Retinopathy of prematurity: an evaluation of existing screening criteria in Pakistan

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ABSTRACT

Aim To evaluate if broadening the criteria for retinopathy of prematurity (ROP) screening to include babies with gestational age $\geq$32 weeks and/or birth weight $\geq$1500 g, would have an impact on the number of babies diagnosed as having ROP.

Methods A prospective cohort study was carried out at the Aga Khan University Hospital, Karachi, Pakistan. Infants with gestational age $\leq$35 weeks or birth weight $\leq$2000 g born in this hospital from May 2010 to December 2012 were screened for the presence of ROP 4–6 weeks after birth. Subsequent examinations were performed at intervals based on the findings of initial eye examinations. Infants diagnosed as having ROP were treated with argon laser therapy. Neonatal risk factors were also assessed. Cumulative incidence of ROP was calculated for babies falling within and outside current screening criteria. Multivariate logistic regression analysis was performed to examine the predictors of ROP.

Results A total of 301 infants were screened: 27 (9%) babies developed ROP, of which 19 had stage 3 ROP or worse. None of the babies falling outside the current screening criteria developed ROP. The incidence of ROP in the infants meeting the current screening criteria was 11.5%. Multivariate logistic regression analysis showed that only gestational age (adjusted relative risk 0.774, 95% CI 0.603 to 0.994) was independently associated with the development of ROP.

Conclusions In our population ROP was not seen to occur in infants older than 32 weeks gestational age and/or weighing more than 1500 g.

INTRODUCTION

Retinopathy of prematurity (ROP) is a major avoidable cause of blindness in children.[1] In developed countries such as the USA, it is the second most common cause of childhood blindness.[2] Gilbert *et al*[3] suggest that heavier and more mature infants are developing severe ROP in countries with low or moderate levels of development compared with developed countries. ROP is emerging as an important cause of childhood blindness in developing countries because of significant improvement in survival rates of premature and low birthweight infants. However, there is a lack of awareness of the disease process and its screening criteria, compounded by a lack of skilled human resources to care for babies at risk of ROP.[4]

Research from several developing countries, including India and China, has shown that the international screening criteria for ROP—gestational age $\leq$32 weeks and/or birth weight $\leq$1500 g—might not be entirely applicable in this developing part of the world.[5] [6] Babies as heavy as 2000 g at birth and as mature as 35 weeks have been found to develop ROP.[6–8] Several investigators conclude that a significant proportion of ROP cases would have been missed had they used the recommended screening criteria, urging the need for development of region-specific screening guidelines.[9] Hence, we decided to conduct a study to determine if broadening the criteria for ROP screening would have an impact on the number of babies diagnosed as having ROP.

METHODS

All infants—gestational age $\leq$35 weeks and birth weight $\leq$2000 g—born at the Aga Khan University Hospital (AKUH), Karachi, from May 2010 to December 2012 were screened for the presence of ROP. The study was approved by the Ethical Review Committee of Aga Khan University, Karachi. Informed consent was obtained from the parents. Data were collected prospectively on gestational age, birth weight, postnatal age, neonatal illnesses (eg, respiratory distress syndrome, sepsis and apnoea) and treatment received (eg, supplemental oxygen, phototherapy, blood transfusions and surfactant therapy).

All infants meeting the screening criteria were scheduled for their first examination between 4 and 6 weeks of life. Dilated fundus examinations were carried out in the clinic or neonatal intensive care unit (NICU) under topical anaesthesia by the consultant ophthalmologist (TAC). Tropicamide (0.5%) and phenylephrine (2.5%) eye drops were administered three times, 15 min apart, before each examination. Binocular indirect ophthalmoscopy was performed using a 20D and 30D lens. Lid speculum and scleral depressors were used to ensure adequate examination.

The 'International Classification of ROP' guidelines were used to record stage of the disease, location by zone, signs of plus disease and signs of regression.[10] Babies with no ROP were examined at 2-weekly intervals until they reached 40 weeks post-conception age. Babies with stage 1 and 2 disease were followed up weekly to see if disease regressed or if it progressed to stage 3, in which case treatment was then offered. Infants with stage 3 ROP were treated with argon laser, with or without intravitreal injections of bevacizumab, within 72 h of diagnosis and followed weekly.

