ORIGINAL ARTICLE

Comparative analysis of risk factors and severity of retinopathy of prematurity in appropriate for gestational age vs small for gestational age preterm infants

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Abstract

Background: Retinopathy of Prematurity (ROP) is a leading cause of childhood blindness worldwide, with a growing burden in developing countries. *Aim and Objectives*: To examine risk factors associated with ROP in preterm infants, assess disease severity, and compare outcomes between appropriate for Gestational Age (AGA) and Small for Gestational Age (SGA) categories. *Material and Methods*: A prospective cohort of 350 preterm infants (≤ 36 weeks GA, ≤ 2000 g birth weight) was studied from 2019–2021. Infants were categorized as AGA or SGA and screened for ROP. Risk factors were analysed using logistic and multivariate regression. Babies were followed until complete regression of disease. *Results*: Overall incidence of ROP was 40.2% (36.3% in AGA, 45.3% in SGA). Type 1 ROP requiring treatment occurred in 9.8% overall (3% AGA, 13% SGA). Significant risk factors included gestational age and hypoglycaemia in AGA, and gestational age and low APGAR score in SGA. All treated infants (laser photocoagulation or anti-VEGF) showed complete regression. *Conclusion*: SGA infants had higher incidence and severity of ROP compared to AGA. Early identification of risk factors enables timely intervention and improved outcomes. Study limitations included reduced SGA sample size and follow-up challenges during the COVID-19 pandemic.

Keywords: Retinopathy of prematurity, small for gestational age, appropriate for gestational age, risk factors, preterm infants

Introduction

Retinopathy of Prematurity (ROP), as the name suggests, is a potentially devastating retinal vascular disease that causes irreversible loss of vision in preterm infants all over the world. Due to the advances in modern neonatal medicine and improved access to healthcare, extremely preterm infants are now surviving. With the advent of the same, the disease burden and incidence of ROP have increased significantly. The term Retrolental Fibroplasia (RLF) was coined by Terry, in 1942. The appearance of a fibrovascular membrane behind the crystalline lens gave rise to the term RLF. The disease process was little understood and hardly any treatment options existed [1].

All around the world, about 9.9% of births are preterm that is before gestational age 37 full weeks [2]. ROP affects about 50,000 babies worldwide, as estimated by Blencowe *et al*. (2013) in a study [3]. The maximum burden is seen in developing countries, because access to neonatal care has improved without an improvement in the quality of neonatal care. Babies who are born before term or have related neonatal morbidity, like respiratory distress syndrome, poor weight gain, and hyperglycemia, are at the highest risk of ROP. Therefore, rates of ROP depend on the quality of care received, which includes oxygen delivery. Most cases of ROP are mild and resolve naturally with no treatment. A minor percentage proceed to more severe ROP, which, if left untreated, can lead to retinal detachment or scarring of the retina, which can cause permanent blindness [3]. In 2010, India bore the burden of approximately 10% of all projected global visual loss secondary to ROP, with at least 5,000 acquiring severe disease and 2,900 children surviving with visual loss [4].

Various studies have been conducted to compare the incidence ROP in AGA (appropriate for gestational age) vs SGA (small for gestational age) babies, with contrasting results. Some found that the incidence of ROP was similar in both the groups, but some found that SGA babies were at more risk for ROP as compared to AGA babies [5-7]. Knowledge about the risk factors can help in an improved knowledge of the disease, preventing it and modifying the exposure to the risk factors. Given the high burden of ROP in developing countries and the conflicting evidence regarding the influence of gestational growth categories, this study was designed to systematically analyze risk factors and disease severity in AGA versus SGA preterm infants, with the aim of informing targeted screening and management strategies.

