Indian J Pediatr (July 2012) 79(7):911–915
DOI 10.1007/s12098-012-0707-y

ORIGINAL ARTICLE

Retinopathy of Prematurity in a Rural Neonatal Intensive Care Unit in South India—A Prospective Study

Bhavana Hungi · Anand Vinekar · Narendra Datti · Pushpalatha Kariyappa · Sherine Braganza · Susheela Chinnaiah · Krishnamurthy Donthi · Bhujang Shetty

Received: 22 June 2011 / Accepted: 7 February 2012 / Published online: 23 February 2012

Abstract
Objective To report the incidence, spectrum and treatment outcome of Retinopathy of Prematurity (ROP) in a rural neonatal nursery.
Methods This Prospective, observational, non-randomized study was conducted in a level III Neonatal Intensive Care Unit (NICU) at district headquarters in South India. 118 babies with birth weight ≤2000 g and/or period of gestation (POG) ≤34 wk were included in the study. Eligible infants were screened with indirect ophthalmoscopy and wide-field digital imaging (Retcam) until retinal vascularization was complete or disease regressed. Early Treatment Retinopathy of Prematurity (ETROP) guidelines were followed for laser.
Results The overall incidence of ROP was 41.5% and treatable ROP was 26.4% (24/91) of eyes diagnosed with ROP and 10.2% (24/236) of the overall eyes screened. The mean birth weights and periods of gestation with and without ROP were 1555.9 *vs.* 1672.5 g (*P* 0.005) and 32.2 *vs.* 34.6 wk, respectively ($P<0.001$). Half of the treated eyes had aggressive posterior ROP in Zone 1. All treated eyes had a favorable outcome. Respiratory distress syndrome, oxygen therapy, neonatal Jaundice and sepsis were higher in the ROP group but was not statistically significant. Of the overall infants screened, 68 (57.6%) were heavier and older than the American screening cut-off. Of these, 36.8% had some stage ROP and 8% required treatment.
Conclusions This is the first prospective ROP study from a district NICU in India and compares with previously published urban data. If Western-screening guidelines are used in the rural scenario, we risk a significant proportion of infants being missed who may require treatment.

Keywords Aggressive posterior ROP · Laser photocoagulation · Neonatal intensive care unit · Retinopathy of Prematurity · Rural

B. Hungi · N. Datti · K. Donthi
Department of Ophthalmology,
Sri Devaraj Urs Medical College and Hospital,
Kolar District,
Tamaka, Karnataka, India

A. Vinekar · S. Braganza · B. Shetty
Narayana Nethralaya Postgraduate Institute of Ophthalmology,
Bangalore, Karnataka, India

P. Kariyappa · S. Chinnaiah
Department of Pediatrics,
Sri Devaraj Urs Medical College and Hospital,
Kolar District,
Tamaka, Karnataka, India

A. Vinekar (✉)
Department of Pediatric Retina,
Narayana Nethralaya Postgraduate Institute of Ophthalmology,
121/C, 1st R Block, Rajajinagar,
Bangalore 560010, India
e-mail: anandvinekar@yahoo.com

Introduction

Retinopathy of Prematurity (ROP) is a leading cause of childhood blindness in the developed world. [1, 2] In India and other middle-income countries, the disease is rapidly progressing to the proportion of the 'third epidemic' [3]. ROP in India was first reported anecdotally in 1992 [4] and prospectively in 1995 [5, 6]. Since then, over the past two decades, ROP continues to be reported from 'urban' neonatal intensive care units at an incidence ranging from 20 and 51.9% [5–9]. To the authors' best knowledge, there is no report of ROP incidence describing the spectrum of the disease in infants managed at a rural neonatal care facility.

The authors report an 18 mo prospective study describing the incidence, disease characteristics, risk factors and treatment outcomes of rural infants screened and treated for ROP, managed at a level III nursery in a tertiary care medical college teaching hospital situated at the district headquarters of Kolar district of South-Eastern Karnataka state.

