Original Article

Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country

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Background: Retinopathy of prematurity (ROP) is an important cause of childhood blindness in developing countries.

Aim: To report the spectrum of ROP and associated risk factors in babies weighing > 1250 g at birth in a developing country.

Setting and Design: Institutional, retrospective, non-randomized, observational clinical case series.

Materials and Methods: Retrospective analysis (10 years) of 275 eyes (138 babies) with ROP.

Statistical Analysis: Qualitative data with the Chi-square test. Quantitative data using the unpaired t test or the ANOVA and further tested using multivariate logistic regression.

Results: The mean birth weight was 1533.9 g (range 1251 to 2750 g) and the mean period of gestation was 30.9 weeks (range 26 to 35). One hundred and twenty-four of 275 eyes (45.1%) had threshold or worse ROP. Risk factors for threshold or worse disease were, 'outborn babies' ($P < 0.001$), respiratory distress syndrome ($P = 0.007$) and exchange transfusion ($P = 0.003$). The sensitivity of the American and British screening guidelines to pick up threshold or worse ROP in our study group was 82.4% and 77.4% respectively.

Conclusions: Severe ROP is often encountered in babies weighing greater than 1250 g at birth in developing countries. Western screening guidelines may require modifications before application in developing countries.

Key words: Developing countries, heavy babies, incidence, retinopathy of prematurity, risk factors, screening

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Retinopathy of prematurity (ROP) continues to remain an important cause of childhood blindness the world over. The scenario in the developed[1] and developing countries[2] however, differs. In the latter 'larger' and 'older' infants are now more likely to develop ROP than their counterparts in western countries.[1,3] The application of western screening guidelines for developing countries has been questioned.[1]

The CRYO-ROP study included infants weighing < 1251 g at birth alone.[4] There is no agreed policy on the screening of babies larger than 1250 g.[5] The American screening guidelines for ROP suggests that babies ≤ 1500 g birth weight or ≤ 32 weeks gestational age must be screened, with those infants > 1500 g or > 32 weeks be screened at the discretion of the attending neonatologist.[6] However, developing countries may require modification of these screening guidelines.[7-9]

Retinopathy of prematurity was reported in India over a decade ago.[10,11] At that time, 26.1% of babies with ROP weighed > 1250 g at birth.[10] The purpose of the present study was to report the spectrum of ROP in babies > 1250 g at birth and to identify the risk factors responsible for the development of severe ROP in these babies.

Materials and Methods

The study was a retrospective, non-randomized, observational clinical case series. We retrospectively analyzed the records of babies diagnosed to have ROP and registered in the retina clinic between June 1993 and May 2003. This cohort was derived from a larger group screened for ROP in the tertiary level hospital attached to our center and outborn babies directly referred by ophthalmologists and neonatologists from other centers in North India.

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The inclusion criteria for the study were:

1. Premature babies with a diagnosis of ROP weighing > 1250 g at birth.
2. Complete documentation of hospital records including period of gestation, birth weight and details regarding neonatal illnesses and their course.
3. Documentation and categorization according to the International Classification of ROP (ICROP)[12]
4. Treatment wherever required was according to the CRYO-ROP study guidelines with cryotherapy or laser photocoagulation.
5. Minimum three months follow-up period.

The charts were reviewed for the date of birth, birth weight, period of gestation, oxygen exposure, neonatal illness and records of treatment received at the neonatal intensive care unit (NICU). Risk factors looked for included respiratory distress syndrome (RDS), hyaline membrane disease, sepsis, neonatal jaundice, multiple births, apneic episodes, anemia, intraventricular hemorrhage, pneumonia, polycythemia, metabolic acidosis, hypoglycemia, hypotension, shock, necrotizing enterocolitis, meconium peritonitis, hydrocephalus and congenital heart disease. A careful review of the postnatal charts was done to exclude babies with hydrops so as to avoid erroneously exaggerated birth weight records. Treatment received at the NICU including ventilation, oxygen administration, surfactant therapy, phototherapy, exchange blood transfusion, was recorded wherever applicable. Oxygen supplementation was recorded in 'hours of delivery'. 'Hours of active ventilation' referred to ventilator support recorded as the total number of hours of continuous positive airway pressure (CPAP) and synchronized intermittent mandatory ventilation (SIMV).

