· Original article ·

Analysis of retinopathy of prematurity screening between 2009 and 2013 in Tianjin, China

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2009 至 2013 年天津早产儿视网膜病变筛查分析

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摘要

目的:分析天津地区早产儿视网膜病变(ROP)筛查的结果,研究肺表面活性剂及经鼻连续正压通气(NCPAP)对于 ROP 的影响。

方法:多中心回顾性研究。2894 例早产儿(1592 男婴,1302 女婴)主要来自于天津市几家大型医院,筛查时间从 2009-01/2013-12,对人口统计学信息,眼科检查结果和可能的全身危险因素均进行记录。孕周、出生体重、吸氧、肺表面活性剂和 NCPAP 对 ROP 的影响进行了评估。

结果:224 例 448 眼患有 ROP(7.7%)。其中,49 例 98 眼为严重 ROP。在对照组与 ROP 组之间呼吸窘迫综合征(RDS)、NCPAP、肺表面活性剂的应用差异有统计学意义(P<0.01)。Logistic 回归分析结果表明小孕龄、低出生体质量、吸氧是导致 ROP 发生的危险因素。随着肺表面活性剂与 NCPAP 的使用率增加,吸氧率逐渐下降,ROP 的发生率也在下降。

结论:低出生体质量、低孕龄、吸氧史与 ROP 的发生密切相关,肺表面活性剂与 NCPAP 的使用可能是降低 ROP 发生的因素。

关键词:早产儿视网膜病变;发生率;危险因素;肺表面活性剂;经鼻连续正压通气

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Abstract

• AIM: To analyze the findings of retinopathy of prematurity (ROP) exam in Tianjin, and study the impact of pulmonary surfactant Curosurf and nasal continuous positive airway pressure (NCPAP) in ROP.

• METHODS: A multicenter retrospective review. Totally 2894 preterm infants (1592 males, 1302 females) from several hospitals in Tianjin were screened from January 2009 to December 2013. Demographic information, ophthalmic outcomes and possible systemic risk factors were recorded. Gestation age, birth weight, oxygen supplementation, Curosurf and NCPAP were used to estimate risk factors for ROP.

• RESULTS: ROP was found in 448 eyes of 224 patients (7.7%). Among which, severe ROP developed in 98 eyes of 49 patients (21.9%). There was significant statistical difference in respiratory distress syndrome (RDS), NCPAP, and Curosurf usage between control and ROP groups (P<0.001). Multiple logistic regression analyses of ROP indicated that lower birth weight, younger gestational age, and oxygen supplementation were the risk factors leading to ROP. As the usage rate of Curosurf and NCPAP increased year by year, the usage of oxygen supplementation gradually decreased, the incidence of ROP was also on the decline.

• CONCLUSION: Low birth weight, young gestational age and oxygen supplementation are associated with ROP. The use of Curosurf and NCPAP may be the factor that reduces the occurrence of ROP.

• KEYWORDS: retinopathy of prematurity; incidence; risk factor; pulmonary surfactant; nasal continuous positive airway pressure
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INTRODUCTION

Retinopathy of prematurity (ROP) is avasoproliferative disorder of eye that can lead to the loss of vision in premature neonates. This blinding disease of retina was first reported in 1942[1]. However, ROP is still the leading cause

of blindness in neonates in the United States and other industrialized nations[2-3], and its incidence is rising rapidly in middle - and low - income countries[4-5]. Multicenter Cryotherapy for Retinopathy of Prematurity (CRYO - ROP) was the first treatment that explained the related risk factors, screening criteria, and treatment opportunity for the occurrence of ROP in 1988[6]. Early treatment for retinopathy of prematurity (ETROP) then redefined treatment options in 2003[7]. During the past two decades, the screening criteria of ROP were constantly updated, whereas screening guidelines were different from country to country. Even within the same country, the screening criteria vary across the country[8]. In China, the screening based on greater population is not common, though guidelines on oxygenation policies, prevention and treatment of ROP were already published in 2004[9]. The screening work has been carried out throughout the country, but there are no screening of the incidence and risk factors of ROP in Tianjin has been reported. In order to prevent and reduce neonatal respiratory distress syndrome (NRDS), pulmonary surfactant Curosurf and nasal continuous positive airway pressure (NCPAP) have been applied in Tianjin since 2010. However, there are data deficiency according to the current onset of ROP. It is not yet known the relationship between prophylactic pulmonary disease administration and onset of ROP in premature births. Our study lasted five years and was based on a large amount of samples. The analysis is as follows.

