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Research Article

Comparative Analysis of Demographic and Clinical Profiles of Conventional Retinopathy of Prematurity with Aggressive Posterior Retinopathy of Prematurity

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Abstract

Aim: To compare the demographic and clinical profile of conventional retinopathy of prematurity (ROP) with aggressive posterior retinopathy of prematurity.

Material and methods: A prospective, unmasked, and observational study involving 150 ROP patients was conducted over a period of one year. The risk factors including maternal and neonatal risk factors were recorded. The data was entered into the Excel sheet and analyzed to compare the risk factors between the conventional ROP and APROP.

Results: A total of 17 (11.3%) babies were found to have AP-ROP and 133 (88.7%) babies were found to have conventional ROP. There was no significant difference in average gestational age between infants diagnosed with AP-ROP (29.6 ± 2.9 weeks) and those with Conventional ROP (30.1 ± 2.2 weeks) (p = 0.428). However, infants with AP-ROP had a significantly lower average birth weight (1022.7 ± 123.5 g) compared to infants with Conventional ROP (1208.2 ± 261.0 g) (p = 0.004). Multivariate logistic regression analysis revealed that birth weight, surfactant use, number of days of oxygen supplementation, and metabolic acidosis were independently associated with the development of AP-ROP.

Conclusion: The development of APROP is multifactorial and complex. Although we have identified factors such as birth weight, surfactant use, number of days of oxygen supplementation, and metabolic acidosis in the causation of APROP, further long-term multicentric studies are required for validation.

Introduction

ROP is a complex disease process caused by incomplete retinal vascularization in premature infants [1]. Its incidence increases with decreasing gestational age (GA) and low birth weight (LBW) [2]. Prematurity and LBW are significant and consistent risk factors for the development of ROP, along with other known risk factors such as neonatal respiratory distress, unmonitored oxygen supplementation, use of surfactant, sepsis, apnea, blood transfusion, metabolic acidosis, intraventricular hemorrhage (IVH), and others [3-5]. Recent advances in neonatal care in the last decade have improved the survival rates for premature infants. This has led to a parallel increase in the incidence of ROP. In both developed and developing countries, retinopathy of prematurity is a major contributor to the burden of childhood blindness [6-8].

ROP development involves two phases that occur during the postnatal period. Phase 1 involves delayed physiological retinal vascular development and phase 2 involves vasoproliferation [9].

Later, in 2005, another severe form of ROP, Aggressive Posterior Retinopathy of Prematurity (AP-ROP), was recognized and added to the International Classification of Retinopathy of Prematurity (ICROP). The AP-ROP does not progress through the conventional stages of ROP and rapidly progresses to the advanced stages of ROP (Stages 4 and 5) [10].

AP-ROP is an aggressive and rapidly progressive form of ROP which was previously known as Rush disease. It has been observed mostly in zone I but may also be seen in posterior zone II [10]. The distinctive features of this type of ROP are

its rapid progression, posterior location, very severe plus disease, the ill-defined nature of the junction of vascular and avascular retina, and circumferential growth of blood vessels instead of the normal pattern of vessels growing towards the ora serrata.

A third update of the classification of ROP was published in the year 2021 and it described the term Aggressive Retinopathy of Prematurity (A-ROP) [11]. The hallmark feature of A-ROP is a rapid development of pathological neovascularization and very prominent plus disease which did not undergo the usual progression that is observed in the conventional stages of ROP. Due to recent improvements in the delivery of supplemental oxygen techniques in neonatal intensive care units, the incidence of AP-ROP is seen to be significantly lower than that of conventional ROP in urban settings in India as compared to rural areas [12]. Since this study commenced before the third revision of ICROP, we used the term AP-ROP in this study. This study aimed to compare the clinical and demographic profiles of conventional ROP stages with those of AP-ROP.