Material and Methods

A prospective cohort design was employed to systematically identify antenatal, natal, and postnatal risk factors, assess disease severity, and compare outcomes between AGA and SGA infants. Although this design was appropriate for achieving the study objectives, its single-center setting and instances of loss to follow-up may limit the generalizability of the findings. The study was conducted from September 2019 to December 2021 after obtaining approval from the Institutional Ethics Committee (IEC number 777/2019), and it was registered with the Clinical Trials Registry of India (CTRI/2020/04/0246842). A total of 350 babies were included in the study.

Sample size calculation

The number of patients necessary to carry out the study was computed utilizing the following formula: N = 2 σ 2 (Z1- α/2 + Z1- β) 2

d2 for effect size of d/ σ =0.3; Z1- α/2 = 1.96 at 5% level of significance; Z1- β = 0.84 at 80% power

The minimum sample size required for each group was 175 infants (N), so in total 350 babies (700 eyes) were studied. Informed consent was taken from a parent before enrolment of the baby in the study.

Inclusion criteria: Babies with Gestational Age (GA) at birth of ≤ 36 weeks and a Birth Weight (BW) of ≤ 2000 g, neonates born after 36 weeks gestational age or birth weight above 2000 grams who were at risk of acquiring ROP were included, at the neonatologist's discretion

Exclusion criteria: Babies with inadequate documents on BW or GA were eliminated when born outside our hospital; babies with incomplete records of antenatal clinic details and maternal comorbidities were omitted; babies who died before complete resolution of ROP or did not attend the outpatient clinic for follow-up assessments were eliminated from the study.

Babies were divided as SGA and AGA and then grouped as ROP present (group 1) and not present (group 2). Group 1 was subdivided as Type 1 and type 2 (based on treatment requirement). Babies were screened by a single experienced ophthalmologist under aseptic precautions with an indirect ophthalmoscope and a scleral depressor after pupillary dilation with eye drops containing tropicamide and phenylephrine.

Eyedrops were prepared by taking commercially available tropicamide 0.8 % and phenylephrine 5%

and diluting them to tropicamide 0.4% and phenylephrine 2.5% with a tear supplement in a sterile aseptic environment to achieve a concentration of 1:1, which causes less systemic side effects for these preterm. The clinical condition and vitals of the baby were monitored throughout the screening procedure. The anterior segment of each eye was observed for tunica vasculosa lentis, amount of pupillary dilation, and media transparency. Then the posterior segment was examined to identify retinal alterations. ROP was graded based on the International Classification of ROP. The retinal maturity, zone of involvement, clock hours of involvement, plus disease if present, and stage was entered into the proforma. Treatment was initiated for infants with type 1 ROP. Babies were followed up till complete vascularization and till complete regression of the disease after treatment. On each follow up visit, the above procedure was repeated, and examination findings after instilling dilating eyedrops were recorded. Data from records of babies screened for ROP in the Neonatal Intensive Care Unit (NICU), inpatient neonates in the department of pediatrics and babies attending the outpatient department of ophthalmology was collected.

Risk factors studied

Antenatal

Use of antenatal steroids, multiple gestation such as twins and triplets (monochorionic vs dichorionic), antenatal neuroprotection with magnesium sulphate, chorioamnionitis leading to preterm birth, use of assisted reproductive technology for conception.

Natal

Respiratory Distress Syndrome (RDS) at birth, poor APGAR score, Intraventricular Haemorrhage (IVH), Low Birth Weight (LBW), location of birth (at our hospital or delivered outside)

Postnatal

Use of pulmonary surfactant for RDS, exposure to oxygen therapy, packed red blood cell transfusion, Patent Ductus Arteriosus (PDA), Necrotizing Enterocolitis (NE), recurrent apnea, tachypnoea, development of sepsis, early postnatal hypoglycemia, early enteral nutrition, and Kangaroo care. Data analysis for incidence, risk factors and severity of the disease was done using the Statistical Package for the Social Sciences (SPSS) statistical software. Multivariate regression was done to determine substantial risk factors of ROP in both AGA and SGA.

