Examination of preterm babies for ROP referred to an eye department from an urban and semi-urban neonatal intensive care unit: implications for practice.

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Research article

Keywords: proportion, retinopathy of prematurity, rural, semi-urban, urban

Posted Date: October 11th, 2019

DOI: https://doi.org/10.21203/rs.2.9416/v4

Abstract

Background: To study and analyse the factors affecting the proportion of retinopathy of prematurity (ROP) distribution between the urban and semi-urban regions in North India. Methods: Retrospective, observational, cross-sectional study. All babies referred for ROP examination by paediatricians or other general ophthalmologists between 2013 – 2016 were included in the study. Demographic, clinical and treatment related findings were recorded. Results: Five hundred and fifty-eight (467: urban & 91: semi urban) babies were examined for ROP. The mean birth weight in the urban and semi-urban setting was 1348.6 ± 395.21 gm and 1703.77 ± 401.76 gm respectively. The mean gestational age was 30.99 ± 2.93 weeks and 30.73 ± 2.08 weeks in the urban and semi-urban cohorts respectively. The average time for first ophthalmic examination following birth was 23.82 ± 13.69 (range: 3-77) days in the urban and 101.16 ± 238.26 (range: 13- 330) days in the semi-urban setting. 94% of the babies completed all screening examination visits. Any ROP was identified in 11.6% and 33.0% of the urban and semi-urban cohorts respectively; Type 1 was detected in 7.5% of urban babies and 23.1% of semi-urban babies Conclusion: Differences in the proportion of babies developing any ROP and Type 1 ROP between the semi-urban and urban groups is likely due to selection bias, as a high proportion of semi-urban babies did not attend for examination or failed to complete all the examinations necessary. This was particularly true for females. More needs to be done to increase access to regular, systematic screening of preterm babies within neonatal units.

Background

Retinopathy of prematurity (ROP) is a retinal vascular condition, commonly seen in preterm, low birthweight babies. With the improvement in health care facilities, the number of preterm infants who survive annually is on the rise; thus, making ROP a leading public health problem globally and in India. [1–4] The prevalence of ROP in India is reported at 24–47%. [2, 5–7] The profile of babies who develop ROP in the low and middle income countries are older and heavier babies. [8, 9] This is different in comparison to that of the developed countries; thereby increasing the burden of babies who need to be included for screening in our population. Until recently, most of the reports regarding the screening [8, 9]and profile of ROP babies in India have come from tertiary centres in bigger cities. However, prevalence of ROP reported recently from several rural and outreach centres from Karnataka state, indicate that ROP in these babies is as high if not higher than urban centres. [8–10] With variable level of neonatal care in some of these outreach zones, the severity of ROP, including severe zone 1 disease, is likely to be high. [11]

A recent Supreme Court of India judgement on the medicolegal negligence of the paediatrician on not providing for ROP screening on time, has enhanced the awareness with specialists and parent groups alike. An acute shortage of qualified ROP specialists across the nation further worsens the situation. Hence, more babies need to be screened with limited resources.

In this study, babies examined for ROP who received neonatal care in two neonatal units in two different states in North India were compared and analysed.

Methods

In this study, babies examined for ROP from 2 different states between August 2013 and September 2016 were included. Institutional review board (SCEH-2013-09-003) and ethics committee clearance was obtained for this study and informed written consent of the parents/child's guardian for participation in the study were also obtained.

In our study, examination for ROP was conducted in the retina clinic of a tertiary eye care institute on fixed days of each week – (every Monday in Delhi and every Thursday in Alwar). All the medical professionals, including the paediatricians and other ophthalmologists in the surrounding areas were informed regarding the screening and ROP examination guidelines via regular meetings and providing study materials. As per the National ROP guidelines, infants born < 1750 g at birth and/or < 34 weeks of gestation were enrolled into the study. [13] Every week, the concerned NICU would telephonically supply information regarding the number and names of babies eligible for ROP examination as per guidelines. Babies were referred to the retina clinic after the stabilisation of their systemic condition. For premature babies requiring long duration of NICU stay, examination was conducted in their respective neonatal care units. In our study, we primarily received referrals from 2 NICUs – urban NICU at the Chacha Nehru Bal Chikitsalaya (CNBC), New Delhi and semi-urban NICU at B. LAL Children Hospital, Alwar, Rajasthan. The NICU of CNBC at New Delhi is a level 3, out born tertiary care intensive care unit while that at Alwar was a level 2 out born NICU.