The babies were divided into two groups for the purpose of this study. Group 1 comprised of stages 1, 2 and 3 less than threshold disease and Group 2 comprised of threshold ROP, stages 4 and 5. The highest stage of ROP reached in either eye determined the inclusion into the group.

We routinely screened all infants whose birth weights were ≤ 1700 g and / or whose gestational age at birth was ≤ 32 weeks. Infants outside these criteria were also screened if the attending neonatologist sought a referral for this purpose based on the 'stormy' postnatal course. The initial examination was carried out at four to six weeks after birth or between a post-conceptual age of 31 to 33 weeks, whichever came earlier. The frequency of subsequent examinations depended on the findings at the initial presentation. Stages 1 and 2 ROP were followed up once in two to three weeks. Prethreshold (any stage ROP in Zone 1 or 2 with plus disease or Zone 2 ROP with Stage 3 not reaching threshold ROP clock hours) was followed weekly till regression or progression into threshold ROP was observed. Threshold ROP (five contiguous or eight cumulative clock hours of ROP Stage 3 with plus in Zone 1 or 2) was treated within 72h of diagnosis with either laser photocoagulation or cryotherapy.

Ocular examination was carried out in the retina clinic, the pediatric nursery or at the NICU for incubator-dependent babies.

Examination under anesthesia was carried out for older babies referred from other centers. Ultrasonography (B-scan) was used to evaluate eyes with opaque media and Stage 5 disease. All cases suspected to have alternate diagnoses simulating ROP such as familial exudative vitreoretinopathy were excluded on the basis of history and clinical examination.

Statistical analysis

Data were tabulated and compared between the two groups. Qualitative variables such as the presence or absence of a neonatal risk factor were tested for statistical significance using the Chi-square test. Quantitative data such as gestational age and birth weight was expressed in the form of mean ± standard deviation and analyzed using the unpaired t test or the ANOVA. The compound effect of significant variables on univariate analysis was further tested using multivariate logistic regression.

Results

During the period between June 1993 and May 2003, 592 infants with the diagnosis of ROP and a minimum follow-up of three months were seen at the Retina Clinic of our center. Of these, 138 infants (23.3%) were > 1250 g at birth and fulfilled the inclusion criteria. Group 1 (Stage 1, 2 and prethreshold ROP) had 76 babies and Group 2 (threshold ROP, stages 4 and 5) had 62 babies. One hundred and fifty-one eyes of 76 babies in Group 1 and 124 eyes of 62 babies of Group 2 were included for analysis. Of these 138 babies, 84 (60.9%) were male and 54 (39.1%) were female. The sex distribution between the two groups was not statistically significant (P = 0.54). The overall median follow-up period was five months (range 3 to 80 months). The mean follow-up was 8.58 months (range 3 to 48) and 18.98 months (range 3 to 80) for Group 1 and 2 respectively.

The birth weight ranged from 1251 to 2750 g with a mean of 1533.9 g (± 286). The mean period of gestation was 30.9 weeks (± 1.8, range 26 to 35).

Group 1

Of the 152 eyes (76 babies), one eye did not develop any ROP and was excluded. The other 151 eyes had Stage 1 in 30 eyes (19.9%), Stage 2 in 101 eyes (66.9%) and Stage 3 (prethreshold) in 20 eyes (13.2%). One hundred and forty-one eyes (93.4%) had Zone 2 disease, the remaining 10 eyes (6.6%) had Zone 3 involvement. The mean clock hour involvement was 4.8 (range 2 to 8). Plus disease was seen in 49 eyes (32.5%). No eye in this group was treated. The mean birth weight and period of gestation of Group 1 babies was 1550.3 ± 239 g (range 1251 to 2300 g) and 31.1 ± 1.6 weeks (range 28 to 35 weeks) respectively.

Group 2

Of the 124 eyes of 62 babies, 10 eyes of 10 babies (8%) had prethreshold ROP in one eye which resolved before reaching threshold ROP. These babies were included in Group 2 because the fellow eye had threshold or worse disease. Of the remaining 114 eyes, threshold ROP was seen in 79 eyes (63.7%), Stage 4 in 12 eyes (9.7%) and Stage 5 in 23 eyes (18.6%). The mean birth weight and period of gestation of Group 2 babies was 1514 ± 336 g (range 1255 to 2750 g) and 30.5 ± 2.0 weeks (range 26 to 35 weeks) respectively. The demographic details of babies in this group has been summarized in Tables 1 and 2.