Material and Methods

The prospective study was conducted at the level III neonatal intensive care unit (NICU) of RL Jalappa Hospital, affiliated to Sri Devaraj Urs Medical College Tamaka, Kolar during the period, December 1st 2008 through May 31st 2010. All the infants admitted to the NICU were born in the study hospital or referred immediately after birth from sub-district level hospitals in Kolar district.

Infants born less than or equal to 2000 g at birth and/or less than or equal to 34 wk of gestation were considered eligible for ROP screening. Any infants outside these criteria were also considered for screening if the treating neonatologist felt that the child had a stormy postnatal course. The first screening examination was performed between wk 2 and 3 after birth, or at least one examination prior to discharge from the NICU, whichever came earlier. Subsequent screening visits were determined based on the clinical findings at that visit [10].

ROP screening was performed using a binocular indirect ophthalmoscope (Heine Beta 500, Heine, Germany) by any two of the three authors (BH, AV, SB) at every visit with a 20D aspheric lens using a Flynn infant atraumatic scleral depressor. Anterior segment examination was carried out in all the babies prior to and following dilatation using the magnification of the 20D lens. Posterior segment examination was carried out under full pupillary dilatation using phenylephrine 2.5% and cyclopentolate 0.5% (Auropent Plus, Aurolab, Madurai, TN) instilled 2 to 3 times with an interval of 15 to 20 min prior to the examination. Analgesia was obtained by using topical Proparacaine 0.5% (Paracain, Sunways, Mumbai, India) and oral sterile pellets soaked in Dextrose 10% placed during the length of the procedure [10].

In addition all infants were subjected to wide-field digital imaging (WFDI), using a portable infant retinal camera, RETCAM Shuttle (Clarity MSI, Pleasanton, CA, USA). Images were acquired by a team supervised by one of the authors (AV or SB). An anterior segment photograph of the maximally dilated pupil and 7 or more images of the retina (disc centered, macula centered, macula temporal, and 4 peripheral quadrants) were captured. Multiple images of a quadrant with pathology were acquired wherever applicable. This protocol has been modified from the PHOTO-ROP trial. [11, 12]

ROP was classified according to Revised International Classification of Retinopathy of Prematurity [2] and treatment was based on the Early Treatment of ROP (ETROP) guidelines [1].

Laser photoablation was done using a 532 nm green laser [13] (Iris Medical, Iridex, USA) delivered using laser-indirect ophthalmoscopy, under topical anaesthesia and oral dextrose pellets [10] under the monitoring of the neonatologist. Confluent to near confluent laser spots were delivered to the avascular retina anterior to the ridge. Aggressive posterior ROP was treated using the method previously described [12] and supplement treatment was given a week later. Cases undergoing treatment were followed up until complete resolution was observed. Those eyes with less than treatment threshold ROP (Type 2 ROP) [2] were serially followed until complete retinal vascularization was noted. [10] The median number of follow up visits was 4 for infants not requiring treatment.

Babies who did not complete follow-up or those with incomplete neonatal details were excluded from the analysis. Subsequent follow up to determine visual acuity, refractive errors and long term sequelae and outcomes [14–16] were performed at Bangalore.

Informed consent was obtained from the parents or guardians prior to each screening. A special written consent was obtained prior to laser treatment. The study was approved by the Ethics Committee of Sri Devaraj Urs Medical College, Tamaka, Kolar and the Institute Research Committee of Narayana Nethralaya Postgraduate Institute of Ophthalmology, Bangalore.

The data was analyzed by SAS 9.0, SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11. Univariate analysis was done using Chi-Square and Fisher Exact test.

Results

157 infants were eligible for inclusion during the study period. Of these, 39 infants did not complete follow up and were excluded. Hence, 118 babies (236 eyes) were included for the analysis. Of the 118 babies, 69 (58.5%) were boys and 49 (41.5%) were girls (P=0.6).