Data recording at the initial examination included: 1) premature infant's gender; 2) time for first ophthalmic examination; 3) birth weight (BW) and gestation age (GA); 4) presence, stage and zone of ROP; 5) presence of plus disease; 6) treatment required if any and 7) whether treatment was given. Eye examinations of all babies were done by a single examiner to standardize the examination technique and the results were analysed. The intent of the initial examination was to detect babies with ROP and enrol them in the study. Ophthalmic examination was done with an indirect ophthalmoscope and a +20D lens at weekly intervals. Eyes were examined with an infant speculum and a wire-vectis as scleral depressor, under topical anaesthesia using 2% proparacaine drops. The pupils were dilated by using 0.4% tropicamide and 2.5% phenylephrine eye drops two or three times, till full dilatation occurred. Retinopathy was graded into stages and zones as per the ICROP classification. [14, 15] Infants with normal vascularization up to the periphery were not examined again. Those with ROP were examined every week/2 weeks till regression occurred or till they reached the indications for laser treatment.

Treatment in the study was performed by laser photoablation using the Early Treatment for Retinopathy of Prematurity guidelines with the 532-nm green laser. [16] As far as possible, the treatment was performed at the base hospital (Delhi) by the vitreo-retina specialist. Babies requiring laser treatment in the semi-urban set-up were shifted to the base hospital in Delhi on the same day or after discharge from

NICU with clearance from the treating paediatrician. For babies in the urban set-up requiring treatment, laser therapy was carried out on the same or next day at our base hospital. Once the babies were discharged from the NICU, they were followed up in the out-patient clinic of the retina department for further evaluation. If regression was found to be inadequate or skip areas were seen on subsequent examination, laser was repeated after one or two weeks. Intravitreal Bevacizumab injection was given to babies diagnosed with aggressive posterior ROP.

Results

During the period from August 2013 and September 2016, a total of 721 (240 – semi-urban; 481 – urban) preterm babies were eligible for ROP examination of which 558 (77%) babies were examined. 467 (84%) babies in the urban cohort and 91 (16%) babies in the semi-urban cohort were examined (Table 1). The proportion of babies who completed all examination visits was 98% in the urban cohort and 71% in the semi-urban cohort. More males underwent ROP examination than girls [376 (67%) males and 182 (33%) females)] in both urban and semi-urban settings. The mean BW in the urban and semi-urban setting was 1348.6 ± 395.21 gm and 1703.77 ± 401.76 gm respectively. The mean GA of the premature babies was 30.99 ± 2.93 weeks and 30.73 ± 2.08 weeks in the urban and semi-urban cohorts respectively. The average time for first ophthalmic examination following birth was 23.82 ± 13.69 (range: 3-77) days in the urban and 101.16 ± 238.26 (range: 13- 330) days in the semi-urban settings. Proportion of any ROP in the urban cohort was 11.7% (n=55) and in the semi-urban cohort was 31.9% (n=29). Stages of ROP identified in the urban and semi-urban groups are described in Table 2 and the characteristics of infants with and without ROP are shown in Table 3. Four babies in the semi-urban cohort and 13 babies in the urban cohort were identified with plus disease. Aggressive posterior ROP (APROP) was noted in 1 preterm baby in the semi-urban group and 5 babies in the urban group. Severe ROP (i.e., Stages 3, 4 or 5 or APROP or plus disease) developed in 35 (7.5%) babies in the urban group and 21)23.1%) in the semi-urban group. Overall proportion of ROP was 15.1% (84) and it was not influenced by gender. Treatment for ROP was offered to the 56 babies with severe ROP disease. 85.7% babies in the urban and semi-urban cohorts underwent treatment for different stages of ROP. Out of the 56 babies needing treatment, 41 babies required laser alone and 6 babies required laser and anti-vascular endothelial growth factor (VEGF) therapy; 30 (55.5%) belonged to the urban cohort and 17 (58.6%) to the semi-urban cohort. Treatments offered and taken by the babies are mentioned in Table 2.

Discussion

In our study, the overall proportion of ROP was 15.1%. We found a higher proportion of ROP in babies with BW ≤ 1500 g, GA ≤ 28 weeks, screening before 30 days of life and in the semi-urban setting. The proportion of ROP was almost 3-fold higher in the semi-urban setting (31.9%) compared to the urban setting (11.7%). Also, the drop-out rate for ROP examination was higher in the semi-urban setting. 29% of the babies in the semi-urban setting did not complete their all required examination visits.

In this study, in both settings a higher proportion of those examined were boys (67%), and the girls were less likely to complete all the examinations required. One of the more probable reasons could be that the parents consider the boys to be more valuable and hence, they bring them for examination and treatment.

