Original Article

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Paediatrics Section

Risk Factors for Retinopathy of Prematurity with Specific Emphasis on Postnatal Weight Gain: An Observational Study

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ABSTRACT

Introduction: Retinopathy Of Prematurity (ROP) is a vasoproliferative disorder that affects premature infants with multiple risk factors. Timely screening and treatment can help decrease this preventable cause of blindness.

Aim: To assess the risk factors for development of ROP, and to study its association with postnatal weight gain.

Materials and Methods: This was an observational study with both prospective and retrospective arms. In the retrospective component, the case files and ROP screening records of the infants were screened, in the duration of July 2019 to February 2020. The prospective data was collected from the ongoing screening sessions, during March 2020 to November 2020. The risk factors for ROP, and postnatal weight gain was observed during the ROP screening programme conducted at the intramural Neonatal Intensive Care Unit (NICU) of Sir Sayajirao Hospital, Vadodara, Gujarat, India. Infants with Birth Weight (BW) <2000 g and Gestational Age (GA) <34 weeks and those with high risk factors {prolonged oxygen exposure, mechanical ventilation, anaemia requiring blood transfusion, Intraventricular Haemorrhage (IVH), Respiratory Distress Syndrome (RDS), Bronchopulmonary Dysplasia (BPD), recurrent apnea, hypotension requiring inotropes, surgery during first week of life, sepsis and hypoglycaemia} were included in the study. Subjects were followed-up till 44 weeks Post-Menstrual Age (PMA), or till complete vascularisation of retina or regression of ROP on retinal examination whichever was earlier. Risk factors were studied using univariate analysis and multivariate regression. Weight gain was studied using independent sample t-test.

Results: A total of 486 neonates were enrolled, who underwent serial ophthalmological examinations. Out of these, 375 infants (198 (52.8%) male and 177 (42.7%) females) underwent examinations until 44 weeks of PMA or till complete retinal vascularisation, or till complete regression of ROP with or without treatment. Out of these, 173 patients had no ROP, 120 patients developed ROP which got spontaneously regressed over time and 82 patients developed severe ROP which required treatment. Mean Gestational Age (GA) in the study population was 34.35 week (±2.64 wk), and mean Birth Weight (BW) was 1.67 kg (±0.45 kg). In the group of severe ROP, mean GA was 32.03 week (±1.33 wk) and mean BW was 1.33 kg (±0.35 kg); and the mean number of positive risk factors were 5.93 (±1.77). Poor postnatal weight gain was associated with more risk of severe ROP. GA <34 week (p-value <0.0001), BW <1750 g (p-value <0.0001), oxygen exposure (p-value <0.0001), IVH (p-value <0.0001), RDS (p-value=0.0111), BPD (p-value=0.0058), hypotension requiring inotropes (p-value=0.0001) and sepsis (p-value <0.0001) were significant risk factors. On multivariate logistic regression, BW <1750 g, GA <34 week, sepsis and hypotension requiring inotropes were most important risk factors for ROP, along with poor postnatal weight gain.

Conclusion: Poor postnatal weight gain is associated with increased risk of severe ROP.

Keywords: Birth weight, Gestational age, Retinal vascularisation, Sepsis

INTRODUCTION

Advances in neonatal care have increased the chances for survival of preterm babies. But survival is not the only outcome, since these babies suffer many complications later on. ROP is a potentially blinding disease caused by abnormal development of retinal blood vessels in these high-risk neonates. Incidence of ROP has been variable. It was first noted in the 1940s and 1950s mainly as a consequence of the use of unmonitored supplemental oxygen ("first epidemic") [1].

As survival of extremely premature infants improved over the next decades and despite better methods of monitoring oxygen supplementation, a rising incidence of ROP re-emerged ("second epidemic") [2]. The "third epidemic" of ROP appears to be a result of both increased number of preterm births in low- and middle-income countries, and also improved quality of neonatal care but inadequate equipment to monitor the supplemental oxygen therapy [3]. The incidence of ROP in India is variable. According to a study conducted from 2000 to 2006, the incidence of ROP was 22.3% [4]. In a recent study (2018), the incidence of ROP was found to be 19.2% [3]. Inconsistencies of neonatal care have led to large variability in ROP incidence and severity within India [4].

Screening for ROP has to be performed at intervals of two to three weeks, till the retinal vascularisation is complete or till 44 weeks of PMA. Patients have to be examined even after treatment [5,6]. The present study aimed to stratify various risk factors of ROP, with specific emphasis on the postnatal weight gain.

