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EPIDEMIOLOGY AND CLINICAL PROFILE OF RETINOPATHY OF PREMATURITY IN AT RISK NEW BORNS IN NEONATAL INTENSIVE CARE UNITS IN A TERTIARY CARE HOSPITAL, TELANGANA INDIA.

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Abstract

Background: The incidence of Retinopathy of Prematurity (ROP) in different regions across India has been reported to range from 38% to 47%. **Objective:** This study aims to identify the incidence and determinants of ROP among "at-risk" newborns treated at neonatal intensive care units (NICU) in a tertiary care hospital.

Methodology: A prospective observational study done during 2021-23, in 100 at risk new borns for ROP in a tertiary care hospital. Screening for ROP was done, as per guidelines by national health mission. The international classification of retinopathy of prematurity was used for disease staging. All enrolled patients were followed up even after discharge from the NICU, end point was until treatable stage of ROP was reached, or spontaneous regression and/or completion of vascularization. Data was analyzed with IBM SPSS 23 (SPSS, Chicago, Illinois, USA). P value < 0.05 was considered significant.

Results: Incidence of ROP was 42% (with Type 1 in 9% & Type 2 in 33%), of which 9 had laser surgery prior to discharge, and all were followed up. Average birth weight was 1793 g, average gestational age 32weeks. Determinants of ROP identified in the current study were gestational age, pre term delivery, neonates who received mechanical ventilation, also mean number of days on mechanical ventilation and CPAP with Fio2 >50(4.4 days in neonates with ROP and 1.4 days in neonates without ROP).

Conclusion: ROP is essentially asymptomatic in the early stages, standards of practice now demand carefully timed retinal examination of at risk infants**.** The burden of Type 1 & APROP is increasing, as seen in higher gestation and birth weights.

Keywords: At risk newborn, Retinopathy of prematurity, NICU, Screening.

INTRODUCTION

Advances in neonatal care have led to a significant reduction in the minimum age of viability for preterm infants. These improvements, ironically, have led to the development of retinopathy of prematurity (ROP).[1] Retinopathy of Prematurity (ROP) is a potentially blinding disease of the eye that could affect infants born four or more weeks preterm and have received intensive neonatal care.[2,3] ROP is emerging as a leading cause of avoidable childhood blindness in India and other low- and middle-income countries (LMIC).[4] The key pathological changein ROP is peripheral retinal neovascularization.ROP can be mild and resolves spontaneously but may lead to blindness in its severe form.[5]

The incidence of ROP in different regions across India has been reported to range from 38% to 47%. Inconsistencies of neonatal care have led to large variability in ROP incidence and severity within India.[6] This requires that all neonatal intensive care units have a system in place to screen and treat ROP to save sight. If detected late or untreated, severe sequelae can result in irreversible blindness and all the psychosocial, educational and economic implications.[7] The minimum necessity is that all babies at risk of ST-ROP are screened and treated.

Timely screening based on birth weight and gestational age, leads to early management and improved outcome thus reducing ROP-related morbidity. As there are disparities in the epidemiology of ROP globally and nationally due to regional variations in newborn care, leaving a sizable portion of newborns at risk of undiagnosed and untreated ROP blindness.[8] The current study is undertaken to understand the epidemiology and also identify the clinical profile of newborns with ROP.

MATERIALS AND METHODS

A prospective observational study was done in at risk newborns for ROP admitted or transferred to NICU in a tertiary care hospital in Telangana India. Study was conducted during april 2021 to

July 2023. In NICU the target oxygen saturation was maintained between 90-95% (monitored by pulse oximetry) for at risk newborns to avoid hyperoxia, using non blended oxygen. After obtaining institutional ethical committee clearance and written informed consent from parents/ care givers, At risk newborns who met the criteria of screening for ROP as per guidelines by national health mission were included in the study (birth weight <2000gms, gestational age <34 weeks, exposure to excessive oxygen is major risk factor for ROP. Other risk factors include sepsis, intra-ventricular hemorrhage, respiratory distress, failure to gain weight and blood transfusions).[9,10] Those who died or were transferred out before ROP screening, major congenital malformations, chromosomal disorders, inherited metabolic diseases or parental refusal to participate in study were excluded. Purposive sampling method was used.

Sample size was calculated using formula for finite population. Where, Z α is the standard normal deviate, 1.96 at 95% confidence interval.