In the semi-urban setting, the median time interval between birth and first day of examination of these premature babies was 60 (mean = 101.16 ± 238.26; range: 13-330) days while in the urban setting it was 21 (mean = 23.82 ± 13.69; range: 3-77) days. Jalali et al [17] had discussed the role of early screening strategy for preterm babies. Their study suggested early screening before one month of age in neonatal centres can detect early disease and prompt treatment can lead to favourable outcomes. In our study, the mean time interval for the first ROP examination in the urban group was considerably lower than the 30 days recommended, and the large standard deviation suggested that some may have been examined far too early. In the urban setting, 66% of the babies were examined before 25 days of life and 28% were examined after 30 days of life. While, in the semi-urban setting, more proportion of babies (68%) were examined after 30 days of life. Thus, systematic screening in the neonatal unit is more likely to lead to the first examination being undertaken at the correct time i.e., between 25 and 30 days after birth. Also, the results from this study suggested that one of the important reasons for the delay in ROP examination could be that babies were only referred to the retina clinic after they had been stabilised, except in a few instances where visits were made to the NICU to examine babies in the unit. This approach of ROP examination is far from ideal as sick babies are those most at risk of ROP. The impact of late examination is shown in Table 2 where 5 of the 30 (16.7%) babies in the semi urban group with any ROP had stage 4 or 5, compared with 1 of the 54 (1.8%) in the urban group who were examined earlier. The median time interval for first examination babies with stage 4 or stage 5 ROP in the urban and semi-urban cohort was 77 and 156 days respectively. The low uptake for ROP examination and the lateness of examination highlight how this approach for ROP evaluation is far away from ideal. In our study, we found the mean GA to be similar in both groups while in semi-urban setup more heavier babies were screened for ROP (1348.6 ± 395.21 gm in urban; 1703.77 ± 401.76 gm in semi-urban setting). Our study revealed higher proportion of stage 5 ROP with total inoperable retinal detachment in 4 eyes in the semi-urban cohort and none in the urban population; thereby further stressing on the need for timely screening for ROP to detect the disease early.

Only 91 babies of the eligible 240 babies underwent ROP examination in the semi-urban cohort accounting to a drop-out rate of about 62% while the drop-out rate in the urban cohort was only 2.9%. In India, currently, most of the ROP examinations are done by retina specialists. Paediatric ophthalmology is still not a well-established separate subspecialty in India. [18, 19] Most of the vitreo-retinal surgeons and paediatric ophthalmologists practise in bigger cities. As a result, there is a paucity of ROP care givers in semi-urban and rural areas. Also, the profile of babies who develop ROP in developing countries like ours are older and heavier babies. [8, 9] This further increases the burden of babies who need to be included for screening in our population. Hence, preterm babies born in the semi-urban/rural areas are not being subjected for ROP examination as per the screening guidelines. Studies have shown paediatricians and ophthalmologists practising in the interiors of the country to have poor knowledge regarding ROP and its screening strategies. [20, 21] Creating awareness amongst the medical staff like ophthalmologists,

paediatricians, gynaecologists and nurses in the NICU and providing training and basic infrastructure like indirect ophthalmoscopy for screening preterm babies can increase the overall screening rate. Also stressing the need for screening at the time discharge to parents/guardians can help in increasing the ROP screening rate in rural/semi-urban areas.

Lack of availability of treatment facilities like laser in these areas could be responsible for the high drop-out rate as well. Providing treatment to such high-risk babies at the screening site would be beneficial in preventing childhood blindness due to ROP. Currently in India, there are massive efforts made to integrate screening for ROP into government neonatal units and Special New-born Care Units at district level. Screening was integrated into sick new-born care units at the district level and treatment facilities were provided and improved at the closest publicly funded medical schools. In the first two years, there were substantial improvements in awareness, screening, treatment and partnership between stakeholders, and changes in public health policy. [22] Other strategies which are being currently used include training members of the neonatal team to capture retinal images using wide-field imaging which are then read by ROP experts. A KIDROP like screening model can provide ROP screening in low-resource settings, remote centres, and regions with few ROP specialists. [10, 23]In our study, we did screen preterm babies from 2 population groups who were socially and economically unequal.

The quality of neonatal care provided in the urban and semi-urban NICUs is highly variable. The urban NICU at Delhi is a level IIIA NICU providing a high level of neonatal care to very low birth-weight premature babies. They have a wide variety of trained staff available on-site including neonatologists, neonatal nurses and respiratory therapists who are available 24-hours a day. In comparison, the semi-urban NICU at Alwar is a level II NICU providing care to infants who are moderately ill with problems that are expected to resolve rapidly. [24, 25] Care in this setting is usually limited to new-born infants who are > 32 weeks' GA and weigh > 1500 g at birth or who are recovering from serious illness treated in a level III NICU. The NICU in Alwar takes care of extremely sick babies and this could contribute to the higher proportion of severe ROP cases seen in this semi-urban cohort. A recently published meta-analysis showed that lower Spo2 target range was associated with a lower risk of retinopathy of prematurity treatment and a higher risk of mortality and necrotizing enterocolitis. [26] Chow et al had observed a significant decrease in the prevalence of ROP with training of the NICU staff and better implementation and enforcement of clinical practices related to oxygen (O_2) management and monitoring. In their study, the prevalence of ROP decreased consistently in a 5-year period from 12.5% in 1997 to 2.5% in 2001. The need for ROP laser treatment decreased from 4.5% in 1997 to 0% over the last 3 years. [27] Even in our study we found a significantly lower prevalence of ROP in the urban setting due to the high level of neonatal care provided, increased awareness for early screening of preterm babies and better understanding of the disease amongst the paediatricians.