MATERIALS AND METHODS

This observational study with both retrospective and prospective arms, was conducted in the Sir Sayajirao General Hospital, Vadodara, Gujarat, India. Approval was obtained from the Institutional Ethics Committee (approval letter no. IECBHR/49-2020).

Data was collected prospectively during ROP screening sessions from January 2020 to November 2020. Retrospective data, from July 2019 to December 2019, was collected from the case files. The patients from retrospective arm were contacted and called for follow-up. Consent form was taken from parents at the time of enrolment of neonates.

Sample size calculation: In the study institute, each month almost 10 infants are treated for severe ROP. For each case of severe ROP, two controls with no ROP or ROP not requiring treatment were taken.

Inclusion criteria: Those infants with birth weight <2000 g, Gestational Age <34 weeks, Infants with BW <2000 g but with risk factors or those infants with GA >34 weeks but with high risk factors were included in the study. High risk factors for the study were prolonged oxygen exposure, mechanical ventilation, anaemia, requiring blood transfusion, IVH, RDS, BPD, recurrent apnoea, hypotension requiring inotropes, surgery during first week of life, sepsis, hypoglycaemia.

Exclusion criteria: Those infants with BW >2000 g, and GA >34 weeks, and absence of any risk factors were excluded from the study.

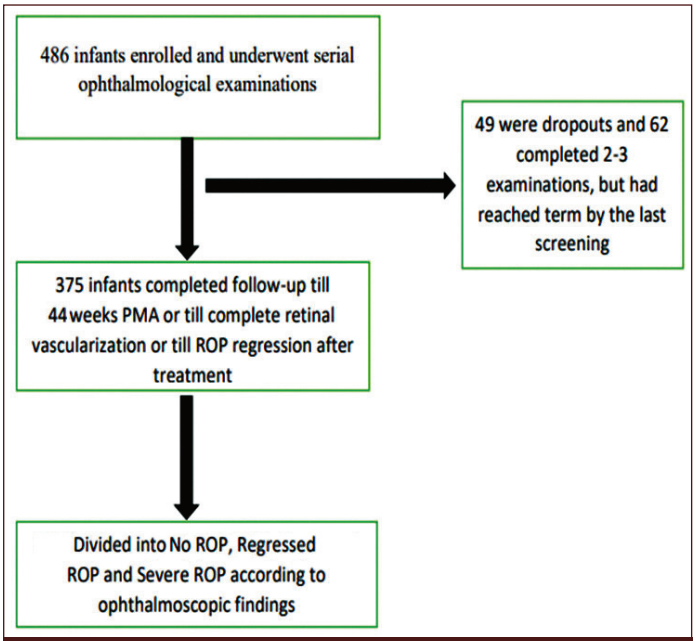
The total of 375 infants enrolled, analysed and followed-up in the study, were divided into:

Group 1: Including 293 infants with no ROP (n=173) or regressed ROP (n=120).

Group 2: Including 82 infants with severe ROP.

Study Procedure

All the preterm infants fulfilling the inclusion criteria were observed weekly or biweekly at the ROP screening programme conducted at the intramural NICU. Preterm infants who were fitting in the inclusion criteria were observed for risk factors, weight measurements were recorded during each screening, noted in table and marked on the Intergrowth-21 chart. Patients were followed-up till 40-44 weeks PMA, or till complete vascularisation of retina or regression of ROP on retinal examination; whichever was earlier [Table/Fig-1].



[Table/Fig-1]: Flowchart showing progress of the study.
PMA: Post menopausal age; ROP: Retinopathy of progression

Electronic weighing scale, infantometer, non expandable tape, dilator and anaesthetic eye drops, Alphonso speculum, 20D and 28D lens, indirect ophthalmoscope, scleral depressor.

Data collection: During each ROP screening session, average 20 patients were screened and enrolled in the study. After instillation of dilator and anaesthetic eye drops, indirect ophthalmoscopy was done by vitreoretinal surgeon and findings were noted in the prescribed format and follow-up date given. Weight recordings done at each screening till 44 weeks PMA and weekly for the patient admitted in the nursery. Average weight gain was calculated after the second week, considering the initial weight loss in the first week, and also considering that preterm infant and those who have NICU stay and exposed to multiple risk factors, may take about two weeks to regain the BW. A 70 g/kg/week (10 g/kg/day or 1%) of the BW was considered as the cut-off value.

STATISTICAL ANALYSIS

Risk factors studied with univariate analysis and multivariate regression. Weight gain pattern studied using independent samples t-test. Medical Calculators (Med Calc) version 12.5.0.0 (Trial version) was used for the analysis of the data and p-value <0.05 was considered as statistically significant. Microsoft word and excel have been used to generate graphs and tables. In order to apply the independent samples t-test, the 3 groups were merged into 2 groups. The weekly weight gain was calculated and average of the weight gain values was taken. Average is the sum of given numbers divided by the total of numbers being averaged. Whereas mean is the sum of the smallest value and largest value in the data set divided by 2.

