Original Article

Evaluation of clinical profile and screening guidelines of retinopathy of prematurity in an urban level III neonatal intensive care unit

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Purpose: To evaluate the clinical profile and screening guidelines of retinopathy of prematurity (ROP) in an urban level III neonatal intensive care unit (NICU). **Methods**: Infants with ≤2000-gm birth weight or <34 weeks gestational age were prospectively screened for ROP in an urban level III NICU between January 2018 and December 2020, based on national screening guidelines. Standard guidelines were used for ROP classification and treatment. **Results:** In total, 211 infants completed screening; 46 (21.8%) infants developed ROP and 13 (6.2%) had type 1 (laser treatable) ROP. Of the 46 infants with ROP, 44 (95.65%) had zone 2 and two (4.34%) had zone 1 disease. In the 102 infants with ≤1500-gm birth weight, the incidence of ROP and type 1 ROP were 41.18% and 11.76%, respectively. Out of the 109 infants with >1500-gm birth weight, four (3.67%) developed ROP and one (0.91%) infant (an outborn) required treatment. **Conclusion:** The majority of infants developing ROP in a level III urban NICU had ≤1500-gm birth weight. Zone 1 ROP was uncommon. Incidence of ROP in heavier infants (>1500-gm birth weight) was low, and treatment was required in a rare instance. In an urban NICU, the burden of ROP screening and treatments shifts to small and low-birth-weight infants.

Key words: Incidence, low birth weight, retinopathy of prematurity, ROP, ROP screening guidelines, urban NICU

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Retinopathy of prematurity (ROP) is a disorder of developing retinal vasculature in premature infants.[1,2] The main risk factors for development of ROP are low birth weight, gestational age, and oxygen supplementation.[3] With improvements in neonatal care, middle-income nations, including India, are currently experiencing the "third epidemic" of ROP due to improved survival rates of premature infants, but without sophisticated oxygen monitoring protocols.[4,5] Even heavier (>1500 gm) birth-weight infants have been reported to develop severe treatable ROP, including aggressive posterior ROP.[6] This is in contrast to the developed countries where the majority of infants developing ROP have very low birth weight (<1500 gm) and low gestational age (<32 weeks).[7] Recent reports from India suggest variability in the incidence of ROP between various urban and rural centers. In the last decade, rural centers in India have reported high incidence of ROP ranging from 22.4% to 41.5%, while urban/semi-urban centers have reported a lower incidence varying from 14.8% to 26.6%.[8-13] The present study was conducted to analyze the incidence and profile of ROP in an urban level III NICU.

Methods

Infants managed in a level III urban NICU between January 2018 and December 2020 were prospectively screened for ROP. The study center is a level IIIA NICU accredited by the national neonatology forum accreditation program.[14] A level IIIA NICU is a subspeciality NICU that routinely provides comprehensive care to extremely low-birth-weight infants and infants <28 weeks gestation, accepts referrals, and has facilities for ventilator support. ROP screening was done in accordance with national screening guidelines given by the Rashtriya Bal Swasthya Karyakram (RBSK), Government of India, which include infants <2000-gm birth weight or <34 weeks gestational age.[15] ROP was classified in accordance with the revised international classification of ROP.[16] Laser treatment was done for type 1 ROP according to the early treatment for retinopathy of prematurity (ETROP) study.[17] All screenings were done by a single experienced surgeon well versed with ROP screening and treatment. Indirect ophthalmoscopy with a 20-D lens was used for all screenings. ROP screening was done till complete vascularization of the retina occurred or the baby required treatment. The highest stage of ROP reached in either eye was recorded.

For each infant, baseline demographic data including birth weight, gestational age, and inborn/outborn status were noted in ROP case records. Inborn infants meant babies born and managed at the study center, while outborn infants were those who were born at another facility and later shifted to the study center for management.

