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Insights into retinopathy of prematurity incidence: Contrasting small vs. appropriate size for gestational age premature infants at a tertiary eye care institute in central India

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ABSTRACT

Purpose: To compare the incidence of retinopathy of prematurity (ROP) in small for gestational age (SGA) premature infants with those of appropriate size for gestational age (AGA) attending ROP screening clinic in a tertiary eye care institute of Central India 2018-2019.

Materials and Methods: All premature infants attending the screening program with gestational age of <37 weeks and weight less than 90th centile as per gestational age were included in the study. The presence of any stage of ROP and severity of ROP was compared between SGA and AGA infants using chi-square test and SPSS software.

Results: Total 603 premature infants up to 36 weeks underwent eye screening; 250 (41.4%) were SGA infants. SGA infants born 29-32 weeks were at higher risk for development of ROP ($p<0.01$) than their AGA peers. However no group was found to have higher severity of ROP than the other.

Conclusion: SGA infants who underwent eye screening in central India from January 2018 to June 2019 were at a significant high risk of developing ROP then AGA infants.

1. Introduction

During the 1940s, Retinopathy of prematurity (ROP) was referred to as retrolental fibroplasia (RLF), a term attributed to Terry in 1942.[1] Initially, this progressive disorder, characterized by the formation of fibrous tissue behind the lens, was exclusively observed in premature infants of low birth weight, often resulting in blindness and severe visual impairment. At its inception, RLF garnered little attention from pediatricians and ophthalmologists due to its infrequent occurrence, possibly due to lesser survival rates of preterm infants. However, a decade later, the landscape changed dramatically as the increased survival rates of preterm infants propelled ROP into prominence, transforming it into a significant concern affecting thousands of children globally.[2]

Today, ROP is one of the major preventable causes of childhood blindness, particularly prevalent in middle-income countries and various Asian states.[3] The improved care and subsequent increased survival of preterm and small-for-date neonates in developing nations have precipitated a surge in ROP incidence among infants. Dominant risk factors for ROP include low gestational age, low birth weight, and extended exposure to supplemental oxygen therapy. In contrast, additional risk factors encompass vaginal delivery, bronchopulmonary dysplasia,

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multiple gestation, and necrotizing enterocolitis.[4]

Retinopathy of prematurity (ROP) is a multifactorial condition influenced by various risk factors, including but not limited to gestational age, birth weight, oxygen therapy, and other medical complications during the neonatal period. Studies have reported that preterm infants, especially those with low birth weight and prolonged exposure to supplemental oxygen, are at greater risk for developing ROP. Additionally, factors such as apnea, blood transfusions, and respiratory distress syndrome have been related to the development and progression of ROP. These risk factors focus attention on the complex interplay of prenatal and postnatal variables that contribute to the pathogenesis of ROP.[5]

Although retinopathy of prematurity is commonly associated with infants of relatively lower gestational age and lower birth weight, it is noteworthy that infants with comparatively higher gestational age and birth weight also develop ROP in developing countries like India.[6] This serves as a sobering reminder of the widespread impact of this condition, transcending conventional risk profiles to affect a diverse population of infants.

We report the incidence of Retinopathy of prematurity in small for gestational age premature infants (SGA) and appropriate size for gestational age (AGA) premature infants, and also the severity of Retinopathy of prematurity in both of the groups along with the associated risk factors between the two, who were screened during the period of 1.5 years, i.e., from January 2018 to June 2019 in tertiary care center of central India. By contrasting the prevalence of ROP in these two groups, the study seeks to understand the correlation of birth weight and gestational age on the development of ROP in a specific geographical region. The findings of this research could contribute to the development of targeted interventions and guidelines for the management of ROP in preterm infants.

2. Materials and Methods

This was a prospective observational study in which all infants meeting the specified criteria were evaluated by experienced Ophthalmologists at a tertiary care center in Central India for Retinopathy of prematurity (ROP). The study included infants below 37 weeks of gestational age and weighing less than the 90th percentile for their gestational age who underwent ROP screening from January 2018 to July 2019. These infants were further categorized into appropriate-for-gestational age (AGA) and small-for-gestational-age (SGA) groups based on their weight relative to their gestational age. Infants above 37 weeks of gestational age and those considered large for gestational age (weighing above the 90th percentile for their gestational age) were not included in the study.