SUBJECTS AND METHODS

Subjects A total of 2894 preterm infants (1592 males, 1302 females) were screened from January 2009 to December 2013. All infants studied were from four Neonatal Intensive Care Units (NICUs) in Tianjin, China. Including: 1) Tianjin Medical University General Hospital; 2) The Second Hospital of Tianjin Medical University; 3) Tianjin First Center Hospital; 4) Tianjin Central Hospital of Gynecology Obstetrics. The sample included premature infants born at less than 34wk of gestation. Screening range expanded if patients suffered from severe cardiopulmonary disease or other systemic serious diseases. The first screening examination should take place at 4 - 6wk postpartum or at 31wk post - menstrual age (PMA), whichever is later. Special attention to those infants born before 25wk gestation age (GA) with screening at 6wk postpartum permits the early detection of aggressive posterior ROP (AP - ROP)[10]. In NICU all the ophthalmologic examinations were performed by 2 - 3 retina specialists. This was done after pupillary dilation using a binocular indirect ophthalmoscope and a scleral depressor. After infants were discharged from NICUs, they were followed constantly at Tianjin Eye Hospital. According to GA, all infants were divided into three groups: Group 1A contained infants with GA less than 29wk, Group 1B consisted of infants with GA between 29 and 32wk, Group 1C comprised infants with GA greater than 32wk. According to birth weight (BW), all infants were divided into three groups: Group 2A consisted of infants with BW less than 1500 g, Group 2B comprised infants with BW between 1500 g and 2000 g, Group 2C contained infants with BW greater than 2000 g.

Examination Methods Compound tropicamide eye drops were instilled 4 times at five to ten minutes intervals, then Benoxil was used for topical anesthesia before examination. Infants' retinas were photographed and interpreted by skilled ophthalmologists using a RetCam Ⅱ System (Clarity Medical Systems, Pleasanton, CA, USA). Lomefloxacin hydrochloride eye ophthalmic gel was applied to above steps.

Assessment of Retinopathy The International Classification of ROP describes three locations (zones Ⅰ - Ⅲ), five stages (stages 0-5), and the presence of plus disease[11-13]. Plus disease is the dilation and tortuosity of retinal arteries and veins in the posterior pole compared to a standard photograph[13]. ROP is recorded as "+" if plus positive and extent of disease described as clockwise direction. Prethreshold ROP includes any stage at zone Ⅰ; stage 2+, stage 3, and stage 3+ at zone Ⅱ. Threshold disease is defined as five contiguous clock hours or eight noncontiguous clock hours of stage 3 ROP with plus disease in zone I or zone II. AP-ROP is a subtype of ROP that behaves very aggressively and unpredictably. It describes posterior disease (in zone I or posterior zone II) with plus disease out of proportion to that characteristically presenting with a flat neovascularization at the vascular-avascular junction[10].

Identification of Risk Factors The potential risk factors were retrospectively recorded, including: 1) maternal exposing risks: maternal age, hypertensive disorder complicating pregnancy (HDCP), premature rupture of membrane (PROM), eclampsia and multiple gestation; 2) neonate related risk factors: gestational age (GA), post - menstrual age (PMA), birth weight (BW), sex, oxygen supplementation, Curosurf, NCPAP, fetal distress, pneumonia, apnea, necrotizing enterocolitis (NEC), respiratory distress syndrome (RDS), *in vitro* fertilization and embryo transfer (IVF-ET).

Follow - up Time According to developing condition in retinal vessels: 1) The infants were examined until complete vascularization of the retina; 2) Prethreshold ROP needs to be observed for pathogenetic condition closely; 3) Threshold ROP were treated with peripheral cryotherapy or laser ablation according to the timings suggested by the CRYO-ROP and the ETROP studies[7]; 4) Stages 4 and 5 ROP with retinal detachment were treated with vitrectomy and/or scleral buckle.