At the end of the study period, infants who expired before completing screening, lost to follow-up, or shifted to

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another facility were excluded. Data for remaining infants were tabulated to calculate the incidence of any stage ROP and type 1 ROP (treatable ROP). Sub-analysis was done to compare ROP incidence for various birth weight and gestational age categories. We also evaluated the sensitivity of the lower screening cut-off criterion of ≤1500-gm birth weight and ≤30 weeks gestational age.

Statistical analysis

Categorical data were analyzed using Fisher's exact test and continuous data using independent samples *t* test. $P < 0.05$ was considered statistically significant.

Results

In total, 231 infants underwent ROP screening during the study period. Of these, six infants expired before completing ROP screening, two infants were shifted to another facility, and 12 infants were lost to follow-up. Overall, data pertaining to 211 infants who completed ROP screening are included. The mean birth weight and gestational age of included infants were 1553.27 ± 443.64 gm and 31.86 ± 3.14 weeks, respectively. Forty six (21.8%) of the 211 infants developed any stage of ROP. Thirteen (6.2%) of the 211 infants developed type 1 ROP and hence required laser treatment [Table 1]. Of the 46 infants developing ROP, 44 (95.65%) had zone 2 ROP and only two (4.35%) had zone 1 ROP. Aggressive posterior retinopathy of prematurity (APROP) in zone 1 was seen in two infants. These infants were a pair of outborn twins (born at 29 weeks 3 days and with a birth weight of 1000 and 800 gm, respectively) who received prolonged oxygen at another facility and were shifted to the study center. During the 3-year study period, one inborn developed APROP (in posterior zone 2). The baby was born at the gestational age of 28 weeks 5 days and weighed 1070 gm at birth.

Of the infants developing ROP, the majority (42/46) were ≤1500-gm birth weight. Only four infants (2 inborn; 2 outborn) with >1500-gm birth weight developed ROP. The incidence of ROP was highest for infants with <1250-gm birth weight and decreased for successive heavier birth weight categories [Table 2]. The overall incidence of ROP in infants with ≤1500-gm birth weight was 41.18% (42/102) compared to 3.67% (4/109) for infants with >1500-gm birth weight ($P < 0.0001$). The incidence of type 1 ROP in infants with ≤1500-gm birth weight was 11.76% (12/102) compared to 0.92% (1/109) for infants with >1500-gm birth weight ($P = 0.001$). All seven inborn infants requiring treatment were <1100-gm birth weight (birth weights: 790, 940, 1030, 1060, 1090, 1070, and 820 gm). Of the six outborn infants requiring treatment, five were ≤1100-gm birth weight (birth weights: 800, 876, 1000, 1065, and 1100 gm). One outborn infant weighing >1500 gm (birth weight: 1814 gm, gestational age: 30 weeks) required treatment. This infant had severe birth asphyxia, respiratory distress syndrome requiring prolonged oxygenation, patent ductus arteriosus, sepsis, necrotizing enter colitis requiring resection anastomosis, humerus fracture, and periventricular leukomalacia.

The incidence of ROP was highest for infants with ≤30 weeks gestational age and decreased for successive gestational age categories [Table 3]. The incidence of ROP in infants with ≤32 weeks gestation was 38.1% (40/105) versus 5.66% (6/106) for infants with >32 weeks' gestation ($P < 0.0001$). The incidence of type 1 ROP for infants with ≤32 weeks' gestation was

Table 1: Outcomes of ROP screening for infants completing screening and treatment (*n*=211)

	Outcome	Number of infants *n* (%)
1	No ROP	165 (78.2%)
2	Type 2 ROP (Spontaneous regression)	33 (15.6%)
	a Stage 1 in zone 2, no plus disease	10 (4.7%)
	b Stage 2 in zone 2, no plus disease	22 (10.4%)
	c Stage 3 in zone 2, no plus disease	1 (0.5%)
3	Type 1 ROP (laser treatment)	13 (6.2%)
	a Aggressive posterior ROP zone 1	2 (0.95%)
	b Aggressive posterior ROP posterior zone 2	1 (0.5%)
	c Stage 2 in zone 2, plus disease	6 (2.8%)
	d Stage 3 in zone 2, plus disease	4 (1.9%)