Materials and methods

This prospective, unmasked, observational study was conducted on 150 preterm infants admitted to the Neonatal Intensive Care Units (NICU) of our tertiary care hospital and premature babies referred from other hospitals who were diagnosed with ROP. Ethical approval was obtained from the Institutional Review Committee (Reference number: BREC/Th/19/ophthal08). The study was conducted over a period of one year from Feb 2020 to March 2021. All neonates with gestational age < 34 weeks, birth weight < 2000 grams (g), and babies with GA between 34 to 36 weeks but with risk factors such as: a) Cardio-respiratory support, b) Prolonged oxygen therapy, c) Respiratory distress syndrome, d) Chronic lung disease, e) Fetal hemorrhage, f) Blood transfusion, g) Neonatal sepsis, h) Exchange transfusion, i) Intraventricular haemorrhage, j) Apneas, k) Poor postnatal weight gain were screened in the NICU as early as 2–3 weeks of postmenstrual age to identify severe forms of ROP according to the institute's screening protocol [13]. ROP was classified according to the revised ICROP guidelines.10 AP-ROP was defined as extreme vessel dilation and tortuosity in four quadrants, direct arteriovenous shunting, flat neovascularization, and rapid evolution, without following stage 1–3 progression. The babies with the conventional stages of ROP with plus disease were screened weekly for progression or regression, and those without plus disease were examined every 2 weeks until either the regression occurred, or until they reached the pre-threshold stage (any stage 3 ROP with plus disease with five contiguous or eight cumulative clock hours of disease in zone 1 or 2) when they were recommended for treatment.

Statistical analysis

The data were entered into an Excel spreadsheet and analyzed using Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, Illinois, USA). Student's t-test was used to compare normally distributed numerical variables, and the chi-square test was used for categorical variables. Differences were considered significant when the p-value was less than 0.05 (two-sided). Multivariate binary logistic regression analysis was performed to identify independent risk factors for AP-ROP compared to Conventional ROP.

Results

A total of 150 babies were screened from February 2020 to March 2021, of whom 17 (11.3%) were found to have AP-ROP and 133 (88.7%) were found to have Conventional ROP. The average gestational age among those who were diagnosed with AP-ROP was 29.6 ± 2.9 weeks and 30.1 ± 2.2 weeks in the Conventional ROP group (p = 0.428). Seventy (46.7%) babies were female and 80 were male (53.3%). The mean gestational age (GA) of screened babies was 30.001 ± 2.27 (range 24-36 weeks) and the mean birth weight (BW) was 1187.13 ± 255.02 (range 540-2000 g).

The birth weight was significantly lower in patients who developed AP-ROP (1022.7 ± 123.5 g) than in those who developed conventional ROP (1208.2 ± 261.0 g) (Table 1).

There was a significant association between AP-ROP development and oxygen therapy, surfactant use, and metabolic acidosis. Patients with AP-ROP had a longer duration of oxygen therapy–18.8 ± 10.0 days as compared to those who developed conventional ROP–12.5 ± 8.4 days with a statistically significant difference. Of the 68 babies who received surfactants, 4 (23.5%) developed AP-ROP, and 64 (48.1%) developed conventional ROP, indicating the protective influence of surfactants in the development of AP-ROP. Metabolic acidosis was also seen to have a significant

Table 1: Comparison of neonatal Co-morbidities between the AP-ROP and conventional ROP babies.

Parameter	AP-ROP (n - 17)	Conventional ROP (n - 133)	p - value
Gestational age (in weeks) Mean ± SD	29.6 ± 2.9	30.1 ± 2.2	0.428
Birth weight (in grams) Mean ± SD	1022.7 ± 123.5	1208.2 ± 261.0	0.004
RDS	17 (100%)	117 (88.6%)	0.143
Surfactant use	4 (23.5%)	64 (48.1%)	0.046
Apnoea	2 (11.8%)	40 (30.1%)	0.113
Blood transfusion	5 (29.4%)	29 (21.8%)	0.481
Metabolic Acidosis	4 (23.5%)	64 (48.1%)	0.046
Seizures	2 (11.8%)	14 (10.5%)	0.876
Neonatal Jaundice	4 (23.5%)	42 (31.6%)	0.498
NEC	2 (11.8%)	5 (3.8%)	0.141
Sepsis	12 (70.6%)	73 (54.9%)	0.219
Hemoglobin Mean ± SD (mg/dL)	15.4 ± 3.6	15.4 ± 3.2	0.97
Oxygen supplementation Mean ± SD (days)	18.8 ± 10.0	12.5 ± 8.4	0.004