Fourty nine of the 118 babies developed some stage of ROP accounting to an incidence of 41.5% in the 18-mo interval. The birth weight ranged from 940 g to 2700 g. The overall mean birth weight of the whole study group was 1627.8 g (± 308.5). The mean birth weights of the cohort with and without ROP was 1555.9 g (± 278.2) and 1672.5 g (± 317.2) respectively (P=0.005). The mean period of gestation of the whole group was 33.7 wk (± 2.8). The mean gestational ages of the cohort with and without ROP was 32.2 wk (±2.3) and 34.6 wk (±2.7) respectively (P <0.001).

ROP Clinical Spectrum

Ninety one eyes of 98 (49 infants) had some stage ROP. The remaining seven eyes completed retinal vascularization without developing ROP. The stages, zones and plus disease distribution of these eyes classified as classical (79) (Type 1) and APROP (12) have been summarized in Table 1.

Treatment and Outcome

Twenty four eyes of 12 babies underwent treatment having fulfilled the criteria for treatment described by the ETROP guidelines [1]. This translates to 26.4% (24/91) of eyes diagnosed with ROP and 10.2% (24/236) of the overall eyes screened.

Of these 24 eyes that underwent laser photoablation, 12 eyes (50%) had Type 1 ROP (Classical ROP) and 12 eyes (50%) have aggressive posterior ROP (APROP). The zone and PLUS details of these eyes are also summarized in Table 1.

The number of spots delivered in these eyes is summarized in Table 2. Supplement laser was required in all eyes (12) with APROP and 2 of 12 eyes with classical ROP and was given one wk after the first sitting. All eyes (24, 100%), showed favorable outcome as described by the CRYO-ROP study criteria. [16] The mean postmenstrual age (PMA) at treatment was 40 wk (±4.7) for the classical ROP and 34.5 wk (±2.4) APROP respectively (P=0.1). WFDI was successfully obtained in all infants at each visit. No systemic or ocular adverse effects were noted during or immediately following the procedure.

Risk Factor Analysis

In all 17 risk factors were selected for analysis and have been detailed in Table 3. These were derived from previous publications [7, 8, 17–20] and based on the neonatal practice and trends in the authors' hospital.

Table 1 ROP spectrum and clinical features of eyes with the disease (n=91)

Total eyes with ROP =91	Classical=79 eyes (86.8%)			APROP=12 eyes (13.2%)
Stage	**1**	**2**	**3**	**APROP**
No. of eyes	26	51	2	12
(Percentage)	(32.9)	(64.6)	(2.5)	(13.2)
Zone	**I**	**II**	**III**	**I**
n (Percentage)	2(2.1)	29(31.9)	48(52.7)	12(13.2)
PLUS disease		**12**		**12**
Treatment		**12**		**12**

Classical ROP (Type 1 or 2 ROP) and APROP are defined as per the new classification of ICROP [2]

Table 2 Details of laser spots in classical and aggressive posterior ROP using 532 nm green laser

Total Eyes	Mean no. of laser spots*	Standard deviation
Right eye	2546.3	1429.9
Left eye	2967.8	1652.6
Both eyes	2757.0	1526.5
Classical ROP		
Right eye	1423.3	1136.0
Left eye	1585.0	1083.5
Both eyes	1504.2	1061.7
APROP		
Right eye	3669.2	426.0
Left eye	4350.0	495.9
Both eyes	4009.8	566.4

* P<0.001, (Classical *vs*. APROP)

The Laser used in the study was 532 nm Green Laser (Iris Medical, Iridex, USA) and was delivered using the indirect ophthalmoscopic delivery system at the study centre

No risk factor reached statistical significance between the groups with and without ROP. However, the authors' noticed a trend towards clinical significance with 4 systemic conditions, which were more commonly observed in the cohort with ROP compared to the group without. These were respiratory distress syndrome (RDS) (26.5% *vs*. 14.5%), oxygen therapy (18.4% *vs*. 8.7%), neonatal jaundice (32.7% *vs*. 23.2%) and clinically proven sepsis (22.4% *vs*. 15.9%).

