Profile of risk factors for retinopathy of prematurity

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Abstract

Aim: To evaluate risk factors, clinical profile and treatment outcome of retinopathy of prematurity (ROP) among premature infants at tertiary hospital of Uttarakhand. **Methods:** A prospective observational study was performed on 251 premature infants with inclusion criteria of birth weight <2000 grams, gestational age <34 weeks, any preterm if >34 weeks of gestation and birth weight >2000gm with associated risk factors who underwent detailed history and ROP examination using indirect ophthalmoscopy. Neonates with ROP were further classified according to ETROP guidelines. **Results:** Out of the total 251 studied neonates, 123 neonates (49.0%) had any ROP with no gender preference (p value 0.087). Maximum incidence was seen in neonates of gestational age between 28-31 weeks (60.2%) and very low birth weight (53.7%), p<0.05. Amongst maternal risk factors, mode of delivery and premature rupture of membranes had significant p value Oxygen supplementation, apnea of prematurity, sepsis, intravenous antibiotics and blood transfusion amongst neonatal risk factors had p value 0.0001. Clinically, ROP of stage-I (36.5%), zone-III (29.5%) and plus disease (9.6%) was seen in neonates. Treatable ROP, managed by laser and intravitreal injection of anti-VEGF, was seen in 25 neonates (20.3%). **Conclusion:** A boom of surviving premature neonates is major factor for an emerging international ROP epidemic noticed recently. Apart from low birth weight and small gestational age, other risk factors like neonatal sepsis, intravenous antibiotics, oxygen supplementation and blood transfusion also significantly led to development of ROP. Regular antenatal screening and follow up help in identification and management of treatable ROP thus preventing ROP blindness.

Key words: Birth weight; Gestational age; Retinopathy of prematurity; Premature rupture of membrane

Retinopathy of prematurity (ROP) is a potentially avoidable blinding disorder of developing retina in premature and low birth weight (LBW) infants[1]. Since the beginning of recent developments in recovery and scrutiny in neonatal intensive care units, and consequential improved survival-rate of pre-mature babies, ROP is emerging as the significant cause for visual disability in children of developing nations like India[2].

ROP is associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina. It has a wide spectrum, ranging from mild, temporary changes in retina with regression to the severe progressive vaso-proliferation, detachment of retina, scarring and blindness.

The improvement in neonatal health care especially in rural areas have increased the survival of LBW infants leading to a continuous rise in ROP incidence. Out of 26 million annual live births in India, nearly 2 million are low birth weight who are at risk of developing ROP, of these around 500 become blind from ROP[3]. Globally, 50,000 infants are affected by ROP blindness every year. In India, the ROP incidence is between 38% and 51.9% in LBW babies[4].

Prematurity has been observed to be most important risk-factor for ROP, however, other factors like LBW, high oxygen supplementation & its duration, anemia, respiratory distress syndrome (RDS), blood transfusion and sepsis were also seen to have significant association[5]. The clinical profile of ROP is very different in developed and developing world, therefore, timely screening is crucial for early management and improved outcomes[6]. Country's 60% of population is still residing in rural areas where ROP specialists are miserably low, also improved survival of neonates in these areas pose a great challenge in management of "at-risk" neonates leaving a huge segment of rural premature newborns at risk of unscreened and untreated ROP blindness[7].

The present study was conducted at a tertiary care hospital in Uttarakhand which aimed to determine the risk factors and clinical profile of infants with ROP and to

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analyse the treatment outcome of ROP in Uttarakhand region, India. No other study on ROP from Uttarakhand has been reported to best of our knowledge. So the present study may be considered as pilot study for future larger studies on ROP.

Materials and methods:

The prospective observational study was conducted in the department of ophthalmology of a 1500 bedded multi-specialty hospital, catering large number of patients from our region and surrounding districts, after taking an approval from institutional ethics committee for a period of 18 months. Procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. A written and informed consent explaining the nature of the study was obtained from the guardian of each neonate.

Inclusion criteria were preterm babies with birth weight <2000 grams and gestational age <34 weeks admitted in NICU as well as attending ophthalmology OPD, any preterm if >34 weeks of gestation and birth weight >2000gm with associated risk factors such as cardio-respiratory support, prolonged oxygen therapy, respiratory distress syndrome, chronic lung disease, fetal hemorrhage, blood transfusion, neonatal sepsis, exchange transfusion, intraventricular hemorrhage, apneas and poor postnatal weight-gain referred for ROP screening. Exclusion criteria was neonates who did not came for follow-up.

