.95% *CI*)	*P*
GA	0.88 (0.61–1.27)	0.493	0.66 (0.53–0.83)	0.000
BW	0.994 (0.990–0.998)	0.002*	0.998 (0.996–0.999)	0.006
Preeclampsia	0.43 (0.09–2.13)	0.303	5.44 (1.52–19.43)	0.009

BW: Birth weight; *OR*: Odds ratio; *CI*: Confidence level; GA: Gestational age.

threshold ROP. More studies and a meta-analysis are needed to investigate the impact of preeclampsia on ROP.

In addition, our study found that the incidence of ROP is lower in Zhujiang Hospital in South of China than in The Fourth Hospital in Shijiazhuang in the north with $P = 0.048$. This is consistent with other results published in Chinese journals.[32] The discrepancy is probably associated with the child healthcare in different regions including prenatal care, delivery care, and postnatal care as well as general socioeconomic conditions, such as household income, educational levels and government initiatives.[43] It was also established in our study that different regions have different risk factors of ROP. This could also be an explanation of the prevalence variation of ROP. The incidence of threshold ROP is lower in Zhujiang Hospital but without significantly difference. Difference risk factors of threshold ROP in two hospitals may be responsible. Some of the differences could due to observer differences, changes in the indications for treatment and variation in exposure to risk factors. At the same time, the mean BW of infants in Zhujiang Hospital was higher than those in the Fourth Hospital in Shijiazhuang. It also may contribute to the difference of the incidence of ROP between two hospitals.

The follow-up of infants with threshold ROP is essential to minimize blindness and long-term visual morbidity in these infants. More efforts need to be done not only to reduce the incidence of ROP but also improve the guideline to ensure that all babies at risk receive a timely screening examination.

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