Results

Identification of risk factors for all preterm babies

Logistic regression was carried out for all the 350 infants to identify the risk factors. The variables that were identified to have significant effect on occurrence of ROP included: GA, LBW, indications for Lower Segment Cesarian Section (LSCS), eclampsia, preterm Premature Rupture of the Membranes (PPROM), preterm labour and twin labour, Intraventricular Hemorrhage (IVH), early neonatal hypoglycemia.

Identification of risk factors in AGA babies

Separate regression analyses were carried out for AGA cases to see if there was any variation in the risk factors. A total of 198 AGA cases were subjected to regression analysis.

The variables that were identified to have significant effect on occurrence of ROP in AGA babies were: GA, head circumference, gender, indications for LSCS, eclampsia, PPROM, preterm labor, oligohydramnios, Absent End Diastolic Flow (AEDF) on Ultrasound (USG), tachypnea, IVH, early neonatal hypoglycemia.

Identification of risk factors in SGA babies

A total of 152 SGA cases were subjected to regression analysis. The variables that were identified to have significant effect on occurrence of ROP in SGA babies were: GA, low APGAR score at 5 minutes of life, being born outside our institute (out born), neonatal hyperbilirubinemia, IVH, hypoglycemia and NE. Binomial logistic regression was done to determine the risk factors and to compare the two categories and it was found to be significant as the values of p was < 0.05. Out of the 350 babies, 40.3% were males and 59.7 % were females who had ROP. The incidence of ROP in AGA/SGA is shown in Table 1. Overall incidence was 40.2%. Distribution of ROP in both the groups is shown in Table 2 and Figure 1. ROP was seen in 72 and 69 cases in AGA and SGA group, respectively. The stage of ROP present in AGA/SGA is shown in Table 3 and Figure 2. Most common stage was zone II and stage II in SGA and AGA group i.e. in 25 babies in both. Of the 350 infants, 125 were < 30 weeks, 104 were born at 31-32 weeks, and 121 were born after 32 weeks of gestation. Average GA at birth was 31 weeks as shown in table 4.

Maternal and antenatal risk factors vs stage of ROP in both groups

The stage of ROP in relation to maternal and antenatal risk factors which were indications for LSCS is shown in Table 5.

Table 1: Incidence of ROP in AGA/SGA babies and their treatment methods

	ROP		Total n (%)
	No n (%)	Yes n (%)	
SGA	83 (54.6)	69 (45.3)	152 (100)
AGA	126 (63.6)	72 (36.3)	198 (100)
Total	209 (59.7)	141 (40.2)	350 (100)

ROP – retinopathy of prematurity; AGA – appropriate for gestational age; SGA – small for gestational age

Table 2: Distribution of ROP in AGA/SGA babies

	Incidence of ROP n (%)	Incidence of treatment requiring ROP n (%)	Treatment with laser photocoagulation n (%)	Treatment with intravitreal anti-VEGF n (%)
Overall incidence	40.2 (141)	9.8 (14)	13 (3.7)	1 (0.002)
SGA	45.3 (69)	11.5 (8)	7 (53.8)	1 (100)
AGA	36.3 (72)	8.3 (6)	6 (46.1)	0 (0)

ROP – retinopathy of prematurity; AGA – appropriate for gestational age; SGA – small for gestational age

Table 3: Stage of ROP present in AGA/SGA babies

	Stage of ROP							Total
	No ROP	Zone II stage I	Zone II Stage II	Zone II Stage III	Zone III Stage I	Zone III Stage II	Zone III Stage III	
SGA	83	13	25	6	9	13	3	152
AGA	126	8	25	4	13	21	1	198
Total	209	21	50	10	22	34	4	350

ROP – retinopathy of prematurity; AGA – appropriate for gestational age; SGA – small for gestational age

Table 4: Average GA (gestational age) at birth of babies

GA in weeks	ROP		Total
	No	Yes	
24	0	1	1
25	1	1	2
26	2	9	11
27	2	11	13
28	8	18	26
29	12	27	39
30	19	14	33
31	20	21	41
32	43	20	63
33	33	12	45
34	29	4	33
35	25	1	26
36	14	2	16
37	1	0	1
Total	209	141	350