All the preterm infants referred for ROP screening underwent detailed maternal and neonatal history and ROP examination. Neonates were examined with indirect ophthalmoscope using 20/28 D lens under the supervision of retina specialist. After the instillation of topical anesthetic drops like proparacaine, a wire speculum was inserted to keep the eyelids apart. Firstly the anterior segment of eye was scrutinized to look for pupillary dilation, tunica vasculosa lentis, & lens/media clarity; followed by posterior pole forthe plus disease; then the sequential assessment of all clock hours of peripheral retina. The scleral depressor was used to indent eye externally to inspect the areas of interest, stabilize and rotate the eye if required.

Preterm neonates received first screening at 4 weeks of age or 30 days of life if gestational age was more than 28 weeks and at 2-3 weeks after delivery if period of gestation was less than 28 weeks or less than 1200 grams birth weight, as per the protocol.

After screening, preterm neonates were classified according to the gestational age at birth and birth weight into different sub-categories. A neonate was classified as preterm when born before 37 weeks of gestation[8]. Preterm neonate was further classified as: Extreme preterm (<28 weeks), Very preterm (28-31 weeks), Moderate preterm (32-33 weeks) and Late preterm (34-36 weeks). Preterm neonates were also classified according to their birth weight as: Extremely low birth weight (ELBW: <1,000 grams), Very low birth weight (VLBW: 1,000 grams to <1,500 grams), Low birth weight (LBW: 1,500 grams to <2,500 grams) and Normal birth weight (NBW: ± 2,500 grams) [9].

Clinically, neonates were classified according to international classification of ROP (ICROP) [10]. All babies were divided into two groups i.e. No ROP and Any ROP. Any ROP were further labeled as non-treatable and treatable ROP according to ETROP classification. All the preterm babies screened for ROP were followed up at an interval according to the disease severity[11].

Treatment was given to preterm babies with severe ROP (Zone II Stage 2 or 3 with plus disease; Zone I any stage with plus disease or Zone I Stage 3 without plus disease) according to the ETROP guidelines[12]. Two treatment modalities were used: laser therapy and intravitreal injection of anti-VEGF. Laser therapy [double frequency Nd-YAG laser (532nm)] was given within 72 hours of diagnosis of ROP, using the indirect ophthalmoscope in a confluent or subconfluent scatter pattern to the avascular retina anterior to the ridge. Anti- VEGF injection was also administered to eyes with APROP, in operation theatre under the supervision of attending pediatrician and anesthesiologist, 1.5mm posterior to the limbus after instilling topical anesthesia.

Statistical analysis:

Statistical analysis was performed using the SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed and presented as complete numbers and percentage. Nominal categorical data between groups were compared using the chi-square test.

Results:

Total 251 neonates (502 eyes) were enrolled in the study over a period of 18 months. Out of the total studied neonates, 123 neonates or 246 eyes (49.0%) were found

Table-1: Distribution of study neonates (based upon number of eyes) according to gestational age at birth and birth weight

Gestational age group	ROP				Total	p-value
	No ROP		Any ROP			
Extreme preterm	14	5.5	18	7.3	32	
Very preterm	72	28.1	148	60.2	220	0.001*
Moderate preterm	72	28.1	42	17.1	114	
Late preterm	98	38.3	38	15.4	136	
Birth weight (Kg) group						
Normal birth weight	6	2.3	0	0.0	6	
Low birth weight	138	53.9	82	33.3	220	0.001*
Very low birth weight	84	32.8	132	53.7	216	
Extremely low birth weight	28	10.9	32	13.0	60	

*: statistically significant

to be with any ROP while 128 neonates or 256 eyes (51.0%) were without ROP. There was no statistically significant difference among males and females with respect to prevalence of ROP as P=0.087, though prevalence was found to be more among males.

Majority of the eyes with any ROP were in very preterm and very low birth weight category according to the gestational age at birth and birth weight respectively. Association of gestational age and birth weight with ROP was found to be statistically significant (P=0.001) as shown in table-1.

Mode of delivery and premature rupture of membranes were found to be statistically significant (P<0.05) amongst maternal risk factors (table-2). The neonatal risk factors i.e. oxygen supplementation, apnea of prematurity, sepsis, intravenous antibiotics and blood transfusion were found to be statistically significantly associated with any ROP (P<0.05) (table-3).

Majority of eyes with ROP belonged to stage 1, zone 3 without plus disease. APROP was seen in four eyes (table-4).