AP-ROP: Aggressive Posterior Retinopathy of Prematurity; RDS: Respiratory Distress Syndrome; NEC: Necrotizing Enterocolitis; SD: Standard Deviation

protective effect in the causation of AP-ROP compared to conventional ROP ($p < 0.05$). Other factors such as RDS, sepsis, seizures, NEC, and blood transfusion were (Table 2) observed more frequently in infants who developed AP-ROP than in infants who developed Conventional ROP. However, these factors did not show an independent association with the development of AP-ROP compared to Conventional ROP.

Discussion

This study, conducted in a tertiary care government institute, highlights the proportion of AP-ROP and the risk factors associated with the causation of AP-ROP in this region. The proportion of AP-ROP in this study was 11.3%, which was slightly higher than the one documented in previous literature [14-16]. Bastola, et al. in their study in 2023 reported the incidence of AP-ROP to be 16.10% [17]. Diwedi, et al. reported a 13.04% proportion of babies who developed AP-ROP in their study [18]. The high incidence of AP-ROP in our study could be attributed to the fact that most of the referred patients are from rural backgrounds where oxygen delivery is unmonitored.

The major finding of this study was that along with lower BW, surfactant use, oxygen supplementation, and metabolic acidosis played a significant role in the causation of AP-ROP compared to conventional ROP. The mean BW for babies with AP-ROP and conventional ROP was 1022.7 ± 123.5 g and 1208.2 ± 261.0 g respectively. A similar result was seen in a retrospective study analysis conducted by Tekchandani, et al. [19] in the year 2021, and babies with AP-ROP were found to have a mean BW of 1280 ± 364 g. In a study by Sathar, et al. [17] in 2017, a mean BW of 990 g was reported in infants with AP-ROP. Ahn, et al. also reported a study in 2017 that found the mean BW in babies with AP-ROP to be 920 ± 440 g and 1150 ± 300 g in babies with non- AP-ROP group [16]. Although various Indian studies have highlighted the development of severe ROP in bigger babies, our study did not have ROP in any patient weighing more than 1750 grams.

Table 2: Multivariate logistic regression analysis predicting the development of APROP.

	Adjusted OR (aOR) for predicting AP-ROP	95% C.I. for aOR		*p* - value
		Lower	Upper	
Gestational Age (in weeks)	1.232	0.755	2.008	0.404
Birth Weight (in g)	0.996	0.993	0.998	0.006
Gender Distribution	0.446	0.112	1.773	0.252
RDS	1.000	0.000	10.999	0.998
Surfactant use	0.073	0.011	0.457	0.005
Oxygen use (in days)	1.107	1.022	1.199	0.013
Apnoea	0.399	0.056	2.820	0.357
Blood transfusion	1.422	0.315	6.414	0.647
Metabolic Acidosis	0.214	0.046	0.999	0.050
Seizures	2.797	0.390	20.041	0.306
NNJ	0.667	0.205	2.167	0.500
NEC	2.355	0.160	34.556	0.532
Sepsis	1.644	0.378	7.148	0.507
APGAR score at 1 minute	0.958	0.697	1.316	0.789
APGAR score at 5 minutes	0.993	0.718	1.373	0.964
Pre-eclampsia	0.218	0.019	2.475	0.219
Maternal bleed	0.260	0.025	2.695	0.259
Multiple gestations	0.341	0.017	6.966	0.485
Maternal diabetes	1.125	0.130	9.744	0.915

AP-ROP: Aggressive Posterior Retinopathy of Prematurity; RDS: Respiratory Distress Syndrome; NNJ: Neonatal Jaundice; NEC: Necrotizing Enterocolitis