As per study by Tekchandani et al Eczema cases form almost 32.3% of all at risk newborn cases in a tertiary care hospital. [11]

Hence P = Prevalence is 32.2%. i.e P = 0.32.2, 1-P = (1-0.32.2)

e = allowable error was 5%

N = study population (At rsik newborns admitted in to NICU in the institution in the previous 2 year during the April 2018 to April 2020) = 120,

$$Sample\ size(n) = \frac{\frac{z^2 X\ p(1-p)}{e^2}}{1 + \frac{z^2 X\ p(1-p)}{e^2 N}}$$

$$Sample\ size(n) = \frac{\frac{(1.96)^2 X\ 0.32.2(1-0.32.2)}{(0.05)^2}}{1 + \frac{(1.96)^2 X\ 0.32.2(1-0.32.2)}{(0.05)^2\ 120}}$$

$Sample\ size(n) required\ is = 89$ for estimating the expected proportion of 32.2% with 5% absolute precision and 95% confidence. With adjustment for 10% of nonresponse rate sample size was 99, which was rounded up to 100.[12]

Methodolody: Clinical and demographic data was collected from patient`s medical records. ROP screening was performed by one trained ophthalmologist after pupillary dilation with combination of 0.4% tropicamide and 2.5% phenylephrine eye drops using binocular indirect ophthalmoscopy. Timing of first eye examination was based on gestational age at birth and follow-up examinations were based on retinal findings. All enrolled patients were followed up even after discharge from the NICU, end point was until treatable stage of ROP was reached, or spontaneous regression and/or completion of vascularization. The international classification of retinopathy of prematurity was used for disease staging.[13] ROP was distinguished between severe ROP (or Type 1 ROP) and Type 2 ROP. The former includes ROP in zone I of any stage with plus sign, stage 3 with and without plus sign and zone II stage 2 or 3 with plus sign. The Type 2 ROP includes zone I stage 1 or 2 without plus and zone II stage 3 without plus. Laser treatment was done for type 1 ROP according to the early treatment for retinopathy of prematurity (ETROP) study.[14]

Statistical Analysis:

Data were presented as mean (SD), or count (%). Categorical data was analyzed using chi-square test and continuous data using independent t test. Potential independent effect variables on the occurrence of treatment requiring Type 1 ROP & APROP were selected by logistic regression analysis. Effect estimates were expressed as odds ratio (OR) and 95% confidence interval (95% CI). Data was analyzed with IBM SPSS 23 (SPSS, Chicago, Illinois, USA). P value < 0.05 was considered significant.

RESULTS

A total of 100 at risk newborns who were eligible for ROP screening, had completed the retinal examination.

There were 59 (59%) at risk newborn males. Mean and SD of birth weight of newborns was 1793.28 g (range: 984-1567 g, SD 53 g). The average gestational age was 32 weeks (range: 28-37 weeks, SD 2.08 weeks). Forty nine (49%) weighed less than 1500 grams, among them 4 were less than 1000 grams. Fifty-six at risk newborns were admitted to NICU immediately after birth, 24 within 1st day after birth, and remaining 20 within 3 days of birth. Forty neonates were delivered by Cesarean section. Two newborns had APGAR below 7 at 5 minutes. (Table1).

Table 1: Baseline characteristics of infants

Variables	Group	N	%
Sex	Male	59	59
	Female	41	41
Birth Weight(g)	≤1000	4	4
	1001-1500	45	45
	1501-2000	26	26
	≥2001	25	25
Gestational age (weeks)	≤28 weeks	4	4
	29-31 weeks	9	9
	31-34 weeks	36	36
	≥34 weeks	41	41
Multiple Gestation	No	95	95
	Yes	5	5
APGAR at 5 minutes	Below 7	2	2%
	≥ 7	98	98%

IUGR was noted in 15% of newborns and pre term delivery in 78%, whereas history of PROM for >24hrs in 10% of newborns. Birth asphyxia, clinical sepsis in newborn and neonatal anaemia was seen 75%, 52% and 7% respectively. Mechanical ventilation and continuous positive airway pressure (CPAP) was received by 19% and 67% of at risk newborns. Mean and SD of ventilated days and CPAP days were 1.1(0.3) and 2.6(0.35). Other risk factors identified were intra ventricular haemorrhage (IVH), neonatal seizures , necrotizing entero colitis (NEC) and patent ductus arteriosus(PDA) in 1 newborn each which were managed medically. None of PDA or NEC were treated surgically. During hospital stay packed RBC transfused in 7(7%) for anemia. Expressed breastmilk feeding through orogastric tube or spoon feeds or direct breastfeeding was done.