Using the current American screening guidelines (≤ 1500 g

Table 1: Birth weight distribution of babies with threshold or worse retinopathy of prematurity (Group 2)

Birth weight (grams)	No. of babies (n=62)	Percentage
1251-1500	37	59.7
1501-1750	15	24.2
1751-2000	06	9.6
> 2000	04	6.5

Table 2: Gestational age distribution of babies with threshold or worse retinopathy of prematurity (Group 2)

Gestational age (weeks)	No. of babies (n=62)	Percentage
< 28	04	6.5
28-32	44	70.9
>32	14	22.6

birth weight or ≤ 32 weeks gestational age), 39 babies (28.3%) would be missed in the whole study group. Of these, 28 babies (71.8%) had prethreshold or less (Group 1) and 11 babies (28.2%) had threshold or worse ROP (Group 2). Hence 11 of 62 babies (17.7%) with severe ROP would have been missed using American guidelines. Using the British screening guidelines (≤ 1500 g or ≤31 weeks), three more babies with severe ROP would have been missed (14 of 62, 22.6%). The sensitivity of the British screening guidelines for severe ROP in our study was 77.4% and for the American guidelines was 82.4%.

Using the American screening guidelines, the characteristics of the babies with threshold or worse ROP have been summarized in Table 3.

Of the 79 threshold eyes, nine eyes showed Zone 1 disease. Notable anterior segment findings were leucocoria (16 eyes), posterior synechiae (11), microcornea (2), tunica vasculosa lentis (18), iris cyst (1) and congenital cataract (1).

Seventy-nine eyes with threshold disease were treated using either cryotherapy (23 eyes) or laser photocoagulation (56 eyes). The laser used was diode laser (44 eyes) (IRIS Medical Oculight SL, 810nm Infrared laser, Iris Medical Inc. USA) and 532 green laser (12 eyes) (532 Iris Green Laser, Oculight GL, Iris Medical Inc. USA). Six eyes (five babies) treated with laser needed supplement treatment.

Of the 79 treated eyes, 70 (88.6%) showed favorable structural outcome. Of the nine eyes (11.4%) with unfavorable structural outcome, five eyes underwent vitreous surgery for Stage 4 and 5. Babies with Stages 4 and 5 on presentation were referred to another center for surgery.

Of the 23 risk factors studied [Table 4] on the basis of univariate analysis five risk factors were found to be significant for developing threshold or worse ROP (Group 2). These were, culture-proven sepsis (P = 0.006), exchange transfusion (P =0.003), being 'outborn' (birth at another center) (P < 0.001), mechanical ventilation (P = 0.014) and RDS (P= 0.007).

Eight out of 76 babies (10.52%) in Group 1 and five of 62 babies (8.06%) in Group 2 never received oxygen and this was not significant. (P = 0.62). The mean hours of delivery of oxygen in both groups were 6.45 and 7.01h respectively.

Of the five risk factors, 'outborn', RDS and exchange transfusion emerged as independent risk factors on multivariate analysis.

Discussion

Our data reveals that severe ROP including threshold or worse disease is not uncommon in babies > 1250 g birth weight in our setting. Almost a decade ago Charan *et al*.[10] reported an incidence of any stage ROP of 47.2% in babies < 1700 at birth from northern India. Of these babies, 26.1% were greater than 1250 g at birth. In another study, Dogra *et al*.[13] reported that 30.7% of babies with threshold ROP treated with cryotherapy were > 1250 g and 15.3% were >1500 g at birth. In a study from southern India, Deshpande *et al*.[14] reported 21.7% infants with threshold ROP having birth weight > 1500 g. Phan *et al*.[3] from Vietnam, reported 21 babies with threshold ROP of which 13 babies (61.9%) were > 1250 g at birth. Fielder[15] commented that 54% of the infants requiring treatment for ROP in Lithuania had birth weight > 1500 g. In the light of these observations, a recent report[1] regarding 'larger' and 'older' infants from developing countries developing more ROP than their counterparts in the United States is relevant. The birth weight of our group ranged from 1251 to 2750 g (mean 1534 g). The period of gestation of the babies in our study varied from 26 to 35 weeks (mean 30.86 weeks).