The termination of acute retinal screening examinations was based on the latest guidelines by the American Academy of Pediatrics (AAP), American Academy of Ophthalmology and American Association for Pediatric Ophthalmology and Strabismus.[5] All data was analysed using IBM SPSS Statistics (V.19, SPSS Inc., an IBM company,

Armonk, New York, USA). Data for gestational age and birth weight for those who did and did not develop ROP were expressed in the form of mean±SD values. Proportions were calculated for categorical variables. The presence of risk factors among those with and without ROP were tested for statistical significance using the χ^2 test or univariate binary logistic regression. Independent variables that were associated with ROP with $p \leq 0.2$ were included in the multivariate binary logistic regression to identify the independent predictors of ROP. A p value < 0.05 was considered statistically significant.

RESULTS

From April 2010 to December 2012, a total of 424 babies born at the AKUH fulfilled the eligibility criteria and their parents were invited to allow their participation in the study. Of these, 30 died while in the neonatal intensive care unit and 93 patients did not attend the first scheduled appointment. A total of 301 babies were examined; 163 (54.2%) were boys. The mean (±SD) gestational age of study subjects was 31.2±2.3 weeks and the mean birth weight was 1505±427 g (table 1). Overall, 9% (27/301) babies were found to have ROP (table 2). Of 66 infants falling outside the current screening criteria (ie, GA ≤32 weeks & BW ≤1500 g), none developed ROP. Further analysis included only those infants who met the international screening criteria for ROP (n=235). Overall, 11.5% (27/235) babies developed ROP (table 3). Of those with ROP, 18 (66.7%) had stage 3 and 1 had stage 4 disease. The mean number of examinations was 2.06±1.47. Overall 93.7% babies were examined until they reached 40 weeks post-conception age or were fully vascularised.

In the univariate analysis, factors significantly associated with ROP included birth weight, gestational age, supplemental oxygen, surfactant therapy, septicaemia, birth apnoea, blood transfusions and respiratory distress syndrome (table 4). Except supplemental oxygen, all other predictors were included in the multivariate analysis, which showed only gestational age as an independent predictor of ROP (adjusted relative risk 0.774, 95% CI 0.603 to 0.994). All 19 babies with stage 3 ROP or

Table 2 Risk of ROP among premature infants (gestational age ≤35 weeks and birth weight ≤2000 g) included in the study (n=301)

Variable	Examined Count	Infants with ROP Count	Infants with ROP %	p Value*
Overall	301	27	9.0	
Gender				0.289
Male	163	12	7.4	
Female	138	15	10.9	
Supplemental oxygen				0.002
Yes	228	27	11.8	
No	73	0	0	
Surfactant				<0.001
Yes	71	19	26.8	
No	230	8	3.5	
Septicaemia				<0.001
Yes	80	15	18.8	
No	221	12	5.4	
Birth apnoea				<0.001
Yes	57	13	22.8	
No	244	14	5.7	
Blood transfusions				<0.001
Yes	84	21	25.0	
No	217	6	2.8	
Phototherapy				0.091
Yes	214	23	10.7	
No	87	4	4.6	
Respiratory distress syndrome				0.009
Yes	33	7	21.2	
No	268	20	7.5	
Meeting international screening criteria				0.004
Yes	235	27	11.5	
No	66	0	0.0	

*p Values are for χ^2 test (or Fisher's exact test when necessary).
ROP, retinopathy of prematurity.

worse were treated, of whom 16 received laser and intravitreal bevacizumab injection and 3 received laser treatment alone.

DISCUSSION

Contrary to the findings of several previous studies in low-income countries, our study showed that none of the infants falling outside the current screening criteria used across the world (ie, gestational age ≤32 weeks and/or BW ≤1500 g) developed ROP.

Studies from India, China, Saudi Arabia and Turkey suggested that a significant proportion of babies requiring ROP treatment might have been missed had they used a narrower screening criterion.[6 9 11–13] In light of such data, we decided to broaden our screening criteria. However, of 66 infants (GA >32 weeks & BW >1500 g) in our study, none developed ROP. It remains unclear how many babies of this weight and age need to be screened to detect one additional case of ROP and whether these estimates would differ in different settings.

As part of our study, we also identified factors that could increase the risk of such babies for developing ROP. Gestational age emerged as independent risk factors for the development of ROP. It is also important to mention that determination of correct gestational age of a baby is also a significant challenge in

Table 1 Demographic and clinical characteristics of newborn babies enrolled in the study (n=301)

Characteristic		Count	%
Gender	Male	163	54.2
	Female	138	45.8
	Total	301	100.0
Supplemental oxygen if given	Yes	228	75.7
	No	73	24.3
Surfactant	Yes	71	23.6
	No	230	76.4
Septicaemia	Yes	80	26.6
	No	221	73.4
Episode of birth apnoea	Yes	57	18.9
	No	244	81.1
Blood transfusions	Yes	84	27.9
	No	217	72.1
Phototherapy for neonatal jaundice	Yes	214	71.1
	No	87	28.9
Respiratory distress syndrome	Yes	33	11.0
	No	268	89.0

All values are reported as counts and percentages unless noted otherwise. Mean±SD gestational age was 31.2±2.3 weeks, mean±SD birth weight was 1505±427 g.