Incidence of ROP was 42% (with Type 1 in 9% & Type 2 in 33%), of which 9 had laser surgery prior to discharge, and all were followed up. Out of 9% who had laser surgery for Type 1 ROP,

3,4,1 and 1 at risk newborns had APROP zone 1, APROP Posterior Zone 2, Zone 2 stage 2, Plus disease and Zone 2 stage 3 Plus disease respectively. Spontaneous regression in Type 2 ROP was seen in 33 patients. (Table 2)

Table 2: ROP Incidence and management

ROP incidence N=100	Type 1 ROP (Laser Treatment before discharge)	9	9
	Type 2 ROP (Followed-up)	33	33
	No ROP	58	58
Type 1 ROP (Laser Treatment as Final Outcome) N=9			
APROP, Zone 1		3	21%
APROP, Posterior Zone 2		4	36.8%
Zone 2, stage 2, Plus disease		1	26.4%
Zone 2, stage 3, Plus disease		1	15.8%
Spontaneous Regression (During Follow-up) N=33			

Determinants of ROP identified in the current study were gestational age (mean gestational age (29.9(1.3)) in at newborns with ROP was less compared with newborns without ROP (34.9(1.4)), pre term delivery (more proportion of neonates who had preterm delivery (48.8%) developed ROP compared to term delivery (18.8%)), neonates who received mechanical ventilation (more proportion of neonates on mechanical ventilation developed ROP (43.2%) when compared to those not on ventilator(37.1%)) and also mean number of days on mechanical ventilation (1.9 days in neonates with ROP and 0.7 days in neonates without ROP) and CPAP with Fio2 >50(4.4 days in neonates with ROP and 1.4 days in neonates without ROP). (table 3)

Table 3: Determinants of ROP

Parameters		**Total (N=100)**	**ROP Absent (n=58)**	**ROP Present (n=42)**	**χ^2 / t test/ p value**
Gender	Male N(%)	59(59%)	35 (59.3%)	24 (41.7%)	0.3166/ 0.574.
	Female N(%)	41(41%)	22 (53.6%)	19 (46.4%)	
Gestational age (mean ±SD)		32(2.08)	34.9(1.4)	29.9(1.3)	18.15/0.001
IUGR	Present N (%)	15(15%)	9(60%)	6(40%)	0.029/0.86
	Absent N (%)	85(85%)	49(57.6%)	36(42.4%)	

Pre term delivery	Yes N (%)	78 (78%)	40(51.2%)	38(48.8%)	6.56/0.01
	No N (%)	22(22%)	18(81.8%)	4(18.2%)	
H/o PROM>24 hrs	Present N (%)	10(10%)	6(60%)	2(20%)	0.018/0.892
	Absent N (%)	90(90%)	52(57.7%)	40(22.3%)	
Birth asphyxia	Present N (%)	75(75%)	40(53.3%)	35(46.7%)	2.68/0.101
	Absent N (%)	25(25%)	18(72%)	7(28%)	
Clinical sepsis in newborn	Present N (%)	52(52%)	30(57.6%)	22(42.4%)	0.004/0.98
	Absent N (%)	48 (48%)	28 (58.3%)	20 (41.7%)	
Mechanical ventilation	Yes N (%)	19(19%)	7(36.8%)	12(43.2%)	4.31/0.037
	No N (%)	81(81%)	51(62.9%)	30(37.1%)	
Mean number of ventilated days with FiO2>50% (SD)		1.1(0.3)	0.7(.18)	1.9(1.1)	8.173/0.0001
Received CPAP, N (%)	Yes N (%)	67(67%)	40(59.7%)	18(40.3%)	0.95/0.328
	No N (%)	33(33%)	9 (27.3%)	24 (63.7%)	
Mean of number of CPAP days with FiO2>50 % (SD)		2.6(.35)	1.4(.29)	4.4(.92)	18.229/0.0001
Neonatal anemia, N (%)	Present N (%)	7 (7%)	3(42.8%)	4(57.2%)	0.70/0.198
	Absent N (%)	93(93%)	55 (59.1%)	38(40.9%)	