Total neonates screened for ROP were 251, of which 128

Table-2: Association of maternal risk factors with any ROP

	ROP		p- value
	No ROP (n=256)	Any ROP (n=246)	
Mode Of Delivery (Caesarean section/NVD)	76/180	98/148	0.019
Hypertension (Yes/No)	32/224	26/220	0.499
Anemia (Yes/No)	10/246	18/228	0.096
Diabetes (Yes/No)	0/256	2/244	0.148
Assisted Conception (Yes/No)	10/246	2/244	0.057
Premature Rupture Of Membranes (Yes/No)	38/218	62/184	0.005
Smoking (Yes/No)	0/256	0/246	

*NVD: Normal Vaginal Delivery

Table-3: Association of neonatal risk factors with any ROP

	ROP		p- value
	No ROP (n=256)	Any ROP (n=246)	
Sepsis (Yes/No)	176/80	204/42	0.0001
Oxygen Supplementation (Yes/No)	56/200	122/124	0.0001
Apnea Of Prematurity (Yes/No)	86/170	136/110	0.0001
Intravenous Antibiotics (Yes/No)	136/120	156/90	0.024
Blood Transfusion (Yes/No)	4/252	16/230	0.005
Respiratory Distress Syndrome (Yes/No)	168/88	170/76	0.406
Neonatal Enterocolitis (Yes/No)	0/256	2/244	0.148
Anemia (Yes/No)	8/248	16/230	0.094
Thrombocytopenia (Yes/No)	0/256	0/246	
Disseminated intravascular coagulation (DIC) (Yes/No)	2/254	4/242	0.384
Intraventricular Hemorrhage (Yes/No)	0/256	2/244	0.148
Multiple Births (Yes/No)	64/192	64/182	0.794
Patent Ductus Arteriosus (Yes/No)	4/252	8/238	0.215
Rheumatic Heart Disease (Yes/No)	2/254	0/246	0.165

(51%) had no ROP. They were not called for follow-up. 123 (49%) neonates had any ROP and were called for follow up according to the ETROP guidelines. Out of 123 neonates, 98 (79.7%) had type 2 ROP, of which 91 (74%) neonates came for follow up every 2 weekly till 3 months or complete regression of ROP occurred. 7 neonates did not turn up for further follow-up accounting for 5.7% of drop outs. Severe (type 1) ROP which is amenable to treatment was seen in 25 neonates (20.3%). Treatment in the form of laser (22 neonates; 17.9%) and intravitreal injection of anti-VEGF (1 neonate; 0.8%) was done. They were maintaining follow up till date for refractive changes and fundus evaluation. Two neonates (1.6%) with advanced stage ROP were referred to higher centre.

Table-4: Clinical profile of neonates screened

	No. of eyes	Percentage (%)
Stage of ROP (1/2/3/5)	183/42/19/2	36.4/8.4/3.8/0.4
NO ROP	256	51.0
Zone of ROP (1/2/3)	10/86/148	2.0/17.1/29.5
NO	258	51.4
Plus Disease (PLUS/NO)	48/454	9.6/90.4
APROP* (YES/NO)	4/498	0.8/99.2
Total	502	100.0

*: Aggressive posterior retinopathy of prematurity

Discussion:

Our study was conducted in a tertiary hospital of Uttarakhand where incidence of ROP among preterm infants was 49.0%. Similar studies by Dwivedi A et al[6], Anudeep K et al[4], Ahuja AA et al[13] and Paranjpe DG et al[14] also reported the incidence of ROP to be 30.0%, 37.0% 32.6% and 35.63% respectively. The higher value in our study was due to the large sample size. Also, our

centre was a tertiary care centre where high-risk cases were being referred from the surrounding hilly areas, where health facilities are not so developed, leading to more NICU admissions and referral for ROP screening. The cognizance of the pediatric department led to the timely referral of neonates for screening of ROP. The present study had male: female ratio of 1.3:1 overall. Out of the 246 neonates with ROP, 60.2% were males and 39.8% were females and the association was found to be statistically not significant (p>0.05). Although male predominance was seen in studies by Le C et al[15] (59.0% male, 41.0% female), Dwivedi A et al[6] (59.6% male, 40.4% female) and Goyal K et al[16] (52.5% male, 47.5% female; p=0.524) but was not clinically significant in these studies also. Thus, ROP does not have any sex predilection as mentioned in the literature.

Gestational age at birth and birth weight of majority of neonates with ROP in our study was 28-31 weeks and 1,000-1,499 grams respectively. This correlation was found to be statistically significant (p-value<0.05). Dwivedi A et al[6], Molugan M and Kumaravel KS[17] also reported similar findings.