Statistical Analyses Statistical analyses were performed using the SPSS software package (version 16.0 for Windows, SPSS Inc., Chicago, IL, USA). Independent Samples t-test was applied to compare continuous variables between groups. Categorical variables were analyzed by Chi - square and Continuity Correction χ^2. This study evaluated the possible risk factors for any stage ROP by logistic regression. Variables were analyzed in multivariate models if they meet statistical significance in univariate comparison . We also estimated odds ratio (*OR*) and defined 95% confidence intervals (95% *CI*) for all possible risk factors. Above variables were considered

statistically significant for $P<0.05$.

The study protocol followed the tenets of the Declaration of Helsinki, and was approved by Tianjin Eye Hospital Institutional Review Board (IRB). Informed consent was obtained from all subjects who participated in the study.

RESULTS

From 2009 to 2013, 2894 preterm infants from four NICUs were admitted to this study in Tianjin, China. The mean GA and BW of the samples was 31.65±2.31wk and 1682.5±456.41 g, respectively. Among these, 1592 (55%) were males and 1302 (45%) were females. Singleton and multiple births accounted for 76.7% (2219) and 23.3% (675), respectively.

During the screening period, the incidence of ROP was 7.7% (224/2894). The occurrence time of ROP was 37.68±4.38wk (PMA). Among 224 neonates of ROP, Stages 1, 2, 3, 4 and 5 ROP was found in 169, 29, 11, 5, and 4 cases, respectively. And 5 cases from AP-ROP; 175 (78.1%) cases tended to be self-healing, 49 (21.9%) cases progressed, and 26 cases give consent to medical treatment.

All neonates were divided into two groups (control group and ROP group). In control group, the mean GA and BW were 31.85±2.21wk and 1712.6±448.92 g, respectively, which were higher than those of ROP group (GA was 29.29±2.20wk and BW was 1321.1±385.98 g). The difference was statistically significant (GA: $t=16.63$, $P<0.001$; BW: $t=14.33$, $P<0.001$). Infants with oxygen supplementation in control group and ROP group account for 44.3% and 69.2%, respectively. The difference was statistically significant ($\chi^2=51.341$, $P<0.001$). There were significant difference in RDS, NCPAP and Curosurf usage between control group and ROP group ($\chi^2=21.643$, $P<0.001$; $\chi^2=27.406$, $P<0.001$; $\chi^2=26.243$, $P<0.001$). However, difference between the two groups was not statistically significant in PROM, HDCP, multiple gestation, IVF-ET, and pneumonia ($\chi^2=0.038$, $P=0.846$; $\chi^2=0.991$, $P=0.319$; $\chi^2=2.073$, $P=0.150$; $\chi^2=0.717$, $P=0.394$; $\chi^2=2.652$, $P=0.103$).

In addition to that, variables that meet statistical significance in univariate comparison were analyzed in logistic regression. This explanatory model demonstrated that younger GA, lower BW and supplemental oxygen were the risk factors leading to ROP (Table 1).

According to the guidelines of retinal prevention published in 2014[14] and screening criteria in United Kingdom (GA<32wk or BW<1500 g)[15], infants were divided into three groups. The incidence in group 1A was clearly higher than that in group 1B and group 1C. The lower the GA, the higher the incidence of ROP. Similar result was found for BW, the incidence in group 2A was higher, compared to bigger BW groups. The BW in group 1A was lower than that in the other two groups. The GA in group 2A was lower than that in the other two groups. But the use of oxygen, NCPAP and Curosurf, and the incidence of RDS were higher than those of the other two groups (Tables 2 and 3).

Table 1 Logistic regression of factors related to ROP

Factors	Odds ratio	95% confidence interval	*P*
GA	0.678	0.616-0.747	0.000
BW	0.999	0.998-1.000	0.000
Oxygen supplement	2.257	1.650-3.087	0.000
Curosurf	0.751	0.386-1.459	0.398
NCPAP	0.970	0.554-1.699	0.916
RDS	1.483	0.816-2.693	0.196
Pneumonia	5.337	0.987-28.857	0.052

GA: Gestation age; BW: Birth weight; NCPAP: Nasal continuous positive airway pressure; RDS: Respiratory distress syndrome.