Table 3 Risk of ROP among premature infants with gestational age ≤32 weeks and birth weight ≤1500 g (n=235)

	Examined Count	Infants with ROP Count	Infants with ROP %	p Value*
Overall	235	27	11.5	
Gender				0.383
Male	123	12	9.8	
Female	112	15	13.4	
Supplemental oxygen				0.014
Yes	196	27	13.8	
No	39	0	.0	
Surfactant				<0.001
Yes	67	19	28.4	
No	168	8	4.8	
Septicaemia				<0.003
Yes	72	15	20.8	
No	163	12	7.4	
Birth apnoea				<0.001
Yes	49	13	26.5	
No	186	14	7.5	
Blood transfusions				<0.001
Yes	75	21	28.0	
No	160	6	3.8	
Phototherapy				0.135
Yes	172	23	13.4	
No	63	4	6.3	
Respiratory distress syndrome				0.006
Yes	25	7	28.0	
No	210	20	9.5	

*p Values are for χ^2 test (or Fisher's exact test when necessary).
ROP, retinopathy of prematurity.

developing countries especially among less educated. Incorrect measure of GA may have resulted in misclassification of risk in this study as well as other studies.

The incidence of ROP in our study (11.5%) is much lower than that reported in several previous studies. A possible explanation for these variations, besides genetics, could be the relative distribution of extremely premature babies and distribution of ROP risk factors.

Threshold ROP (stage 3 or worse) was seen in 19 of the 27 babies (70.4%) who developed ROP. A study from India also reported threshold disease in 62/138 (45%) babies.[6]

A limitation of our study was that it looked at ROP incidence in just one hospital at a major Pakistan University with good neonatal care. Things may be very different at smaller hospitals in the country where neonatal care is not as advanced. Future studies should include multiple high-volume centres to increase generalisability. Patient compliance with regular follow-up examinations was a limitation of our study. Reasons for low compliance likely include lack of understanding of the seriousness of ROP as well as the financial constraints of the patients' families. Lack of appropriate counselling of parents by paediatricians/neonatologists regarding the need for ophthalmic examination in at-risk infants continues to be a factor for failure to have their babies screened. Thus, we continue to see cases where patients seek medical care only when the disease has reached an irreversible stage with loss of red reflex and permanent loss of vision.

Our current screening criteria adopted from the guidelines set by the AAP, the American Association for Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology appear appropriate for the clinical setting of ROP screening in Pakistan. However, a larger multicentre study is needed to determine how many babies above this criterion

Table 4 Univariate and multivariate analysis of factors associated with the risk of ROP among premature infants with gestational age ≤32 weeks and birth weight ≤1500 g (n=235)

	Crude relative risk	p Value	Adjusted relative risk	p Value
Birth weight	0.996 (0.994 to 0.998)	<0.001	0.999 (0.996 to 1.001)	0.178
Gestational age	0.589 (0.501 to 0.691)	<0.001	0.774 (0.603 to 0.994)	0.044
Surfactant		<0.001		0.261
Yes	5.955 (2.607 to 13.603)		1.778 (0.651 to 4.854)	
No	1.0		1.0	
Septicaemia		0.007		0.668
Yes	2.830 (1.325 to 6.046)		1.206 (0.513 to 2.832)	
No	1.0		1.0	
Birth apnoea		0.001		0.209
Yes	3.525 (1.657 to 7.499)		1.723 (0.737 to 4.029)	
No	1.0		1.0	
Blood transfusions		<0.001		0.349
Yes	7.467 (3.014 to 18.499)		1.757 (0.540 to 5.721)	
No	1.0		1.0	
Phototherapy		0.169		0.951
Yes	2.106 (0.728 to 6.090)		0.963 (0.292 to 3.183)	
No	1.0		1.0	
Respiratory distress syndrome		0.014		0.714
Yes	2.940 (1.243 to 6.953)		1.194 (0.464 to 3.071)	
No	1.0		1.0	

ROP, retinopathy of prematurity.

Global issues

need to be screened to detect one additional case of ROP and how cost effective such a programme will be.

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