Table 3 Comparison of risk factors analyzed between infants with and without ROP

Sl.no	Risk factors	No ROP (%)	Had ROP (%)
1.	Respiratory distress syndrome (RDS)	14.5	26.5
2.	Oxygen	8.7	18.4
3.	Neonatal jaundice	23.2	32.7
4.	Sepsis	15.9	22.4
5.	Twins	21.7	28.6
6.	Cesarean Section	20.3	14.3
7.	Pregnancy induced hypertension	17.4	20.4
8.	Anemia	1.4	4.1
9.	Pneumonia	0.0	2.0
10.	Hydrocephalous	0.0	2.0
11.	Birth asphyxia	15.9	14.3
12.	Meconium aspiration	4.3	2.0
13.	Thrombocytopenia	8.7	6.1
14.	Meningitis	2.9	0.0
15.	Plasma transfusion	2.9	0.0
16.	Polycythemia	1.4	0.0
17.	Disseminated intravascular coagulation	1.4	0.0

Applicability of American Screening Guidelines [21] in the present study

Using the current American screening guidelines (≤ 1500 g birth weight or ≤30 wk gestational age), [21] 73 (73/118, 61.9%) babies overall would have missed ROP screening based on birth weight cut off alone and 103 (103/118, 87.3%) would have missed screening based on gestational age alone. If both criteria are considered together, 68 (68/118, 57.6%) babies were heavier than 1500 g and older than 30 wk. Of these 25 infants (25/68, 36.8%) had some ROP and 2 infants (2/25, 8.0%) reached treatment-requiring ROP and would have been missed if US criteria had been chosen. These two infants who required treatment were 1600 g and 33 wk and 1640 g and 32 wk respectively and had Zone 1 APROP.

Discussion

This prospective study set in a district level teaching hospital, suggests that ROP is a relevant problem in rural India. All previous data has been reported from urban nurseries [4-9,14,15,17-20]. To the authors' best knowledge this is the first prospective study from India that reports the spectrum and outcome of ROP in a rural cohort.

The incidence of any stage ROP in the present study was 41.5%. This is comparable to urban areas of India which report a range between 20% [8] and 51.9% [9] It is noteworthy that these studies used different weight cut-offs for screening and hence the incidences are not directly comparable. The authors used a birth weight of 2000 g. Recently, reports from India [10, 17, 22, 23] and other Asian countries [24, 25] have suggested that babies 'heavier' and 'more mature' that their Western counterparts are at risk of developing severe ROP and would be missed if Western guidelines were used. [3, 10]

In 18 mo, of the 118 infants that were enrolled in the present study, 57.6% of these were outside the American screening cut off considering even a combination of birth weight and gestational age criteria. Of these, 36.8% developed some stage of ROP and would have been missed. Eight percent of these required treatment and risked blindness should the authors have adhered to Western guidelines. Interestingly, these infants had APROP. Recently, a screening cut off of 1750 g has been suggested for India [10]. Whereas nurseries in the cities have shown an improving trend of neonatal care with decreasing trends of severe disease in the heavier cohorts of infants, [10, 26], the present study shows rural infants are at a cumulative risk of ROP including severe disease to an equal or greater proportion that their city dwelling counterparts. Hence, any screening guidelines for our country must appreciate this rural perspective and must provide for a larger safety net to prevent susceptible 'at risk' infants from being missed.

Aggressive posterior ROP has been considered a severe form of the disease affecting the sickest and lightest infants and has been reported increasingly as a significant proportion of ROP requiring treatment from urban Indian reports. [22, 27, 28] The authors recently reported that APROP is an emerging problem in rural and semi-urban areas of our country. [29] This study shows that 13.2% of ROP accounted for APROP. All of them presented with severe plus disease and in Zone 1. Two of these infants were outside the American screening cut off. All the cases reported a favorable outcome following laser. Several reasons for this 'better outcome' in Indian infants have been recently proposed. [22] They include darker retinal pigment epithelium, better 'take' of the laser burns, early detection, aggressive confluent laser burns, absence of fibrosis and a possible genetic predilection. Further, longitudinal studies will be required to confirm the hypothesis.