Multiple logistic regression analysis was done to identify determinants for type 1 and type 2 ROP. It showed birth weight >1500grams have 0.5 times odds of developing ROP compared to < 1500 gms for Type 1 ROP and 0.81 times odds for type 2 ROP which was significant. Gestational age >32 weeks have 0.6 times odds of developing ROP compared to >32 weeks for Type 1 ROP and 0.4 times odds for type 2 ROP which was significant. Clinical Sepsis in newborn have 2.9 times odds of developing ROP compared to newborns without sepsis for Type 1 ROP and 4.6 times odds for type 2 ROP which was significant. Ventilation requirement have 2.1 times odds of developing ROP compared to no requirement for Type 1 ROP and 1.6 times odds for type 2 ROP which was significant. CPAP respiratory support with FiO2>0.5 have 2.4 times odds of developing ROP compared to no CPAP for Type 1 ROP and 3.8 times odds for type 2 ROP which was significant. Neonatal anemia have 1.7 times odds of developing ROP

compared to no anaemia for Type 1 ROP and 2.3 times odds for type 2 ROP which was significant. (table 4). Thus the determinants identified were low birth weight (≤1500gms), gestational age < 32 weeks, clinical sepsis in newborns, mechanical ventilation, respiratory support with CPAP and neonatal anaemia.

Table 4: Multiple logistic Regression analysis of risk factors for Type-1 ROP and Type 2-ROP

Risk Factors	**Type-1 ROP**		**Type 2-ROP**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Male Sex versus female sex	0.97(0.2-1.3)	0.2	1.2(0.8-1.3)	0.3
Birth weight>1500 gram	0.5(0.22-0.73)	0.03*	0.81(0.72-0.97)	0.02*
Intrauterine growth restriction	0.31(0.21-1.7)	0.9	0.5(0.2-1.5)	0.6
Gestation age >32 weeks	0.6(0.51-0.8)	0.00*	0.4(0.3-0.8)	0.03*
PROM >24 hrs	0.7(0.1-1.6)	0.2	0.52(0.1-1.8)	0.2
Clinical Sepsis in newborn	2.9(1.4-7.5)	0.04*	4.6(1.5-8.5)	0.03*
Ventilation requirement	2.1(0.1-4.5)	0.04*	1.6(1-1.9)	0.02*
CPAP respiratory support with FiO2>0.5	2.4(1-5.4)	0.03*	3.8(1-11)	0.08*
Neonatal anemia	1.7(0.9-4.5)	0.03*	2.3(1.5-5.6)	0.02*

DISCUSSION

The survival rate of preterm infants has significantly increased worldwide in the past 20 years, especially in developing countries such as India, with over 3.5 million preterm infants born and surviving annually.[15]

The occurrence of ROP in India and other developing nations, also known as the "third epidemic" of ROP, is the result of a combination of uncontrolled supplemental oxygen (first epidemic pattern) and the evolving but uneven care of very preterm infants (second epidemic pattern).[16,17] Blindness in infancy can lead to many disability-adjusted life-years lost and is considered a developmental emergency.

Literature review indicate high rates of ROP in middle-income and urban areas of low-income countries where expanded coverage of neonatal inpatient care is enabling the survival of less

mature and sicker babies, without adequate concern for the competence of newborn care professionals.[4] This research provided broadly representative infants data who underwent ROP screening and treatment in our hospital.

The current study identifies the incidence at 42 % in at risk newborns which was lesser than study by Uday T et al whose study showed 32.3% [18], also study by Sujit S patel 24.1% [19] and in study by Bharath reddy et al incidence was 13.5%. [20] ROP incidence varies considerably, reflecting the differences in screening, neonatal care and population heterogeneity.

In study by Uday T et al mean birthweight of infants screened was 1451 ± 405 g (range 560–3600 g). The mean period of gestation was 31.3 ± 2.8 weeks (range 20–41 weeks). [18] Study by Bhaskar et al stated prematurity as the single most important risk factor for ROP. Also in their study both the incidence and severity of ROP are inversely related to gestational age.[20] Most studies report the mean birth weight of babies developing ROP above 1500 g, and the mean gestation over 30 weeks. We screened infants for ROP as per NHM Indian recommendation. In our study the average birth weight was more than 1793 g, and mean gestation over 32 weeks. Type 1 ROP was detected in 9% of screened babies.