Table 5: Stage of ROP in relation to maternal and antenatal risk factors which were indications for LSCS

Risk factors	Stage of ROP							Total
	No ROP	Zone II stage I	Zone II Stage II	Zone II Stage III	Zone III Stage I	Zone III Stage II	Zone III Stage III	
Preeclampsia	26	6	9	1	6	6	0	54
Eclampsia	8	0	3	1	1	0	0	13
PPROM	29	5	7	2	3	3	0	49
Preterm labour	14	0	1	2	0	2	0	19
Fetal distress	16	2	10	0	3	4	0	35
Maternal COVID-19	10	1	0	1	0	1	1	14
Complicated pregnancy	4	1	0	0	0	0	0	5
Placenta previa	7	0	5	0	0	0	0	12
Oligohydramnios	17	2	0	1	4	4	0	28
Decreased fetal movements	5	0	0	0	0	0	0	5
Twin labour	16	0	0	0	0	1	0	17
AEDF	7	1	0	0	0	2	0	10
Cord prolapses	0	1	1	0	0	0	0	2
Fetal malposition	3	0	5	0	0	0	0	8
Miscellaneous (Rh negative pregnancy, Non-progession of labour, Elective LSCS)	47	2	9	2	5	11	3	79
Total	209	21	50	10	22	34	4	350

ROP – retinopathy of prematurity; PPROM - preterm premature rupture of the membranes; AEDF - absent end diastolic flow; LSCS – lower segment caeseran section

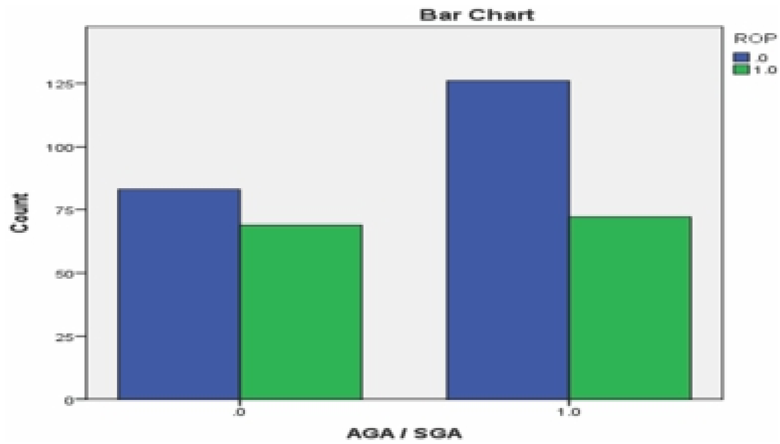

Figure 1: Distribution of ROP in AGA/SGA babies, 0- No ROP, 1- ROP Present

ROP – retinopathy of prematurity; AGA – appropriate for gestational age; SGA – small for gestational age

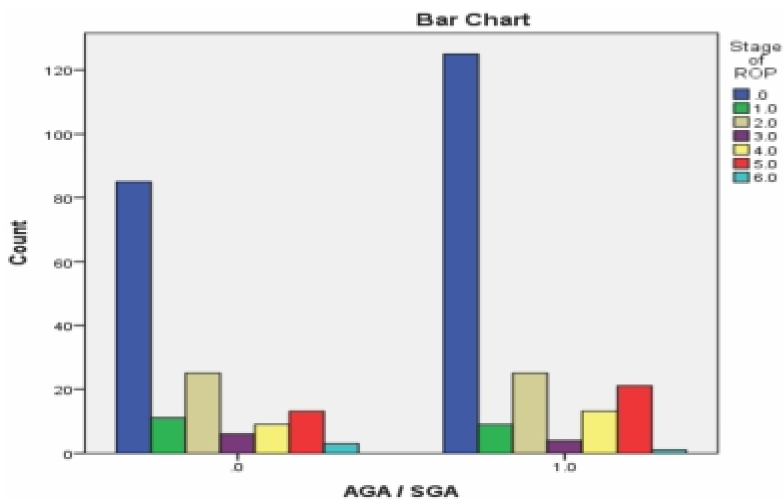

Figure 2: Stage of ROP present in AGA/SGA babies, 0- No ROP, 1.0- Zone II Stage I, 2.0- Zone II Stage II, 3.0- Zone II Stage III, 4.0- Zone III Stage I, 5.0- Zone III Stage II, 6.0- Zone III Stage III.

