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COMPARATIVE ANALYSIS OF CLASSICAL AND AGGRESSIVE RETINOPATHY OF PREMATURITY: A ONE-YEAR PROSPECTIVE STUDY AT A TERTIARY OPHTHALMIC CENTRE IN NORTH INDIA

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ABSTRACT This one-year prospective cross-sectional study aimed to analyse and compare the demographic characteristics, incidence, and risk factors associated with classical retinopathy of prematurity (ROP) and aggressive ROP (AROP) in neonates. Conducted at a tertiary ophthalmic centre in North India, the study included 343 neonates with birth weights ≤ 2000 grams and gestational ages ≤ 35 weeks. The neonates diagnosed with ROP were divided into two groups: classical ROP (Group A) and AROP (Group B). Of the 343 neonates screened, 165 developed ROP, resulting in an overall incidence of 48.10%. Classical ROP accounted for 44.02% (151 cases) and AROP for 4.08% (14 cases). Pre-plus and plus disease incidence among eyes with ROP were 10% and 5.15%, respectively. Zone 2 disease was observed in 98.78% of eyes, and Zone 1 in 1.21% of eyes. There were 203 eyes with stage I, 100 with stage II, and 25 with stage III disease. Early gestational age (p=0.045) and low birth weight (p=0.00) were significantly associated with disease severity. Significant maternal and neonatal risk factors included gestational diabetes (p=0.0005), placental bleeding (p=0.0026), respiratory distress syndrome (p=0.0009), and surfactant administration (p=0.00). The duration of oxygen supplementation was an independent risk factor (p=0.00). Increasing awareness about ROP, regulated oxygen administration, timely screening, and early treatment of high-risk infants can lead to favourable structural and functional outcomes.

KEYWORDS : Retinopathy of prematurity, Classical retinopathy of prematurity, Aggressive retinopathy of prematurity, risk factors.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vision threatening condition that affects the development of retinal blood vessels in premature and low birth weight infants. This disorder can lead to visual impairment or blindness if not properly managed. It occurs because the retinal blood vessels, which usually complete their development in the last few weeks of pregnancy, are not fully developed in premature infants. This abnormal vessel growth can result in scarring and retinal detachment.[1] The incidence of ROP has risen due to the improved survival rates of preterm infants, particularly in middle-income countries like India, where advancements in neonatal care have played a significant role. [2] In these regions, the "Third epidemic of ROP" is driven by higher survival rates of preterm babies, suboptimal quality of neonatal care, and inadequate ROP screening and treatment coverage. [3,4]

Approximately 45 million people worldwide are blind, with 30% residing in Asia. Childhood blindness accounts for 4% of total blindness, and India bears 20% of the global burden of childhood blindness. [5] ROP affects over 300,000 infants globally. [6] In developing countries like India, the incidence of ROP among high-risk preterm infants ranges from 24% to 47%. This condition is significant not only due to the economic burden it imposes but also because of its severe social implications, which extend over a long duration in terms of blind years.

Prematurity stands out as the foremost risk factor for ROP. Additionally, factors such as low birth weight (LBW), prolonged and high levels of oxygen supplementation, respiratory distress syndrome (RDS), anaemia, sepsis, and blood transfusions have been identified as significantly linked to the occurrence and severity of ROP. These variables collectively contribute to the challenges in managing and preventing ROP in premature infants.[7] While ROP can lead to severe visual impairments, the condition fortunately has a good prognosis when early screening and management are implemented. Therefore, an effective screening protocol is crucial for timely detection and treatment. [6]

The objective of this study is to determine the incidence of ROP in a tertiary care centre and to analyse and compare the established risk factors associated with ROP among neonates diagnosed with classical ROP and aggressive ROP (AROP).

MATERIALS AND METHODS

Following approval from the institutional ethical committee, a one-year prospective cross-sectional study was conducted at a tertiary ophthalmic centre in North India. The study enrolled neonates with a birth weight ≤ 2000 grams and gestational age ≤ 35 weeks who were either admitted to the Neonatal Intensive Care Unit (NICU) or presented at the outpatient department (OPD). Written and informed consent in their vernacular language was obtained from all the parents of the infants enrolled in the study. Infants lost to follow-up, or whose parents refused consent were excluded, resulting in a total of 343 infants. Screening and comprehensive retinal examinations were performed using an indirect ophthalmoscope equipped with a +28D or +20D lens. Pupils were dilated widely with phenylephrine 2.5% and tropicamide 0.5%, administered three times at 10-minute intervals, starting at 4 weeks or 28 days of life.