Table 2: Incidence of ROP in relation to birth weight

Birth weight (gm), Mean (SD)	Incidence of ROP *n* (%)	Incidence of type 1 ROP *n* (%)
≤1250 gm (*n*=57)	34 (59.64%)	12 (21.05%)
1251-1500 gm (*n*=45)	8 (17.77%)	0 (0%)
>1500 gm (*n*=109)	4 (3.67%)	1 (0.92%)

Table 3: Incidence of ROP in relation to gestational age categories

Gestational age	Incidence of ROP *n* (%)	Incidence of type 1 ROP *n* (%)
≤30 weeks (*n*=47)	30 (63.83%)	11 (23.4%)
>30 to ≤32 weeks (*n*=58)	10 (17.24%)	1 (1.72%)
>32 weeks (*n*=106)	6 (5.66%)	1 (0.94%)

Table 4: Sub-analysis of infants ≤1500 gm birth weight

	Group A (ROP) *n*=42	Group B (no ROP) *n*=60	*P*
Birth weight	1061.93 (184.19)	1273.85 (167.29)	<0.0001
Gestational age (weeks), Mean (SD)	29.1 (2.00)	31.61 (2.15)	<0.0001
Inborn	27 (64.29%)	37 (61.67%)	1.000
Outborn	15 (35.71%)	23 (38.33%)	1.000

Table 5: Application of lower screening cut-off criterion to present cohort

	Sensitivity for ROP	Sensitivity for type 1 ROP
Birth weight ≤1500 gm	42/46 (91.3%)	12/13 (92.3%)
Gestational age ≤30 weeks	30/46 (65.2%)	11/13 (84.6%)
Birth weight ≤1500 gm and Gestational age ≤30 weeks	43/46 (93.5%)	13/13 (100%)

11.43% (12/105) versus 0.94% (1/106) for infants with >32 weeks' gestation ($P = 0.0013$).

As the majority of the infants developing ROP had a birth weight of ≤1500 gm, we did a further sub-analysis of this cohort. The mean birth weight and gestational age were significantly lower for infants developing ROP as compared to infants not developing any ROP [Table 4].

Applying the lower screening cut -off criterion of both ≤ 1500 gm birth weight and ≤ 30 weeks gestational age , 3 of 46 infants developing ROP were missed (sensitivity :93.5%), while none of the infants developing type 1/ treatable ROP were missed in this study(sensitivity :100%) [Table 5].

Discussion

The incidence of ROP in the present study conducted at an urban level III NICU was 21.8%, and the incidence of treatable ROP was 6.2%. This incidence is similar to previous reports from urban centers in India. Murthy *et al*.[11] reported an incidence of 16.5% of ROP and 6.17% of treatable ROP in a cohort of infants from two urban NICU in south India. However, this was a RetCam-based study and used a broad screening criterion of <36 weeks. A prospective cohort study of infants <1700-gm birth weight in a tertiary hospital of North India reported incidence of ROP at 26.6% and stage 3 ROP as 12.8%.[12] Rural centers report a higher incidence of ROP. Hungi *et al*.[8] reported the incidence of ROP as 41.5% and treatable ROP as 10.2% in a rural neonatal intensive care unit in infants with <34 weeks gestational age and <2000-gm birth weight. A recent study from a center catering to the rural population in central India reported an incidence of ROP as 30% and treatable ROP as 14%.[10] The difference in the incidence of ROP among various NICU is likely due to variability in neonatal care and oxygen practices.