The classification of newborns was based on their gestational age and birth weight, with SGA infants being below the 10th percentile, AGA infants between the 10th and 90th percentile birth weight, and large-for-gestational-age (LGA) infants above the 90th percentile birth weight.[7] All screenings were conducted in the presence of a pediatrician or neonatologist, with the first screening taking place within four weeks (30 days) of life for infants over 28 weeks of gestational age. For infants with a gestational age of less than 28 weeks or a birth weight of less than 1200 grams, screening was performed earlier, usually 2-3 weeks after birth.[8]

Pupillary dilation was achieved using 0.5% Tropicamide and 2.5% Phenylephrine topical drops, followed by fundus examination using an indirect ophthalmoscope and a 28/20 dioptre lens. The International Classification of Retinopathy of Prematurity (ICROP) revised 2005 version was used to grade Retinopathy of Prematurity0] So, terms like A-ROP and stage secondary to notch were not used in our study. Detailed information on the infants' gestational age, birth weight, type, and mode of delivery, as well as significant prenatal and postnatal history, was recorded. Follow-up was conducted according to Indian guidelines.[8]

The data collection process meticulously utilized performed proformas, capturing critical variables such as date of birth, gestational age, postmenstrual age, birth weight, and an array of known risk factors associated with Retinopathy of prematurity (ROP). Each infant underwent classification either as small for gestational age (SGA) or appropriate for gestational age (AGA) based on growth chart criteria.[7]

For comprehensive analysis, the maximum severity of ROP in the more affected eye of each infant was diligently documented. Statistical analyses were conducted using the sophisticated SPSS program, whereby contingency table examinations were executed through the chi-square (2) test with Yates' correction, resorting to Fisher's exact test when dealing with scant data. Significance levels were determined utilizing a threshold of $p<0.05$.

Stringent ethical considerations were adhered to throughout the study, with ethical clearance obtained from the institutional review board. Prior to any involvement, written informed consent was thoughtfully obtained from the parents or guardians of the infants, ensuring transparency and respect for ethical standards.

3. Results

From the month of January 2018 to the month of June 2019, a total of 603 premature infants were screened, out of which 103 (17.08%) were diagnosed with some stage of ROP. The total AGA infants screened were 353, and ROP was diagnosed in 57 (16.14%) infants; 250 SGA infants were screened, and 46 (18.4%) infants were diagnosed with some stage of ROP. Among AGA & SGA infants, male and female ratios were 189:164 and 139:111, respectively. Mean birth weight was 1603.9 grams with a standard deviation of 720.4

grams (range from 600-2900 grams) and 1348.7 grams with a standard deviation of 501.2 grams among AGA & SGA infants, respectively. The mean gestational age of AGA was 33.40±4.4 weeks, ranging from 24-36 weeks, and the mean gestational age of SGA was 33.93± 3.6 weeks, ranging from 28-36 weeks.

3.1. Prevalence and severity of ROP

Table 1 displays the incidence of Retinopathy of prematurity (ROP) based on gestational age in appropriate-for-gestational age (AGA) and small-for-gestational-age (SGA) infants. It was observed that SGA infants born between 29-31 weeks of gestational age were at a higher risk of developing any stage of ROP compared to their AGAcounterparts ($p<0.01$). Regarding the severity of ROP between AGA and SGA infants, both groups exhibited no statistically significant difference in the development of severe ROP. Refer to Table 2 for a detailed presentation of these findings.

3.2. Risk factors connected with the development of ROP

Table 3 unveils the identified risk factors for Retinopathy of prematurity (ROP) among appropriate for-gestational age (AGA) and small-for-gestational-age (SGA) infants. Although no significant difference in the association between risk factors and the occurrence of Retinopathy was observed in each group, it was noted thatapnea, followed by blood transfusion and oxygen supplementation, were the most prevalent and closely associated risk factors in both groups.

Table 4 llustrates the outcomes of Retinopathy of prematurity (ROP) in follow-up assessments. Among the 57 appropriate-for-gestational-age (AGA) infants and 46 small-for-gestational-age (SGA) infants diagnosed with ROP, spontaneous regression was observed in 21 AGA cases and 17 SGA cases. Additionally, 12 AGA cases and 4 SGA cases did not attend follow-up appointments. Notably, no distinct statistical significance was found in the outcomes of ROP between the two groups.