RESULTS

A total of 375 out of 486 infants were followed-up till 44 weeks PMA, till complete retinal vascularisation or till regression or ROP. Total 198 (52.8%) infants were male and 177 (42.7%) were females. On the basis of ophthalmological examination, the population was divided into three groups. Those who did not develop any ROP findings were labelled as 'no ROP' (n=173, 46%). Those who developed ROP which regressed spontaneously were labelled as 'regressed ROP' (n=120, 32%). Those who developed severe forms of ROP which required treatment were labelled as 'severe ROP' (n=82, 21%).

Mean BW of the population was 1.67 kg (±0.45). As the BW increased, the risk of severe ROP increased (p<0.0001) [Table/Fig-2]. The mean GA was 34.35 weeks (±2.64). As the GA decreased, the risk of severe ROP increased (p<0.0001) [Table/Fig-3].

Birth weight (BW)	No ROP (n=173)	Regressed ROP (n=120)	Severe ROP (n=82)
<1000 g	0 (0.00%)	4 (3.33%)	13 (15.85%)
1000-1249 g	8 (4.62%)	15 (12.50%)	20 (24.39%)
1250-1499 g	31 (17.92%)	23 (19.17%)	27 (32.93%)
1500-1749 g	53 (30.64%)	52 (43.33%)	15 (18.29%)
1750-1999 g	45 (26.01%)	19 (15.83%)	2 (2.44%)
2000-2499 g	34 (19.65%)	7 (5.83%)	5 (6.10%)
≥2500 g	2 (1.16%)	0 (0.00%)	0 (0.00%)
Mean (SD)	1.73 (±0.31)	1.55 (±0.30)	1.33 (±0.35)

[Table/Fig-2]: Comparison of Birth Weight (BW) and outcome of ROP (p-value for the overall BW comparison <0.0001; chi-square test).

Gestational age (GA)	No ROP (n=173)	Regressed ROP (n=120)	Severe ROP (n=82)
≤30 wk	2 (1.16%)	12 (10.00%)	22 (26.83%)
31-32 wk+ 6 days	11 (6.36%)	23 (19.17%)	25 (30.49%)
33-34 wk+ 6 days	44 (25.43%)	36 (30.00%)	25 (30.49%)
35-36 wk+ 6 days	85 (49.13%)	42 (35.00%)	7 (8.54%)
≥37 wk	31 (17.92%)	7 (5.83%)	3 (3.66%)
Mean (SD)	34.97 (±1.61)	33.61 (±2.12)	32.01 (±1.33)

[Table/Fig-3]: Comparison of Gestational Age (GA) and outcome on ROP (p-value for the overall BW comparison <0.0001; Chi-square test).

The group with severe ROP showed a greater number of positive risk factors than the one with no and regressed ROP [Table/Fig-4]. Risk factors were compared with univariate analysis and eight out of 11 risk factors were found to be significantly positive in the group with severe ROP. These factors were BW <1750 g, GA <34 week, oxygen exposure, IVH, RDS, BPD, hypotension requiring inotropes and sepsis [Table/Fig-5].

Average no. of co-morbidity	Group 1	Group 2
Mean	3.75	5.93
SD	1.95	1.77

[Table/Fig-4]: Mean number of positive risk factors in group 1 (no or regressed ROP) vs group 2 (severe ROP).

Risk factors	Group 1 (n=293)	Group 2 (n=82)	p-value	95% CI
GA <34 wk	125 (30.94%)	71 (86.58%)	**<0.0001**	42.143% to 66.202%
BW <1750 g	186 (46.03%)	76 (92.68%)	**<0.0001**	35.463% to 55.345%
Oxygen exposure	156 (38.61%)	67 (81.70%)	**<0.0001**	29.154% to 54.471%
RDS	122 (30.19%)	63 (76.82%)	**<0.0001**	31.375% to 59.192%
Sepsis	204 (50.49%)	77 (93.90%)	**<0.0001**	32.819% to 51.613%
IVH	3 (0.74%)	3 (3.65%)	**0.0111**	-67.798% to 72.916%
Hypotension requiring inotropes	44 (10.89%)	42 (51.21%)	**0.0001**	19.752% to 57.684%
BPD	2 (0.49%)	3 (3.65%)	**0.0058**	19.752% to 57.684%
Blood transfusion	12 (2.97%)	5 (6.10%)	0.2836	-25.665% to 56.086%
Hypoglycaemia	26 (6.44%)	4 (4.88%)	0.3218	-58.885% to 19.213%
Jaundice	171 (42.33%)	60 (73.17%)	0.7349	15.686% to 43.846%