Our study highlights important key issues related to method of ROP evaluation and treatment in the urban and semi-urban population settings. This study stresses the need for more and more medical personnel, especially those belonging to the semi-urban/rural setups to be trained for ROP screening by premier tertiary eye care institutions. Our study also emphasizes on the need for newer ROP screening

strategies like tele-ophthalmology to be implemented in the semi-urban/rural areas. This, in turn will reduce the visual impairment and blindness from ROP in our country.

Conclusion

The proportion of ROP cases was found to be higher in the semi-urban setting due to delayed screening, higher drop-out rate and lack of basic treatment facilities. Stricter adherence to the screening protocols and creating awareness amongst paediatricians and parents regarding ROP can increase the screening rate in the semi-urban areas. Providing training to more medical professionals like paediatricians, general and pediatric ophthalmologists and also utilising the tele-ophthalmology services for ROP screening can reduce the drop-out rate. Also, better understanding of O_2 management and monitoring in NICUs and providing basic treatment like laser at the NICU itself would reduce the prevalence of blindness due to ROP.

Abbreviations

1. ROP – retinopathy of prematurity
2. NICU – neonatal intensive care unit
3. BW – birth weight
4. GA – gestational age
5. APROP – aggressive posterior retinopathy of prematurity
6. VEGF – vascular endothelial growth factor

Declarations

1) Ethics approval and consent to participate – Approval has been obtained from the institutional review board (SCEH-2013-09-003) of Dr. Shroff's Charity Eye Hospital and ethics committee.

2) Consent for publication – written consent has been obtained from the parent/legal guardian during screening for ROP

3) Availability of data and materials - The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4) Competing Interests - The authors declare that they have no competing interests

5) Funding – None

6) Authors' Contribution –

RV – conducting the screening, analysing the results, writing the manuscript and reviewing the paper. PDJ and PG – data entry and screening of babies. MA, MJ and VG – reviewing the paper. All authors

have read and approved the manuscript.

7) Acknowledgements – Not Applicable

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Tables

Table 1: Descriptive Data of babies screened for ROP in Urban and Semi-urban setting

	Urban	Semi urban	P value
Eligible babies for screening	481	240	
Babies who underwent screening	467	91	
Gender			
Male	315	61	0.514
Female	152	30	
Birth weight (gm)	1348.6 ± 395.21	1703.77 ± 401.76	0.000
Gestational age (weeks)	30.99 ± 2.93	30.73 ± 2.08	0.512
First Ophthalmic examination (Days)	23.82 ± 13.69	101.16 ± 238.26	0.000
ROP present	55 (11.7)	29 (31.9)	0.000

Table 2: ROP by stage and treatment in babies examined in two cities in India

	Urban (n=467)		Semi-urban (n=91)	
ROP by stage	**N**	**%**	**N**	**%**
No ROP	412	88.2	62	68.1
Stage 1	19	4.1	2	2.2
Stage 2	6	1.3	7	7.7
Stage 3	28	6.0	16	17.6
Stage 4	1	0.2	1	1.1
Stage 5	0	0	4	4.4
AP-ROP	5	1.1	1	1.1
Any ROP	54	12.8	30	33.0
Other signs / types of ROP				
Plus disease	13	2.8	4	4.4
Treatment				
Offered Male and female	35	7.5	21	23.1
Male	22	63	13	63
Female	13	37	8	37
Given Male and female	21	60	12	57
Male	19	88	11	88
Female	2	12	1	12
Method of treatment				
Laser	25	83	16	89
Laser and AntiVEGF injection	5	17	1	5.5
Vitreoretinal surgery	0	0	1	5.5
Outcomes				
Poor	0	0	1	5.5
Good after laser +/- AntiVEGF	30	100	17	94.5

Table 3: Correlating the independent risk factors with the presence or absence of ROP using the multi-variate regression model:

	ROP Present (n)	ROP Absent (n)	P value
BW <1500 gm	61	296	0.046
BW > 1500 gm	23	178	
GA <28 weeks	43	100	0.000
GA >28 weeks	41	374	
Screening < 30 days	56	125	0.000
Screening > 30 days	28	349	
Urban setting	54	513	0.000
Semi-urban setting	30	61	
Male	54	322	0.295
Female	30	152	