ROP – retinopathy of prematurity; AGA – appropriate for gestational age; SGA – small for gestational age

Risk factors for development of ROP identified in both the categories

GA (weeks), birth weight (g), maternal and antenatal risk factors like preterm labour, twin labour, hypoglycemia and IVH were significant factors as the values of *p* were < 0.001, 0.013, 0.034, < 0.001, 0.040 and 0.043. Maternal and antenatal risk factors like eclampsia and PPROM were found to be not significant as the values of *p* were 0.078 and 0.061.

Risk factor for development of ROP identified in AGA categories

GA (weeks), head circumference (cm), maternal and antenatal risk factors like eclampsia, AEDF, tachypnoea, IVH and early hypoglycemia were significant factors identified as the values of *p* < 0.01, 0.027, 0.012, 0.042, 0.038, 0.044 and 0.002. Gender, maternal and antenatal risk factors like PPROM, preterm labour and oligohydramnios were found to be not significant as the values of *p* were 0.051, 0.073, 0.083, and 0.083.

Identified risk factors in SGA category

GA (weeks), APGAR at 5 min of life, outborn status, IVH and neonatal hyperbilirubinemia were significant factors as the values of p < 0.01, 0.016, 0.038, 0.039 and 0.045 respectively. Hypoglycemia and NE were found to be not to be significant as the values of *p* were 0.064 and 0.054.

Multivariate analysis

Multivariate regression performed to determine significant risk factors of ROP in both AGA and SGA revealed that GA in weeks (*p* < 0.001) and hypoglycemia (p = 0.002) were noteworthy independent risk factors of ROP after correcting for confounding factors. With the increase in GA, risk of ROP significantly decreased. Neonates with early hypoglycemia had significantly higher risk of ROP (Table 6). Multivariate regression performed to determine significant risk factors of ROP in AGA showed that GA (*p* = 0.002) and early neonatal hypoglycemia (p = 0.023) were noteworthy independent risk factors of ROP after correcting for confounding factors. With the increase in GA (weeks), risk of ROP significantly decreased (Table 7). Multivariate regression performed to determine significant risk factors of ROP in SGA showed that gestational age (*p* < 0.001) and low APGAR score at 5 minutes of life (*p* = 0.032) were found to be noteworthy independent risk factors of ROP. With the increase in GA (weeks), risk of ROP substantially decreased. Patients with low APGAR at 5 minutes had significantly high risk of ROP (Table 8).

Table 6: Multivariate logistic regression to determine significant risk factors of ROP in both AGA and SGA

Risk Factors	Beta coefficient	Standard error	*p*	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Gestational age (weeks)	-0.461	0.060	<0.0001	0.631	0.560	0.709
Low birth weight	1.466	1.676	0.382	4.331	0.162	115.647
IVH	-0.716	0.629	0.255	0.489	0.142	1.678
Hypoglycemia	1.099	0.351	0.002	3.002	1.510	5.968

IVH – intraventricular haemorrhage

Table 7: Multivariate logistic regression in AGA cases

Risk Factors	Beta coefficient	Standard error	*p*	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Gestational age (weeks)	-0.384	0.122	0.002	0.681	0.537	0.865
Head circumference	-0.148	0.108	0.169	0.862	0.698	1.065
Gender						
Female				1.000		
Male	-0.206	0.348	0.554	0.814	0.412	1.609
Tachypnea	-0.615	0.370	0.097	0.541	0.262	1.118
IVH	-1.543	0.948	0.103	0.214	0.033	1.370
Hypoglycemia	1.410	0.618	0.023	4.097	1.220	13.764