Table 2 Various incidence of ROP and basic statistics in different GA groups *n* (%)

Characteristics	Group 1A	Group 1B	Group 1C
Total number	571 (19.7)	1216 (42.0)	1107 (38.3)
ROP	137 (24.0)	72 (5.9)	15 (1.4)
BW	1242.9±247.78	1596.5±323.96	2003.3±432.45
Sex (M)	328 (57.4)	688 (56.6)	576 (52.0)
Oxygen supplement	327 (57.3)	606 (49.8)	406 (36.7)
IVF-ET	22 (3.9)	19 (1.6)	4 (0.4)
Curosurf	156 (27.3)	134 (11.0)	13 (1.2)
NCPAP	204 (35.7)	205 (16.9)	40 (3.6)
RDS	177 (31)	164 (13.5)	39 (3.5)
pneumonia	1 (0.2)	6 (0.5)	2 (0.2)
multiplets	148 (25.9)	271 (22.3)	256 (23.1)
HDCP	46 (8.1)	170 (14.0)	86 (7.8)
PROM	135 (23.6)	206 (16.9)	111 (10.0)

ROP: Retinopathyof prematurity; BW: Birth weight; IVF-ET: *In vitro* fertilization and embryo transfer; NCPAP: Nasal continuous positive airway pressure; RDS: Respiratory distress syndrome; HDCP: Hypertensive disorder complicating pregnancy; PROM: Premature rupture of membrane.

Table 3 Various incidence of ROP and basic statistics in different BW groups *n* (%)

Characteristics	Group 2A	Group 2B	Group 2C
Total number	1062 (36.7)	1131 (39.1)	701 (24.2)
ROP	163 (15.3)	47 (4.2)	14 (2.0)
GA	29.87±1.962	32.11±1.78	33.59±1.459
Sex (Male)	535 (50.4)	632 (55.9)	425 (60.6)
Oxygen supplement	551 (51.9)	523 (46.2)	265 (37.8)
IVF-ET	30 (2.8)	12 (1.1)	3 (0.4)
Curosurf	234 (22.0)	62 (5.5)	7 (1.0)
NCPAP	329 (31.0)	104 (9.2)	16 (2.3)
RDS	260 (24.5)	104 (9.2)	16 (2.3)
pneumonia	4 (0.4)	2 (0.2)	3 (0.4)
multiplets	278 (26.2)	273 (24.1)	124 (17.7)
HDCP	195 (18.4)	88 (7.8)	19 (2.7)
PROM	216 (20.3)	148 (13.1)	88 (12.6)

ROP: Retinopathy of prematurity; GA: Gestation age; IVF-ET: In vitro fertilization and embryo transfer; NCPAP: Nasal continuous positive airway pressure; RDS: Respiratory distress syndrome; HDCP: Hypertensive disorder complicating pregnancy; PROM: Premature rupture of membrane.

It was found that the occurrence of ROP was negatively correlated with GA and BW ($r=-0.296$, $P<0.001$; $r=-0.228$, $P<0.001$, respectively), positively correlated with oxygen supplementation, NCPAP, Curosurf and RDS ($r=$

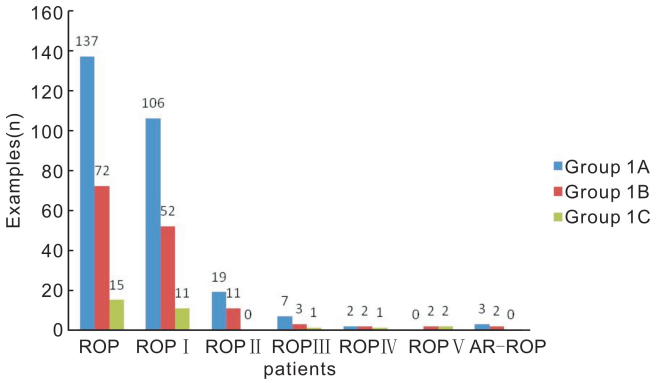

Figure 1 Incidence examples of retinopathy of prematurity (ROP) in different groups of gestational age The lower the GA, the higher the incidence of ROP. The infants of GA longer than 32wk might occur ROP IV or V stage as well.