Neonates diagnosed with ROP were classified according to the international classification of ROP (ICROP).[8,9] Subsequently, infants were categorized into classical ROP (group A) and AROP (group B). Data collected for each case included mother's age, birth weight, gestational age, mode of delivery, type of gestation, neonatal and maternal risk factors, and the worst stage of ROP at the time of NICU admission or OPD presentation. Follow-up screenings were conducted as per the Rashtriya Bal Swasthya Karyakram (RBSK) operational guidelines 2017.[10]

The collected data were tabulated and subjected to statistical analysis. Categorical variables were reported as counts and percentages, while continuous variables were presented as mean ± standard deviation (SD). Univariate analysis was performed using the Chi-square test, with statistical significance set at $p < 0.05$. All data analysis was conducted using IBM SPSS Statistics for Windows.

RESULTS

During 1 year study period 343 neonates who fulfilled inclusion

criteria were screened for ROP. Overall incidence among study population was 48.10% (165) with 44.02% (151) classical ROP and 4.08% (14) AROP. Incidence of pre-plus and plus disease among eyes with ROP (330 eyes) was 10% (33) and 5.15% (17). 326/330 eyes had zone 2 disease while 4 eyes presented with disease in zone 1. Severity of disease progression into subsequent stages has been described in in table 1.

Table 1: Showing Disease Distribution Based On Severity (n=330)

Stages of ROP	Zones of ROP		Total
	Zone 1	Zone 2	
Stage I	0	100	100
Stage II	2	201	203
Stage III	2	25	27
Total	4	326	330

Abbreviation: ROP: retinopathy of prematurity

Mean birth weight (1062.57±302.56 grams) and mean gestational age (GA) (27.71±0.99 weeks) in group B was significantly lower than group A (1204.22±215.22 grams) and (29.52±1.90 weeks) respectively. Baseline characteristics of neonates with ROP is described in table 2. It was found that NVD were significantly higher in both the groups. (p<0.05)

Table 2: Showing Baseline Characteristics In Newborns With ROP.

Characteristics		ROP severity						Total	p-value (C.I 95%)
		Group A (Classical ROP)			Group B (AROP)				
Birth weight (grams)	<1000	21	13.90%	1204.22±215.22	9	64.28%	1062.57±302.56	30	7.37*10-6
	1000-1500	126	83.44%		4	28.57%		130	
	1500-2000	4	2.64%		1	7.14%		5	
GA (weeks)	≤30	108	71.52%	29.52±1.90	14	100%	27.71±0.99	122	0.045
	>30	43	28.47%		0	0		43	
Mother's age (years)	≤30	135	89.40%	26.28±3.09	14	100%	26.64±2.06		0.655
	>30	16	10.59%		0	0			
Gender	Male	66	46.80%		6	42.85%		72	1.00
	Female	85	60.28%		8	57.14%		93	
Birth order	Twin	23	15.23%		5	35.71%		28	0.113
	Single	128	84.76%		9	64.28%		137	
Mode of delivery	NVD	130	86.09%		8	57.14%		138	0.015
	LSCS	21	13.09%		6	42.85%		27	

Abbreviation: ROP: retinopathy of prematurity, AROP: aggressive retinopathy of prematurity, C.I: confidence interval, GA: gestational age, NVD: normal vaginal delivery, LSCS: lower segment caesarean section

Among the maternal risk factors, gestational DM and antenatal haemorrhage were significantly higher in group B. (p<0.05 at 95% C.I.) Maternal risk factors with their statistical significance at 95% C.I. has been described in table 3.

Table 3: Showing Maternal Risk Factors In Newborns With ROP.