There are only limited reports of ROP in infants from the developed countries with birth weights > 1250 g.[16-25] In these reports, severe ROP was either not found in heavier babies[21,23] or was observed rarely.[17,18,20,24] Hutchinson *et al*.[22] reported 25 infants (8%) with birth weights between 1251 and 1500 g who had undergone laser photocoagulation for threshold ROP.

A recent study from the United States[25] on ROP in babies weighing greater than 1250 g at birth showed that of the 185 infants with any stage of ROP, 31 infants (16.8%) had Stage 3 or worse disease. An almost identical 16.9% of threshold or worse ROP has been reported by Phan *et al.* from Vietnam.[3] The higher percentage of 44.9% babies with severe ROP in our study needs further investigation. Our center, which is a tertiary referral center for ROP, may suffer from a selection bias, contributing to the large number of babies with more

Table 3: Characteristics of 11 babies with threshold or worse retinopathy of prematurity who would have been missed if American screening guidelines were applied

			Birth weight (grams)		Gestational age (weeks)	
Retinopathy of prematurity	**No. of babies**	**(%)**	**Mean**	**Range**	**Mean**	**Range**
Threshold	5	45.4	1773	1600-2015	34	33-35
Stage 4	2	18.2	1950	1900-2000	34	33-35
Stage 5	4	36.4	2162.5	1850-2750	33.5	33-34
Total	11	100	1946.82	1600-2750	33.82	33-35

Table 4: Risk factor analysis

Risk factors	Group 1 (%) (n= 76 babies)	Group 2 (%) (n=62 babies)	*P* value
Outborn[1,2]	7 (9.2)	23 (37.1)	<0.001
Exchange transfusion[1,2]	4 (5.3)	14 (22.6)	0.003
Respiratory distress syndrome[1,2]	38 (50)	45 (72.6)	0.007
Mechanical ventilation[2]	17 (22.4)	26 (41.9)	0.014
Sepsis (culture proven)[2]	6 (7.8)	19 (30.7)	0.006
Multiple births[3]	7 (9.2)	3 (4.8)	0.512
Hyaline membrane disease[3]	17 (22.4)	11 (17.7)	0.501
Surfactant therapy[3]	6 (7.8)	1 (1.6)	0.199
Apnea[3]	23 (30.3)	33 (53.2)	0.628
Anemia[3]	12 (15.8)	16 (25.8)	0.145
Polycythemia[3]	5 (6.6)	3 (4.8)	0.945
Pneumonia[3]	16 (21.1)	16 (25.8)	0.510
Neonatal Jaundice[3]	48 (63.2)	38 (61.3)	0.821
Phototherapy[3]	27 (35.5)	19 (30.6)	0.545
Transient tachypnea of newborn[3]	4 (5.3)	3 (4.8)	0.781
Intraventricular hemorrhage[3]	5 (6.6)	3 (4.8)	0.945
Hypoglycemia[3]	6 (7.8)	6 (9.7)	0.711
Hypotension[3]	4 (5.3)	7 (11.3)	0.325
Shock[3]	3 (1.3)	7 (11.3)	0.185
Necrotizing enterocolitis[3]	1 (1.3)	4 (6.4)	0.251
Meconium peritonitis[3]	0 (0)	2 (3.2)	0.389
Hydrocephalus[3]	2 (2.6)	1 (1.6)	0.858
Congenital heart disease[3]	5 (6.6)	3 (4.8)	0.945

[1]Significant on multivariate logistic regression analysis, [2]Significant on univariate analysis, [3]Not significant (*P*>0.05)

severe disease. We saw Stage 5 ROP in 12 babies (23 eyes). All these were outborn and had not undergone any formal ROP screening. Ten of these 12 babies (83.3%) received oxygen without any saturation monitoring as per our discussion with the treating pediatricians.

As part of our study we attempted to identify factors that would help to predict which of the 'heavy' babies would progress to severe stages of the disease so as to develop a 'sickness criteria' as proposed by Gilbert.[26] On multivariate analysis, 'outborn', RDS and exchange transfusion emerged as independent risk factors for severe ROP.