The current study identified 33/42(75.9%) infants with Type -I ROP. Extreme preterm (GA 28 weeks), extremely low birth weight (ELBW 1000g), and prolonged unmonitored oxygen therapy are all identified risk factors for APROP. 9% had laser surgery for Type 2 ROP, 3,4,1 and 1 at risk newborns had APROP zone 1, APROP Posterior Zone 2, Zone 2 stage 2, Plus disease and Zone 2 stage 3 Plus disease respectively. Spontaneous regression in Type 2 ROP was seen in 33 patients. No stage 4 and stage 5 ROP was identified. In study by Uday T et al stage 1 ROP was seen in 204 eyes (12.2%); Stage 2 in 566 eyes (33.7%); Stage 3 in 216 eyes (12.9%); Stage 4 in 106 eyes (6.3%); Stage 5 in 226 eyes (13.5%); and APROP in 342 eyes (20.1%), while 18 eyes (1.1%) presented with features of spontaneously regressed ROP. Spontaneous regression occurred in 758 eyes (45.2%), and 658 eyes (39.2%) required treatment, whereas unfavorable and late presentation with stage 4B or stage 5 was seen in 262 eyes of 131 infants (15.6%). Overall, severe ROP was seen in 920 eyes (17.7%). ROP was present in zone 2 in 1304 eyes (92.1%), zone 1 in 102 eyes (7.2%), and zone 3 in 10 eyes (0.7%).[18] Where as in study by Sujit S

patel out of 69 cases of ROP, 6 (8.7%) cases were in zone 1, 27(39.1%) cases were in zone 2, 36(52.2%) cases were in zone 3. Maximum incidence was in zone 3.[19]

We found significant association between Type1 and type 2 ROP with prematurity, low birth weight, prolonged unblended oxygen requirement. Study by Patel S S et al, the difference in occurrence of ROP in neonates ≤34 weeks and >34 weeks was statistically significant at 95% confidence interval.[19]

In India due to use of unblended oxygen in many NICUs, this has been detected among out born infants with birth weight more than 1500g. None in our study had any complications during short follow-up. Long term follow-up of these children is required for the assessment of refractive errors, strabismus, anisometropia and amblyopia.

Other postnatal risk factors reported for ROP besides prematurity and low birth weight, included the birth asphyxia, mechanical ventilation, clinical neonatal sepsis and neonatal anemia.

In study by Patel S S et al On univariate analysis done by Pearson chi-square test the risk factors significantly associated with ROP were Birth Asphyxia (P value 0.046), Apnea (p value <0.001). Sepsis (P value <0.001),[19]

Study by Bhaskar et al stated other risk factors identified were birth asphyxia, apnea, prolonged oxygen therapy also neonatal anaemia which was similar to our study.[20]

Oxygen monitoring is essential for preterm infants on supplementary oxygen. Chow and colleagues showed that implementing an oxygen policy to avoid higher oxygen saturation (93%–95%) and large fluctuation in oxygen saturation in infants 500 to 1500 g birth weight resulted in a significant decrease in severe ROP and improved survival.[21] According to recent assessment by the networks of the International Network for Evaluating Outcomes in Neonates (iNeo) to assess variations in oxygen saturation, the upper SpO2 target limit should be 94% or 95% (range 90%–98%), with lower SpO2 limit of 90%.[22] FiO2 more than 0.5 emerged as significant reason for more patients with Type-1 & AP-ROP in our study. We recommend availability of blended oxygen along with strict monitoring to maintain optimal saturation target for infants in NICU.

Sixteen studies with a total sample size of 12466 premature infants and 2494 cases of ROP showed that sepsis was closely related to any ROP (OR = 1.57,95% CI 1.31 to 1.89) and severe

ROP (OR = 2.33,95% CI 1.21 to 4.51) in premature infants.[23] Our study also demonstrated significant positive association between clinical sepsis and severe ROP, and APROP.

CONCLUSION

ROP is essentially asymptomatic in the early stages, standards of practice now demand carefully timed retinal examination of at risk infants**.** Incidence in the current study was 42% much higher compared with earlier studies. Incidence of Type 1 & APROP is increasing, and also seen in neonates with higher gestation and weights. The determinants identified were low birth weight (≤1500gms), gestational age < 32 weeks, clinical sepsis in newborns, mechanical ventilation, respiratory support with CPAP and neonatal anaemia.

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