[Table/Fig-5]: Univariate analysis of risk factors (group 1: infants with no ROP and regressed ROP, group 2: infants with severe ROP).
BPD: Bronchopulmonary dysplasia; BW: Birth weight; GA: Gestational age; IVH: Intraventricular haemorrhage RDS: Respiratory distress syndrome

On multivariate regression analysis, BW <1750 g, GA <34 weeks, sepsis and hypotension requiring inotropes were significant risk factors associated with severe ROP (p-value <0.05) [Table/Fig-6].

Risk factors	Odds ratio	95% CI	p-value
GA <34 week	3.71	1.6112 to 8.5427	**0.002**
Inotropes	4.21	2.0481 to 8.6639	**0.0001**
BW <1750 g	3.15	1.1520 to 8.5884	**0.02**
Sepsis	3.09	1.0811 to 8.8291	**0.03**

[Table/Fig-6]: Multivariate regression analysis of risk factors of severe ROP.

Average weight gain was calculated after the second week, considering the initial weight loss in the first week, and also considering that preterm infants and those who have NICU stay and exposed to multiple risk factors, may take about two weeks to regain the BW. A 70 g/kg/week (10 g/kg/day or 1%) of the BW was considered as the cut-off value. Infants with average weight gain, infants with poor postnatal weight gain showed increased risk of severe ROP (independent samples t-test, p=0.00001) [Table/Fig-7].

Average postnatal weight gain	No or regressed ROP	Severe ROP
<0.07 (<70 g/kg/wk)	287	75
≥0.07 (≥70 g/kg/wk)	6	7
Total	293	82

[Table/Fig-7]: Relation between postnatal weight gain and risk of severe ROP.
Average has been taken for weekly (wk) weight gain values; p-value=0.00001; independent samples t-test

Eighty-two infants having severe ROP were treated, out of which 66 required only intravitreal anti-Vascular endothelial growth factor (VEGF) injection, six required only Laser photocoagulation, and 10 needed both. Treatment with anti-VEGF injection had minimal local side-effects eg. rash, exfoliative dermatitis, hand-foot skin reaction, infection or inflammation in the eye, retinal detachment that to in the milder form.

DISCUSSION

The ROP is a reversible vasoproliferative disorder, which has many risk factors. Timely screening of preterm infants may help in timely detection and intervention of ROP and reduce the further blindness [6]. In this study, as the BW decreased, the risk of severe ROP increased [Table/Fig-2]. The American Academy of Pediatrics (AAP) guidelines for ROP screening suggests that babies ≤1500 g BW or ≤32 weeks GA must be screened, with those infants >1500 g or >32 weeks be screened at the discretion of the attending neonatologist [7].

As evident from [Table/Fig-2], 78 out of 234 (33.3%) infants with BW >1500 g developed some form of ROP which got regressed; and 22 out of 234 infants (9.4%) developed severe ROP which required treatment. In the study conducted by Bowe T et al., 25 out of 62 (40.3%) infants with BW>1500g developed severe ROP [6]. In the study conducted by Chaudhari S et al., 31 infants in the BW range of 1500-1999 developed ROP and 6 (19.4%) required treatment; and 3 infants in the BW range of 2000-2499 g developed ROP but not requiring treatment [4]. This indicates that ROP can be observed even at higher BW as compared to that in the developed countries, which makes screening of the heavier infants necessary.

As GA decreased, the risk of severe ROP increased [Table/Fig-3]. As seen in [Table/Fig-3], 85 out of 280 (30.3%) infants with GA >32 weeks developed ROP which got regressed and 35 out of 280 (12.5%) infants developed severe ROP. In the study conducted by Vinekar A et al., 14 out of 62 (22.5%) infants with GA >32 week developed severe ROP [8]. In the study conducted by Chaudhari S et al., 33 infants in the GA range 33-34 week developed ROP and 6 (18.2%) required treatment; while 7 infants >34 week developed ROP but did not require treatment [4]. Therefore, screening of infants with higher gestation but with risk factors is necessary.

The overall incidence of ROP in the study population was 41.5%, while the incidence of severe ROP was 16.8%. Similarly, in the study conducted by Binkhathlan A et al., the incidence of ROP was 56% and the incidence of severe ROP was 15% [9]. The incidence of severe ROP was 6.7% in the study of Bas AY et al., and 14.2% in the study of Dwivedi A et al., [10,11]. The incidence of ROP in different studies is variable depending upon the premature birth rate in the study centre, the level of neonatal care and the BW and GA cut-offs considered for screening purpose. In this study, only those babies admitted to the NICU and survived to undergo the screening; and referred infants from the district referral hospitals were screened. Therefore, the exact incidence in the population cannot be derived.