Recent studies from the United States and other developed countries mention significant systemic illnesses in their infants with ROP.[20,27,28] Wagner in his editorial[1] noted that oxygen monitoring requires sophisticated pulse oximeters and other equipment not readily available in developing countries. As expected, the occurrence of ROP correlated with more supplemental oxygen and the administration of CPAP.[1] In India, Rekha *et al*.[29] reported that duration of oxygen therapy and anemia were independent factors predicting the development of ROP. In another recent study, Dutta *et al*.[30] reported the administration of packed cell and double volume exchange transfusions in the neonatal period as major risk factors for the development of threshold ROP. There is a need to study prospectively, the maternal factors responsible for severe ROP in heavier babies.

The results of our study also raise the issue of screening criteria for ROP in our part of the world. From the West, Goble *et al*.[21] in their series reported that none of the babies with birth weight > 1250 g developed threshold ROP and in fact, did not recommend screening for babies > 1250 g at birth. In contrast, Gilbert[26] reported that lowering birth weight criteria would expose a small number of larger babies who are at risk for developing threshold ROP. More recently, in a study comparing the spectrum of ROP between developed and lesser developed countries, 13% of infants from the poorly developed nations exceeded the screening criteria followed in the United Kingdom.[7] A recent study by Chiang *et al*.[28] looked at a very large database of neonates from New York State in the United States and found that 17 infants with ROP were > 2000 g birth weight, but none required any treatment. In our study, 12 infants were > 2000 g, of which four had threshold or worse ROP. The Vietnam study[3] reported cases of severe blinding ROP in infants up to 1800 g at birth. A recent study from China[31] retrospectively analyzed infants treated for ROP Stages 3, 4 and 5. They found that 27.2% of these babies were > 1500 g at birth. In view of blinding disease in higher birth weight babies in developing countries, we may need to modify screening criteria to suit locally prevalent conditions.

The fact that screening of 'heavy' babies may be missed when we adhere to the western guidelines is evident from our data. When we applied the guidelines recommended by the American Academy of Ophthalmology[6] on our study group, 11

babies (17.7%), with threshold or worse ROP would be either > 1500 g or > 32 weeks and would have been missed. Similarly, applying British screening guidelines,[32] 14 babies (22.6%) would be missed. These figures are comparable with a recent report from China, where 30.4% and 16.2% of infants with ROP Stages 3, 4 and 5 were reported to exceed the screening criteria of the United States and United Kingdom respectively.[31] Recently, in a retrospective study from India, analysis of babies undergoing laser or surgery showed that the mean birth weight of these babies was 1254.5 g (range 710 to 2000) and the mean period of gestation was 29.6 weeks.[8] Another recent study from India, found that 36 of their 54 infants (66.7%) had fulminate ROP. The mean birth weight of this group was 1554 g (range 850 to 2290) and mean gestational age was 31.75 weeks (range 28 to 34).[33] Using American and British screening guidelines, a report from Thailand found a sensitivity of 93.9%, which increased to 100% when all babies < 33 weeks were screened.[9] At our center, using our own screening guidelines of < 1700 g or < 32 weeks, we found that nine babies (14.5%) with threshold or worse ROP (Group 2) were still missed. Since 2004 we have now extended our gestational age to < 34 weeks for screening. If we apply this cutoff, only two infants (3.2%) would have been missed. The sensitivity has increased from 85.5% to 96.8% after this change. The cost-effectiveness of modifying national guidelines, however, needs more prospective, multicentric studies before such recommendations can be advocated.

The limitations of our study lies in its retrospective nature and the inability to calculate the incidence of ROP in infants weighing > 1250 g at birth. Also, treatment of these heavier infants was based on the CRYO-ROP guidelines which included only infants < 1250 g at birth. It is also possible that risk factors such as maternal disease, antenatal factors and genetic mutations in these infants responsible for diseases mimicking ROP, not evaluated in this study may have influenced the results.

In conclusion, ROP, including severe disease in babies weighing > 1250 g is not uncommon in the developing world. A more efficient strategy, which includes, increasing awareness among ophthalmologists and neonatologists regarding the magnitude of the problem is essential. A closer look at the screening guidelines for developing countries is required. Early identification of 'heavy babies' at risk for developing severe ROP would reduce the blindness burden associated with ROP in these babies.

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