Surfactant use was found to have a protective effect against AP-ROP development. This could be due to the role of surfactants in lung development and the prevention of hypoxia development in premature babies. A similar finding was noted in previous studies [20,21]. The mean duration of monitored Oxygen supplementation was 17.9 ± 10.6 days in babies who developed AP-ROP while those with Conventional ROP were given mean oxygen supplementation for 12.6 ± 8.4 days. This difference was statistically significant, attributing to the role of oxygen use in increasing the development of AP-ROP. In a study by Hakeem AH, et al. [22] in 2011, oxygen therapy was found to have a significant role in the development of ROP, and 45.5% of the babies with ROP in their study had received oxygen therapy for < 1 week and 21.2% babies had received oxygen for > 1 week. In a study published in 2024 by Nayyar, et al. [23], the risk factors associated with the development of AP-ROP were similar to the ones in our study i.e. lower BW and longer duration of supplemental oxygen. Similar results were seen by Ahn YJ, et al. [16] and Kim, et al. [24] in their respective studies which focused on risk factors associated with the development of AP-ROP.

In this study, metabolic acidosis was found to have a protective role in the causation of AP-ROP. In this study, among group I (babies with AP-ROP), 4 (23.5%) babies had developed metabolic acidosis while in group II (babies with Conventional ROP), 64 (48.1%) babies had developed metabolic acidosis. This difference was highly significant indicating the role of metabolic acidosis in decreasing the development of AP-ROP by 0.214 times. Very few studies have been found to have studied metabolic acidosis as a risk factor in AP-ROP development. Dhull, et al. in their study found that 52.3% of babies with ROP had developed metabolic acidosis. They also found a notable association between metabolic acidosis in the development of ROP [25].

In this study, AP-ROP patients were compared with conventional ROP cases rather than no ROP as was done in other previous studies, which may be why the authors were unable to identify any statistically significant risk variables for AP-ROP outside of BW, oxygen supplementation, surfactant use, and metabolic acidosis. By focusing on direct comparisons within ROP cases, the study offers valuable insights into the specific characteristics and challenges associated with AP-ROP as opposed to conventional ROP. In this study, the AP-ROP and conventional ROP groups were very comparable to one another, and while AP-ROP patients were more likely to have developed RDS, sepsis, seizures, NEC, and blood transfusion, these differences did not achieve statistical significance.

The author believes that AP-ROP represents a particularly aggressive and severe form of retinopathy of prematurity, necessitating heightened vigilance, early detection, and swift intervention to prevent irreversible visual impairment. This study introduces a novel approach by comparing AP-ROP with conventional ROP, aiming to uncover subtle differences that could aid in reducing the incidence of AP-ROP. By focusing on these comparative aspects, the research seeks to identify key risk factors and refine strategies for early management of this challenging condition.

The present study has several limitations that should be noted. Firstly, the sample size is relatively small, which may affect the generalizability of the findings. Secondly, the research was conducted at a single institution, and the limited number of neonates involved means that the data may not be representative of other regions within our country. This suggests that while there are observable trends, the study's design and sample size might have limited its power to detect statistically significant associations beyond the core variables identified. To address these limitations, multicenter trials could provide more robust data, helping to better determine risk factors, facilitate early diagnosis, and enable timely intervention for babies with AP-ROP and conventional ROP. also, more longitudinal studies may help in outlining the long-term impact of AP-ROP on these neonates. There can also be improvement by incorporating additional variables and including multiple centers that could provide a more wider geographical insight.

Conclusion

The evolution of neonatal care in India has contributed to a rise in cases of ROP and associated blindness among infants. This study aimed to investigate the risk factors contributing to Aggressive Posterior ROP (AP-ROP) compared to Conventional ROP. The research identified a correlation between AP-ROP and lower birth weight compared to conventional ROP. Additionally, prolonged oxygen therapy emerged as a significant risk factor for AP-ROP. Surfactant use was found to have a protective effect, while the development of metabolic acidosis was linked to AP-ROP onset. These findings underscore the importance of early and vigilant screening for extremely low birth weight (ELBW) and very low birth weight (VLBW) infants, as well as those with these specific risk factors. Such screening is crucial for timely intervention to prevent the blindness associated with ROP.

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