Our study showed LBW and low GA to be the highly significant risk-factors for the development of ROP apart from other maternal and neonatal risk factors. The multicenter study of cryotherapy for ROP (CRYO-ROP) followed 4,099 infants with BW d"1251g, and found that lower BW and younger GA were strongly associated with developing "threshold" ROP.[18] In the CRYO-ROP cohort, each 100g increase in BW decreased the odds of reaching threshold ROP by 27%, and each week increase in GA decreased the odds of reaching threshold disease by 19%[18].

Mode of delivery and premature rupture of membranes were found to be significant (p- value<0.05) maternal risk factors associated with ROP. Sathar A et al[2] reported that PROM with or without chorioamnionitis was there in 42.9% cases which was significant (p=0.029).

The neonatal risk factors like oxygen supplementation, apnea of prematurity, sepsis, intravenous antibiotics and blood transfusion were also statistically significantly associated with any ROP (p-value<0.05) in our study while respiratory distress syndrome was not associated significantly with ROP (p>0.05). Goyal K et al[16] similarly reported the most prevalent postnatal risk factors among patients with ROP to be sepsis (36.0%), use of oxygen therapy (34.0%) and blood transfusion (18.0%). RDS was not significantly associated with ROP in some studies.[16] Whereas, other studies showed significant association of RDS with ROP[19,20,21]. In a study by Le C et al[15] the most prevalent postnatal risk factors among patients with ROP were reported to be RDS (58.0%) and use of oxygen therapy (71.0%). 36.0% of infants with ROP were diagnosed with anemia of prematurity, with 26.0% of these infants requiring transfusion of packed red blood cells. Dwivedi A et al[6] reported duration of oxygen therapy (pÂ0.001), post-conceptional age (p=0.002), and respiratory distress syndrome to be significantly associated with ROP.

The majority of the neonates with ROP belonged to stage I zone III (57%) followed by stage II zone II (15.4%) in our study. This was similar to the study by Le C et al[15] which had predominance of stage I zone III (70%) followed by stage II zone II (23%). Paranjpe et al[14] also observed in his study that of 233 neonates screened for ROP, majority were in stage1 (83.13%) with most common involvement seen in Zone III (82%) followed by Zone II (16.87%). We found in our study that of the total 502 studied eyes, 48 (9.6%) were having plus disease and only 4 (0.8%) were having APROP.

In the present study eyes screened for ROP were classified into type 1 and type 2 according to the ETROP guidelines and were called for follow up accordingly. We found 123 neonates with any ROP, of which 98 neonates had type 2 ROP and 25 had severe (type1) ROP. Neonates with type 2 ROP showed spontaneous regression in 91 neonates (74%) on follow up. Majority of them were in stage 1 zone III without plus disease. Neonates with severe (type1) ROP were treated with laser (17.9%) and intravitreal injection of anti-VEGF (0.8%). Majority of them were in stage 3 zone II with plus disease. They were maintaining follow up till date for refractive changes and fundus evaluation.

The further long term follow up by Le C et al[15] reported that following argon laser, regression was observed in 100.0% of infants, with no recurrence upto 4 years after treatment with majority neonates receiving treatment were in stage 3 zone II. Spontaneous regression of ROP is more likely with stage 1 (86.7%), than stage 3 (5.9%). Regression in zone III was 100% as compared to 0% in zone I.[22] Similarly, regression of both stage 3 and plus disease can be 29, 82, 88, and 100% by weeks 1, 2, 3, and 4, respectively.[23] Laser photocoagulation was found to be very effective in regressing ROP, therefore, it is

considered as a gold- standard modality in the treatment of severe ROP.

Inspite of geographical and demographic variations both maternal and neonatal risk factors found are similar to studies conducted in other parts of India. This study on ROP is first of its kind in Uttarakhand state and thus it gives indispensable data on risk factors and clinical profile of ROP in this state.

Conclusion:

Despite of variation in demography and geography of state, present study showed increase in incidence of ROP, accounting for 49%, due to referral from surrounding hilly areas where health services are suboptimal but maternal and neonatal risk factors are similar. ROP is strongly associated with LBW and gestational age. Other risk factors like neonatal sepsis, intravenous antibiotics, oxygen supplementation and blood transfusion also significantly contribute to development of ROP. Maternal risk factors are also associated with ROP. Regular antenatal screening to identify risk factors for preterm delivery is believed to be an important factor in preventing preterm birth. Timely screening and prompt follow up of preterm neonates can help to identify and manage treatable ROP and prevent blindness from ROP. Tertiary centers provide facility for ROP screening but awareness programs and referral services need to be ameliorated to meet the increasing demand. Anti- VEGF and laser photocoagulations are effective measures in treating ROP.

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