Maternal risk factors	Group A (Classical ROP)		Group B (AROP)		p-value (C.I 95%)
	Present	Absent	Present	Absent	
Gestational DM	44 (29.10%)	107 (70.86%)	11 (78.57%)	3 (21.42%)	0.00054
PIH	51 (33.77%)	100 (66.22%)	8 (57.14%)	6 (42.85%)	0.146
Antenatal bleeding	28 (18.54%)	123 (81.45%)	8 (57.14%)	6 (42.85%)	0.0026
Anaemia	54 (35.76%)	97 (64.23%)	9 (64.28%)	5 (35.71%)	0.06
Foetal distress	67 (44.37%)	84 (55.62%)	10 (71.42%)	4 (28.57%)	0.096

Abbreviation: ROP: retinopathy of prematurity, AROP: aggressive retinopathy of prematurity, C.I: confidence interval, DM: diabetes mellitus, PIH: pregnancy induced hypertension.

Among neonatal risk factors, RDS, surfactant administration and apnoea of prematurity were significantly higher in group B. (p<0.05). Neonatal risk factors with their statistical significance at 95% C.I. has been described in table 4.

Table 4: Showing Neonatal Risk Factors In Newborns With ROP

Neonatal risk factors	Group A (Classical ROP)		Group B (AROP)		p- value (C.I 95%)
	Present	Absent	Present	Absent	
RDS	55 (36.42%)	96 (63.57%)	12 (85.71%)	2 (14.28%)	0.0009
Surfactant administration	10 (6.62%)	141 (93.37%)	11 (78.57%)	3 (21.42%)	2.70*10-13
Oxygen supplementation	14 (100%)	0	125 (82.78%)	26 (17.21%)	0.190
Apnoea of prematurity	21 (13.90%)	130 (86.09%)	10 (71.42%)	4 (28.57%)	2.70*10-7
Blood transfusion	116 (76.82%)	35 (23.17%)	10 (71.42%)	4 (28.57%)	0.900
Blood components	111 (73.50%)	40 (26.49%)	12 (85.71%)	2 (14.28%)	0.495
TPN	4 (2.64%)	147 (97.35%)	2 (14.28%)	12 (85.71%)	0.139
Neonatal metabolic acidosis	42 (27.81%)	109 (72.18%)	5 (35.71%)	9 (64.28%)	0.751
Neonatal seizures	6 (3.97%)	145 (96.02%)	2 (14.28%)	12 (85.71%)	0.285
Neonatal jaundice	113 (74.83%)	38 (25.16%)	10 (71.42%)	4 (28.57%)	1.00
Neonatal IVC haemorrhage	6 (3.97%)	145 (96.02%)	1 (7.14%)	13 (92.85%)	1.00
Early onset sepsis	109 (72.18%)	42 (27.81%)	12 (85.71%)	2 (14.28%)	0.435

Abbreviation: ROP: retinopathy of prematurity, AROP: aggressive retinopathy of prematurity, C.I: confidence interval, RDS: respiratory distress syndrome, TPN: total parenteral nutrition, IVC: intraventricular.

Duration of oxygen supplementation was a significant risk factor affecting disease severity (p value=$2.148*10^{-13}$). Duration of O2 supplementation was further tabulated and analysed. (Table 5)

Table 5: Duration Of Oxygen Supplementation In Neonates With ROP.

Duration of oxygen supplementation (n=139)	Group A (Classical ROP) (n=125)	Group B (AROP) (n=14)	p-value (C.I 95%)
≤ 1 week	81(64.80%)	2(14.28%)	2.148*10-13
1-2 week	43(34.40%)	5(41.67%)	
>2 week	1(0.80%)	7(50%)	

Abbreviation: ROP: retinopathy of prematurity, AROP: aggressive retinopathy of prematurity, C.I: confidence interval.

The major limitation of our study is, we did not include non-ROP population in the study to analyse and compare our study parameters.

DISCUSSION

In India, the incidence of ROP varies between 38% and 51.9% [11], with a prevalence of 19.2% to 32.4% [12] among low-birth-weight infants. In our study out of 343 babies, 165 babies developed ROP. The incidence of ROP was 48.10%. The incidence of AROP was 4.08% and that of classical ROP was 44.02% among the study population. A study by N. Hussain et al. [13] in 950 newborns found an incidence rate of 21.3%

(202 out of 950) for any stage of ROP, with 4.6% (44 out of 950) developing stage 3 or 4 ROP. Another study by Bassiouny R et al. [14] found an incidence of 4.2% for APROP, and 59% of the infants developed ROP. Of these, 42.6% had stage 1 ROP, 48.1% had stage 2 ROP, and 5.1% had stage 3 ROP.