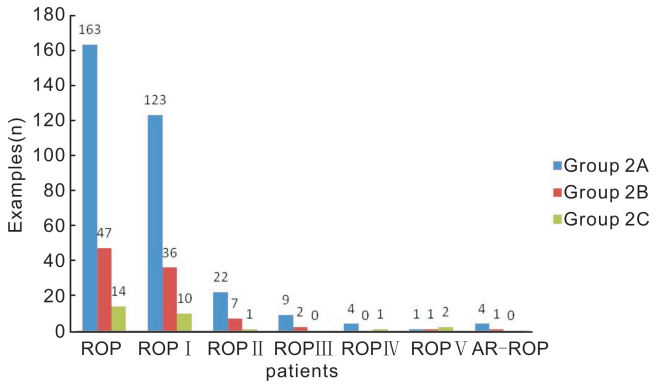

Figure 2 Incidence examples of retinopathy of prematurity (ROP) in different groups of birth weight The lower the BW, the higher the incidence of ROP. The infants of BW bigger than 2000g might occur ROP IV or V stage as well.

0.1333, $P<0.001$; $r=0.095$, $P<0.001$; $r=0.097$, $P<0.001$; $r=0.087$, $P<0.001$, respectively).

In different GA groups or different BW groups, the occurrence of ROP in different stages was different. The lower the GA or BW, the greater the AP-ROP. The infants of GA longer than 32wk or BW bigger than 2000 g might occur ROP IV or V stage as well (Figures 1 and 2).

It was also found that as the usagerate of Curosurf and NCPAP increased year by year, the usage of oxygen supplementation gradually decreased, the incidence of ROP was also on the decline (Figure 3).

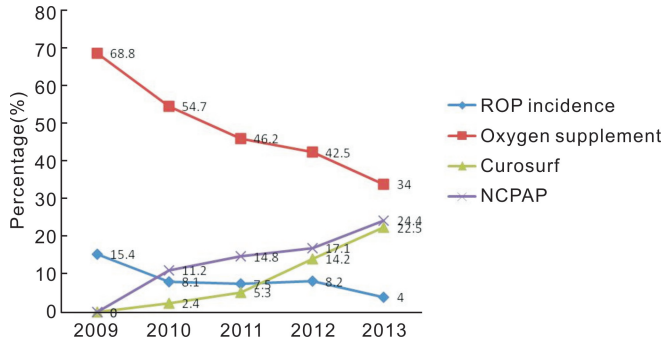

Figure 3 Incidence of retinopathy of prematurity (ROP) and the use of oxygen, Curosurf and NCPAP in each year The usage rate of Curosurf and NCPAP increased year by year, the usage of oxygen supplementation gradually decreased, the incidence of ROP was also on the decline.

DISCUSSION

Jakuskiene *et al*[16] reported that the incidence of any ROP with GA<32wk and BW<1500 g was 27% in European city, Lithuanian. ROP was present in 165/564 (29.2%) based on the criterion of BW<1,500 g in Singapore[17]. Studies from India reported incidence of ROP varies from 20% to 52%, and recent studies showed lower rates of ROP ranging from 20% to 30%[18]. In China, the incidence of ROP decreased from 20.3% in the first time of screening to 10.8% in the latest report, and 3.6% of the latter needed treatment[19-20]. In this study, the incidence of ROP was 7.7%, which was lower than other cities and regions. However the proportion that needed treatment was higher. Screening criteria vary in different units and time-periods[8,21]. Moreover, along with the guidelines of retinal prevention published[9], people may pay more and more attention to the protection of ROP.