Risk factors peculiar to Indian ROP have been previously reported and include packed cell and double volume exchange transfusions [18], anemia [7], outborn status [17], and more recently the authors reported thrombocytopenia. [30] However, in the present study, the authors did not find any systemic condition that could predict ROP with statistical significance. The authors did notice a clinically significant trend in four risk factors namely RDS, oxygen therapy, neonatal jaundice and sepsis in descending order of magnitude. The absence of statistically significant changes in the present report could be attributed to the relatively small numbers of positive patients in both groups. The corollary suggests that the relatively larger proportion of positive patients in the group without ROP indicates an overall sickness in our rural infants where there is an equal proportion of sickness across the spectrum irrespective of their ROP status. This 'relative similarity' would not allow for a significant difference. Further studies, prospectively aimed at risk factor characterization will be required before the sub-group analysis is possible. Furthermore, rural mothers do not always know their gestational ages very accurately and in the absence of any 'sickness score', birth weight is our single most predictable objective criteria for determining the inclusion criteria for rural ROP screening.

The authors noted several advantages of using wide-field digital imaging for ROP screening. Firstly, they served as an objective documentation of the disease process that allowed serial comparison. Secondly, the authors were able to use it as a teaching tool for the parents allowing participation and better follow-up. Thirdly, the authors were able to more accurately document peripherally situated (Zone 3) disease and use it as a tool to follow-up laser treated eyes.

Conclusions

This study by reporting ROP disease spectrum from a rural cohort suggests that the incidence, disease characteristics and behavior to treatment are similar to urban ROP. This is an alarming trend for a disease believed to be restricted to the sick infants in bigger cities. Improving neonatal care and survival in the semi-urban and rural areas of our country are likely to contribute to the rural ROP burden. A comprehensive national screening strategy for ROP that serves both urban and rural interests is the need of the hour and must be customized to meet the needs of our country.

Acknowledgements The authors would like to thank the members of the KIDROP team of Narayana Nethralaya Postgraduate Institute of Ophthalmology - Mr. Praveen Sharma, Mr. Sivakumar Munusamy, Mr. Krishnan N for their help and support in acquiring ROP images and Mr. Suresh K.P for his help with the statistical analysis.

Contributions All authors were involved in concept and design, acquisition of data, analysis and interpretation; drafting of the manuscript and final approval of the version to be published.

Conflict of Interest None.

Role of Funding Source None.