In the present study, the majority (42/46) of the infants developing ROP were ≤1500-gm birth weight. Only four infants with >1500-gm birth weight developed ROP. Over the 3-year study period, none of the inborn infants with >1500-gm birth weight required treatment, while one outborn with >1500-gm birth weight required treatment. In fact, all inborn infants requiring treatments were less than 1100-gm birth weight. According to the American screening guidelines for ROP, all infants with a birth weight of ≤1500 gm or a gestational age of ≤30 weeks or less must be screened for ROP.[18] Applying these criteria to the present study would have missed three (6.52%) of the 46 infants developing ROP, while it would not have missed any of the 13 infants requiring treatment [Table 5]. Neonatal care and oxygen monitoring can be controlled fully for inborn infants. On the contrary, outborn infants may receive a variable level of neonatal care depending on the level of referring NICU and days of care received prior to referral. Heavier infants may be at risk for treatable ROP in such a scenario. Although we would not miss any treatable ROP upon applying the American screening criterion to the present cohort, a safe strategy is to continue screening based on a broader national screening criterion of ≤2000-gm birth weight. This is important till neonatal services uniformly improve across all centers.

Of all the infants screened, two outborn infants developed zone 1 APROP, while one of the inborn infants developed APROP in posterior zone 2. We did not find early APROP at 3 weeks of birth in any of the infants despite routinely beginning ROP screening at 3 weeks after birth weight in infants with <28 weeks gestation age as suggested by national ROP screened guidelines.[15] APROP accounted for three (23.07%) of 13 infants treated for type 1 ROP. In a recent report from south India, APROP was seen in 20.73% of eyes with type 1 ROP in an urban setting.[13] However, reports from rural centers suggest zone 1 APROP contributing to nearly one-third to one-half of all eyes with severe ROP.[10] In the present study, the highest birth weight of a baby developing APROP was 1070 gm. Previous studies suggest that APROP may develop in heavier-birth-weight infants (>1500 gm) exposed to unmonitored oxygen therapy.[6] This phenomenon was not observed in the present study as oxygen supplementation was strictly monitored for all infants.

In the cohort of infants with <1500-gm birth weight, the mean gestational age and birth weight of infants developing ROP were significantly lower as compared to infants without ROP. The main and consistently reported risk factors for ROP include low birth weight, gestational age, and oxygen therapy.[3] Other risk factors reported in the Indian setting include infusion of blood products and septicemia.[13,19] While low birth weight and gestational age are nonmodifiable factors, other factors can be controlled. In our NICU setting, multiple interventions are being implemented for prevention of ROP, including regular use of antenatal steroids, delayed cord clamping, provision for providing blended oxygen in the delivery room, and use of proper equipment such as radiant warmers and transport incubators in the delivery room. We routinely try to minimize oxygen exposure by use of blended oxygen along with a well-implemented policy for SpO2 monitoring and targeting oxygen saturation between 90% and 95%. None of the infants is exposed to unmonitored oxygen, and preferential use of noninvasive modes of ventilation is encouraged. Unnecessary use of blood products is discouraged, and a well-defined and implemented infection control policy in the unit is followed. These protocols have allowed us to limit the incidence of zone 1 aggressive posterior ROP and type 1 prethreshold ROP.

The present study has certain limitations. First, the study is limited by a small sample size. The results cannot be generalized to other nurseries, Second, the observer was not masked to demographic details of the infants. This may induce bias. Third, the present study did not analyze the risk factors for development of ROP in detail.

Conclusion

In conclusion, the majority of infants developing ROP in a level III urban NICU were ≤1500-gm birth weight, while the majority requiring treatments were ≤1100-gm birth weight. Incidence of ROP in infants with >1500-gm birth weight was extremely low, and treatment was required on a rare instance in an outborn infant. With improvements in neonatal care, fewer of the heavier infants (>1500-gm birth weight) develop ROP and may need treatment. In an urban NICU, the burden of ROP screening and treatments shifts to smaller and lower-birth-weight infants.

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Conflicts of interest

There are no conflicts of interest.

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