4. Discussion

Our investigation was conducted over a 1.5-year period at a tertiary care center in central India, revealing a notably higher incidence of Retinopathy of prematurity (ROP) in the group of small for gestational age (SGA) infants within the gestational age range of 29-32 weeks in comparison to their appropriate for gestational age (AGA) counterparts. However, no significant correlation was observed among infants with a gestational age ≤28 weeks, potentially attributable to the limited sample size of SGA infants in this category. Moreover, there was no marked disparity in the incidence of ROP between SGA and AGA infants beyond 32 weeks of gestational age, possibly stemming from the diminished occurrence and minimal risk of ROP development at this particular gestational age. Notably, our study, executed by a team of three consistent observers, was a valuable endeavor as it encompassed the general population of central India and entailed meticulous methodological documentation over the course of 1.5 years via preformed proformas. Furthermore, in a precautionary measure against inter-observer variability, follow-up examinations were executed interchangeably by the observers, bolstering the reliability and robustness of our findings.

Other studies have bolstered our findings regarding the elevated incidence of Retinopathy of prematurity (ROP) in small for gestational age (SGA) premature infants compared to appropriate for gestational age (AGA) counterparts. C A Dhaliwal et al. emphasized that SGA infants born at 26-32 weeks of gestational age face a heightened risk of ROP development, particularly in severe ROP cases, in contrast to their AGA peers.[9] Consistent with our investigation, they also noted a lack of significant disparity in ROP incidence between SGA and AGA infants beyond 32 weeks of gestation.[9]

Furthermore, a meta-analysis highlighted that SGA infants exhibit significantly increased odds of any stage of ROP, as well as elevated risks of severe and treated ROP in preterm infants.[10] Our study specifically identifies SGA infants under 32 weeks of gestation as being at a heightened risk for ROP, although we did not observe a higher likelihood of severe ROP in SGA infants compared to AGA infants. Gortner et al. underscored a higher incidence of ROP in SGA infants compared to AGA infants, although without a marked difference in the prevalence of stage 3 disease between the groups.[11]

Contrary to our findings, a study analyzing the prevalence and risk factors for ROP in SGA and AGA preterm infants indicated that SGA was not a pronounced risk factor for any stage of ROP or severe ROP within the cohort.[6] Nonetheless, they reported similar risk factors for ROP in very low-birth-weight SGA and AGA infants, aligning with our results.[6]

Our study identified apnea, followed by blood transfusion and oxygen supplementation, as the predominant and most associated risk factors in both SGA and AGA groups. In another study, they found septicemia ($P<0.001$), apnea ($P=0.0001$), and oxygen therapy ($P=0.031$) as major risk and significant risk factors for the development of ROP.[12]

Apnea, characterized by a pause in breathing that lasts for more than 20 seconds, is a common issue in premature infants. Apnea leads to fluctuations in oxygen levels in the blood, which can further exacerbate the risk of ROP development. Studies have shown that apnea in premature infants is incorporated with an elevated risk of severe ROP,

Table 1: ROP detected according to gestational age in AGA & SGA infants

Size as per gestational age	ROP present or absent	≤28 Weeks	29-31 Weeks	32 -34 Weeks	>34 Weeks
	Screened	29	60	217	47
AGA (353)	Absent	20	46	188	42
	Present	09	14	29	5
	Screened	3	21	138	88
SGA (250)	Absent	1	09	115	79
	Present	2	12	23	9
Chi square value		1.53	8.15	0.39	0.0056
P valve		0.21 (NS)	0.0097 (HS)	0.48 (NS)	0.82 (NS)

Table 2: Severity of ROP in SGA vs AGA group

	≤28 Weeks	29-31 Weeks	32-34 Weeks	>34 Weeks
Stage 1, 2 ROP (AGA: SGA)	7:0	10:5	18:16	4:8
Stage ≥3 ROP (AGA: SGA)	1:2	4:4	10:5	1:1
P value of difference Stage 3-5 of ROP	0.0667 (NS) ¥ (fisher test)	0.74 (NS)	0.56 (NS)	0.73 (NS)