To compare the occurrence of risk factors is each group, the average number of risk factors in the infants were compared. Group 2 (severe ROP) showed a greater number of positive risk factors 5.93 (±1.77) as compared to 3.75 (±1.95) in group 1 (no and regressed ROP) (p<0.0001); indicating that more the number of associated risk factors, more is the risk of severe ROP.

Univariate analysis showed that GA <34 week, BW <1750 g, oxygen exposure, IVH, RDS, BPD, hypotension requiring inotropes and sepsis were significantly positive in the group of severe ROP [Table/Fig-5]. All risk factors were studied using multivariate regression analysis and BW <1750 g (p=0.02), GA <34 week (p=0.002), sepsis (p=0.03) and hypotension requiring inotropes (p=0.0001) were found to be statistically significant [Table/Fig-6]. The BPD was not significant as an independent risk factor because oxygen exposure was the confounding factor, responsible for both BPD and ROP. Similar results were observed in the studies conducted by Bas AY et al., Vinekar A et al., and Dwivedi A et al., [Table/Fig-8] [8,10,11].

Risk factors	Bas AY et al., (2018) [10] n=2115 mean GA=28.9 wk mean BW=1457 g	Dwivedi A et al., (2019) [11] n=763 mean GA=31.05 wk mean BW=1340 g	Vinekar A et al., (1993) [8] n=138 mean GA=30.9 wk mean BW=1533 g	Present study n=375 mean GA=34.35 wk Mean BW=1670 g
GA	<0.001	<0.001	#	<0.0001
BW	<0.001	<0.001	#	<0.0001
Oxygen exposure	<0.001	*	0.014	<0.0001
RDS	<0.001	0.09	0.007	<0.0001
Sepsis	<0.001	*	0.006	<0.0001
IVH	<0.001	*	0.945	0.0111
Hypotension requiring inotropes	*	0.41	0.325	0.0001

[Table/Fig-8]: Comparison of significant risk factors as per univariate analysis.
*Indicates that these risk factors were not included in the study; #In the study by Vinekar A et al., BW and GA was studied separately and not included in univariate analysis

In the group with no and regressed ROP, 287 infants showed weight gain >70 g/kg/week; which is poor weight gain and 6 infants showed weight gain >70 g/kg/week. Whereas, in the group with severe ROP, 75 infants showed poor weight gain and 7 had weight gain ≥70 g/kg/week; indicating that poor postnatal weight gain is associated with increased risk of severe ROP (independent samples t-test, p=0.00001). In a study conducted by David K et al., infants with mild or no ROP gained a mean of 10.9 g/kg per day in the first 6 weeks of life, compared with an average of 9.6 g/kg/day in those with severe ROP (p-value=0.04) [12]. In the cohort of severe ROP requiring treatment, 66 patients received only anti-VEGF injection; 6 patients received only Laser photocoagulation; and 10 patients received both treatment modalities.

Intravitreal anti-VEGF injection is a short procedure, requiring minimum resources, which can be performed in the NICU itself and does not require administration of anaesthesia, whereas, laser photocoaguation of the retina requires operation theatre with availability of laser equipment and paediatric anaesthesiologist. Therefore, intravitreal anti-VEGF injection was the preferred treatment modality by the vitreo-retinal surgeon in the present setup. Treatment with anti-VEGF injection had minimal local side-effects, and no systemic adverse effects were observed in any of treated patients of the present study. The requirement of serial ophthalmological examinations post anti-VEGF instillation till complete regression of ROP was fulfilled.

Limitation(s)

The prospective part of the study was based on serial ophthalmological examinations, which was difficult during the lockdown period in the Coronavirus Disease-2019 (COVID-19) pandemic. Therefore, many infants could not be followed till complete vascularisation of retina or regression of ROP was seen, and less number of patients could be enrolled. Also, due to resource constraints, most infants received anti-VEGF injections as treatment.

CONCLUSION(S)

This study revealed that the incidence of severe ROP in the present study population is 16.8%. BW <1750 g, GA <34 week, oxygen exposure and sepsis are the most commonly associated risk factors; along with poor postnatal weight gain is also a risk factor for severe ROP. Intravitreal anti-VEGF was the preferred mode of treatment in this study, with only minimal adverse effects like conjunctivitis, and no serious systemic adverse effects.

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