References

1. Early Treatment of Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity. Arch Ophthalmol. 2003;121:1684–96.
2. The International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123:991–9.
3. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle- income countries. Lancet. 1997;350:12–4.
4. Rekha S, Battu RR, Chandrasekhara MK. Retinopathy of prematurity—a preliminary report. Indian Pediatr. 1992;29:623–6.
5. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol. 1995;43:123–6.
6. Gopal L, Sharma T, Ramchandran S. Retinopathy of Prematurity—a study. Indian J Ophthalmol. 1995;43:59–61.
7. Rekha S, Battu RR. Retinopathy of prematurity; incidence and risk factors. Indian Pediatr. 1996;33:999–1003.
8. Maheshwari R, Kumar H, Paul VK, Singh M. Incidence and risk factors of retinopathy of prematurity in a tertiary care new born unit in New Delhi. Natl Med J India. 1996;9:211–4.
9. Varughese S, Jain S, Gupta N, Singh S. Magnitude of the problem of Retinopathy of Prematurity. Experience in a large Maternity Unit with a medium size level—3 nursery. Indian J Ophthalmol. 2001;49:187–8.
10. Pejaver RK, Vinekar A, Bilagi A. National Neonatology Foundation's Evidence Based Clinical Practice Guidelines 2010. Retinopathy of Prematurity (NNF India, Guidelines) 2010; 253–62.
11. Photographic Screening for Retinopathy of Prematurity (Photo-ROP) Cooperative Group, Balasubramanian M, Capone Jr A, Hartnett ME, Pignatto S, Trese MT. The Photographic screening for retinopathy of prematurity study (Photo-ROP): study design and baseline characteristics of enrolled patients. Retina. 2006;26: S4–S10.
12. Vinekar A, Trese MT, Jr Capone A. Photographic Screening for Retinopathy of Prematurity (PHOTO-ROP) Cooperative Group. Evolution of retinal detachment in posterior retinopathy of prematurity: impact on treatment approach. Am J Ophthalmol. 2008;145:548–55.
13. Sanghi G, Dogra MR, Vinekar A, Gupta A. Frequency-doubled Nd:YAG (532 nm green) versus diode laser (810 nm) in treatment of retinopathy of prematurity. Br J Ophthalmol. 2010;94:1264–5.
14. Dhawan A, Dogra M, Vinekar A, Gupta A, Dutta S. Structural sequelae and refractive outcome after successful laser treatment for threshold retinopathy of prematurity. J Pediatr Ophthalmol Strabismus. 2008;45:356–61.
15. Vinekar A, Avadhani K, Sivakumar M, et al. Understanding clinically undetected macular changes in early retinopathy of prematurity on spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:5183–8.
16. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol. 1988;106:471–9.
17. Vinekar A, Dogra MR, Sangatam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies. Indian J Ophthalmol. 2007;55:331–66.
18. Dutta S, Narang S, Narang A, Dogra M, Gupta A. Risk factors of threshold retinopathy of prematurity. Indian Pediatr. 2004;41:665–71.
19. Gupta VP, Dhaliwal U, Sharma S, Gupta P, Rohatgi J. Retinopathy of prematurity—risk factors. Indian J Pediatr. 2004;71:887–92.
20. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center–incidence, risk factors and outcome. Indian Pediatr. 2009;46:219–24.
21. American Academy of Pediatrics, Section on Ophthalmology. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2006;117:572–6.
22. Sanghi G, Dogra MR, Das P, Vinekar A, Gupta A, Dutta S. Aggressive posterior retinopathy of prematurity in Asian Indian babies: spectrum of disease and outcome after laser treatment. Retina. 2009;29:1335–9.
23. Jalali S, Matalia J, Hussain A, Anand R. Modification of screening criteria for retinopathy of prematurity in India and other middle-income countries. Am J Ophthalmol. 2006;141:966–8.
24. Phan MH, Nguyen PN, Reynolds JD. Incidence and severity of retinopathy of prematurity in Vietnam, a developing middle-income country. J Pediatr Ophthalmol Strabismus. 2003;40:208–12.
25. Chen Y, Li X. Characteristics of severe retinopathy of prematurity patients in China: a repeat of the first epidemic? Br J Ophthalmol. 2006;90:268–71.
26. Jalali S, Anand R, Kumar H, Dogra MR, Azad R, Gopal L. Programme planning and screening strategy in retinopathy of prematurity. Indian J Ophthalmol. 2003;51:89–99.
27. Shah PK, Narendran V, Raghuram A, et al. Fulminate retinopathy of prematurity- clinical characteristics and laser outcome. Indian J Ophthalmol. 2005;53:261–5.
28. Vinekar A, Sivakumar M, Shetty R, et al. A novel technique using spectral-domain optical coherence tomography (Spectralis, SD-OCT+HRA) to image supine non-anaesthetized infants: utility demonstrated in aggressive posterior retinopathy of prematurity. Eye (Lond). 2010;24:379–82.
29. Vinekar A, Avadhani K, Dogra M, Gilbert C, Braganza S, Shetty K. Aggressive posterior retinopathy of prematurity is an emerging problem in rural and semi-urban India. Am J Ophthalmol. 2011;152:712.
30. Vinekar A, Hegde K, Gilbert C, et al. Do platelets have a role in the pathogenesis of aggressive posterior retinopathy of prematurity? Retina. 2010;30:20–3.