Table 3: Risk factors for ROP found among AGA & SGA infants

Risk factor	Total % Risk	% Risk in AGA	% Risk in SGA
Ventilator	17.9	20	14.3
RDS	18.03	17.9	18.1
Apnoea	41.6	40	42
Asphyxia	11.5	13.6	10.5
Sepsis	20.4	16.9	20
Oxygen supplementation	20.1	20.6	19.6
Blood transfusion	31	33.3	28
Hyperbilirubinaemia	17.8	17.3	19

Table 4: Fate of ROP in subsequent follow UPS

	AGA	SGA	Chi square value	P Value
Total ROP	57	46		N
Spontaneous regression	21 (36.8%)	17 (36.9%)	0.0062	0.937 (NS)
Regression with intervention	20 (35.1%)	19 (41.3%)	0.517	0.658 (NS)
Refferal	5 (8.7%)	6 (13%)		
Abscond	11 (19.2%)	4 (8.6%)		

particularly when accompanied by fluctuations in oxygen saturation levels. Therefore, effective management of apnea in preterm infants is crucial in reducing the risk of ROP.

Blood transfusions are common in premature infants to correct anemia or thrombocytopenia. However, multiple transfusions have been identified as a risk factor for the development of ROP. The potential link between blood transfusions and ROP is thought to be related to the fluctuations in hematocrit levels, leading to alterations in retinal oxygenation. It is necessary for healthcare providers to carefully monitor the need for blood transfusions in premature infants to minimize the risk of ROP.[13]

The potential link between blood transfusions and ROP is believed to be related to the fluctuations in hematocrit levels that occur with transfusions. Changes in hematocrit levels can affect blood viscosity and oxygen delivery to the developing retina, leading to alterations in retinal oxygenation that may contribute to the pathogenesis of ROP. A study by the Premature Infants in Need of Transfusion (PINT) trial demonstrated that a restrictive (low) transfusion threshold was associated with a reduced risk of ROP compared to a liberal (high) transfusion threshold in relatively extremely low birth weight infants. This suggests that more conservative approaches to blood transfusions

may help mitigate the risk of ROP in premature infants.[13]

Oxygen supplementation is often required in premature infants with respiratory distress to maintain adequate oxygen levels. However, the excessive use of supplemental oxygen has been identified as a major risk factor for the development of ROP. High oxygen levels can lead to vasoconstriction in the developing retinal vasculature, disrupting normal retinal vascular development and increasing the risk of ROP progression. Optimal oxygen saturation targets should be carefully monitored and maintained to reduce the risk of ROP in premature infants.[14]

The heightened prevalence of ROP in SGA infants can be attributed to various factors. SGA infants often experience intrauterine growth restriction, leading to changes in organ development due to fetal hypoxemia, nutrient limitations, and altered endocrine environments.[15] These developmental perturbations may contribute to the increased risk of ROP. Furthermore, the increased illness severity and slower weight gain in SGA infants necessitate more extensive hospital care, potentially increasing their exposure to risk factors like supplemental oxygen, a known ROP risk factor.[16,17] Moreover, small-for-gestational-age (SGA) infants commonly demonstrate decreased serum levels of insulin-like growth factor 1. Evidence indicates that this growth factor, along with vascular endothelial growth factor, can be involved in the etiology and pathogenesis of ROP.[18]

In conclusion, our study underscores the heightened risk of Retinopathy of prematurity (ROP) in infants of small for gestational age (SGA) up to 32 weeks of gestation compared to their appropriate size counterparts. The findings highlight the critical need for vigilant monitoring and timely screening of SGA infants for early detection and intervention or treatment to limit the potential impact of ROP on their visual health. The potential explanations for the amplifying incidence of ROP in SGA infants, including intrauterine growth restriction, physiological vulnerability, intensive hospital care requirements, reduced growth factor levels, and predisposition to risk factors, underscore the multitude of factors contributing to the vulnerability of this population.[8] These insights emphasize the importance of tailored care and targeted interventions to address the specific requirements of SGA infants at risk of ROP. Further research and clinical considerations aimed at understanding and addressing these factors will be instrumental in improving the outcomes for preterm infants at risk of ROP.

5. Source of Funding

None.

6. Conflict of Interest

None.

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