The crucial period for detection of ROP is from 32-40wk of PMA, and it is hardly found ROP before 32wk and after delivery[18]. For carrying out screening of ROP reasonably in Tianjin, China, mean PMA of defected ROP was 37.68±4.38wk combined with this study. Data was divided into three groups of redefined GA and BW based on retinal prevention guide published in China[9] and screening criteria in UK (GA<32wk or BW<1500 g)[15]. Current US guidelines, updated in 2013, recommend screening for infants with birth weight of 1500 g or less or GA of 30wk or less[22]. The analysis results indicated that 14 or 15 ROP infants were at least out of upper standards. And the screening results of mean GA and BW were largely higher than other countries and regions[17,23-24]. This study is consistent with the epidemic characteristics that relatively mature preterm neonates have ROP in China, compared with the developed countries such as US and UK[25]. In this study, not only the domestic and international screening criteria were compared, but also the dynamic analysis of the risk factors of ROP was performed. It was found that patients with 1A and 2A had similar physical condition, treatment, and complications. Patients with 1B and 2B were characterized by mean GA and BW in the concentrated crowd. Patients with 1C and 2C were preterm infants who were ignored in accordance with national screening criteria.

Current research efforts focused on the detection of pre- and postnatal risk factors for ROP progression[10]. The major risk factors of ROP includes neonatal maturity (such as GA, BW) and severe systemic disease (such as RDS, apnea). Periventricular leukomalacia and ROP may develop in preterm infants, and altered oxygen condition is a risk factor for both[26]. As early as 1993, Holmstrom has proposed the relationship between GA and ROP[27]. More studies have shown that GA is one of the significant risk factors of ROP[8]. In this study, mean GA and BW of control group were higher than any stage ROP. The lower the GA and BW, the higher

was incidence of ROP. This also proves that immaturity of preterm infants is related to ROP. In our study, ROP group and control group had statistical significance in RDS, Curosurf, NCPAP. It showed RDS, the application of NCPAP, Curosurf treatment of patients with worse physical condition, susceptibility to ROP. Based on logistic regression analysis, ROP usually occurs in infants with low BW, young GA and oxygen supplementation. The OR value of BW was close to 1, the younger GA was more persuasive. However, koerner *et al*[28] proposed that not only GA itself but also GA related inadequate retinal vascularization display correlation with ROP. According to tradition, exposure to oxygen is the most important risk factor for the onset of ROP. However, oxygen-unrelated pathways associated with delayed anabolism became more significant in recent years[29]. Immature lung of premature infant affects retinal blood oxygen environment. How to change the retina anoxic state and reduce the development of ROP is a subject that is worth further study.

Curosurf as a kind of surfactant replacement therapy (SRT) has been applied to therapy of RDS. In developing countries because of high cost and lack of professional management, Curosurf is not in general use yet. SRT is usually used for neonates with GA greater than 28wk who have better potential to survive in developing countries. Continuous positive airway pressure (CPAP) is approved for RDS and for neonates to who SRT is ineffective[30]. This study observed that as the usage rate of Curosurf and NCPAP increased year by year, the usage of oxygen supplementation gradually decreased, the incidence of ROP was also on the decline (Figure 3). Vidyasagar *et al*[30] reported that the incidence of ROP was 58/147 (39.4%) in presurfactant period (1988 to 1992), compared to 107/417 (25.6%) in surfactant period (1993 to 2001) ($P<0.0001$). Rowlands *et al*[31] found a significant reduction in the incidence of ROP, which was attributed to the improvements in ventilation techniques and overall care of the neonates, in particular the use of prenatal steroids and surfactant. These results suggest that the use of pulmonary surfactant is helpful to the development of lung, which alleviate the hypoxia of retina and reduce the occurrence of ROP. The subsequent effect on ROP is not clear. It needs further research. Furthermore, the decrease of the incidence of ROP may be the result of multiple factors.

Despite modern neonatal intensive care and better oxygen supplementation for premature infants, ROP is still occurring. Appropriately timed examination and treatment of ROP has a major impact on visual development. The incidence of ROP was 7.7% among premature infants in Tianjin, China, which was lower than other cities and regions. And the screening results of mean GA and BW of ROP were largely higher than other countries and regions. ROP occurred in higher BW infants too. Although ROP is most often related to a lower BW and a younger GA, these factors do not necessarily predict the severity of ROP in higher BW infants. The use of Curosurf and NCPAP may reduce the occurrence of ROP. But the influence of Curosurf and NCPAP upon ROP needs further research. The screening criteria and the scope of screening need to be improved to ensure that all high-risk premature infants can be examined in time to prevent serious complications.

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