Mean GA of infants with ROP was 27.71±0.99 weeks in group B and 29.52±1.90 weeks in group A. A significant correlation was found between GA and disease severity, with all babies who developed AROP falling under a GA of ≤30 weeks. The lower the birth weight and the GA, the higher the risk for ROP [15,16]. In our study, the mean birth weight in group B was 1062.57±302.56 grams and, 1204.22±215.22 grams, in group A and it was significantly correlated with the disease severity. Also, there is a statistically significant difference in the mean birth weight and GA between the two groups. In 1991, the CRYO-ROP study found the incidence of ROP to be 65.8% and 81.6% in premature newborns weighing <1250 g and <1000 g, respectively ($p<0.001$) [17]. Another study by Bassiouny R et al. [14] reported a mean GA of 31.5±2.3 weeks (ranging from 24 to 36 weeks) and a mean birth weight of 1514±391 g (ranging from 600 to 2860 g).

Among 165 babies with ROP, 57.14% were delivered by NVD and 42.85% by LSCS in the group B, and 86.09% and 13.90%, respectively, in the group A, and the mode of delivery was significantly associated with severity of ROP. A similar study by Shah V. et al. [18] found that LSCS delivery was significantly associated with ROP.

Gestational diabetes was seen in 78.57% of mothers in the group B and 29.13% of mothers in the group A, and it was significantly associated with the severity of ROP. Dai A. et al. [19] reported that diabetes may have both direct (by increasing retinal VEGF) and indirect (association with RDS) impacts on ROP development. Placental bleeding was seen in 57.14% of mothers in the group B and 18.54% of mothers in the group A, and it was significantly associated with severity of ROP. A study by Dai A. et al. [19] showed that maternal bleeding and iron deficiency anaemia during pregnancy were associated with the development of ROP.

RDS was found in 85.71% of infants in the group A and 36.42% of infants in the group B, and was significantly associated with disease severity. A study by Fehlmann A. et al. [20] confirmed that RDS was significantly associated with a high incidence of ROP. A meta-analysis by Azami M. et al. [21] reported similar findings. 78.57% of infants in the group B were given surfactant, while in group A, it was in 6.62% of infants, and it was significantly associated with the severity of ROP. Whereas, a study by Siegel A. et al. [22] found no association between them.

O_2 supplementation, being one of the major aetiologies in ROP development, was given to 100% of infants in the group B and 82.78% of infants in the group A. Among infants with O_2 administration, the duration of O2 administration was analysed. In the group B, 14.28% of infants were given O2 for ≤ 1 week, and in 35.71% and 50% of infants, it was given for 1-2 weeks and >2 weeks respectively. While in the group A, 64.80%, 34.40%, and <1% of infants were given O2 for ≤ 1 week, 1-2 weeks, and >2 weeks, respectively. And it was significantly associated with the severity of ROP. A study by Teoh S. et al. [23] reported similar results. Another study by Rekha S. et al. [24] showed the duration of O2 as an independent predictor of the progression of ROP. 71.42% of infants in the group B and 13.90% of infants in the group A had apnoea episodes, and it was strongly associated with the severity of ROP. Studies by Kim T. et al. [25] and Azami M. et al. [21] found similar results. Hence, appropriate monitoring of actual PaO_2 in high-risk infants for ROP is essential. It is recommended to keep PaO_2 <100 mmHg (50-70 mmHg) and saturation between 90-95%.

CONCLUSION

ROP is a multifactorial disease, with various risk factors playing roles in its onset. Significant demographic factors affecting disease severity included early gestational age, low birth weight, and mode of delivery. Maternal risk factors that significantly impacted the disease severity were gestational diabetes and placental bleeding. Among neonatal risk factors, RDS, surfactant administration, apnoea episodes and duration of O2 had significant correlations. O2 supplementation, a significant contributor, requires careful monitoring and administration at optimal saturation levels. Effective screening protocols and prompt treatment initiation for high-risk ROP or AROP cases can lead to improved structural and functional outcomes.

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