IVH – intraventricular haemorrhage

Table 8: Multivariate logistic regression in SGA cases

Risk Factors	Beta coefficient	Standard error	*p*	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Gestational age (weeks)	-0.435	0.086	<0.0001	0.647	0.547	0.765
Low APGAR at 5 min	1.557	0.724	0.032	4.745	1.147	19.623
Outborn	0.479	0.510	0.348	1.614	0.594	4.385
Neonatal hyperbilirubinemia	-0.262	0.427	0.540	0.770	0.333	1.778
Early Hypoglycemia	0.656	0.482	0.173	1.928	0.750	4.955
IVH	-0.033	1.014	0.974	0.968	0.133	7.064
NE	-1.529	0.966	0.114	0.217	0.033	1.441

IVH – intraventricular haemorrhage; NE – necrotizing enterocolitis

Treatment group

14 out of 350 babies over the study period underwent treatment for ROP as shown in Table 1. Treatment was done by bilateral laser photocoagulation in most cases, and in one case by intravitreal injection of anti-VEGF. Intravitreal injections were given under aseptic precautions. ROP regressed in all eyes after treatment.

Discussion

ROP is an emerging cause of preventable childhood visual impairment in developing countries, especially in India, which has a high birth rate as well as increasing access to advanced neonatal care. Knowledge about the risk factors can aid in improved knowledge of the disease, preventing it and modifying the exposure to the risk factors. This study aimed to estimate the occurrence of ROP in our hospital, to add to the existing information about the risk factors and to explore other new associations. Various studies have been conducted to compare incidence ROP in AGA vs SGA babies, with contrasting results [5-8]. Our study found that being born with SGA predisposed the infant to a higher risk of developing ROP as well as requiring treatment for ROP than its AGA counterparts. The incidence of ROP in our study population was 40.2% overall, 36.3% in the AGA category and 45.3% in the SGA category. Similarly western studies showed the incidence of ROP to be in a range of 40-65%. The reported incidence in India varies between 38%-51.9% [9-11].

The occurrence of type 1 ROP or treatment requiring ROP in our study population overall was 9%, incidence was 3% in the AGA category and 13% in the SGA category. Similar studies report the incidence of type 1 ROP to be between 6 -27% [12, 13]. The incidence of ROP among SGA babies is reported to be between 23-60%, and in AGA between 20-58 % [14]. SGA infants had a higher incidence of ROP in our study than the AGA category. Other researchers have also reported similar findings that SGA preterms are at a greater risk of ROP development [7, 15]. A study conducted at Israel in a large population of infants with GA in weeks between 24-31 found that SGA infants were at 2 times more risk than that of AGA of developing stage 3–4 ROP [16]. Darlow *et al*. (2005) had reported that the greater the restriction in growth of the neonate before birth, the more severe was the disease [15].

In another similar study, Singh *et al*. described a greater occurrence of retinopathy in the SGA group in extremely premature babies [7]. Dhaliwal *et al*. (2009) described SGA babies with gestational ages between 26–32 weeks to have a higher risk of having retinopathy than the AGA babies [17]. SGA and IUGR have been described as risk factors for developing type 1 disease by Allegaert *et al.* (2003) [18]. In their research, Shah *et al*. (2005) and Arora *et al.* detailed no difference in the occurrence of ROP between SGA and AGA [6, 19]. Shah *et al*. (2005) and Procianoy *et al*. (1980) stated a higher occurrence of ROP in RDS [19, 20]. Administration of pulmonary surfactant and repeated blood transfusions for the infant was identified as risk factors by Shohat *et al*. (1983), Seiberth and Linderkamp (2000), and Maheshwari *et al*. (1996) also reported analogous results [21-23]. Studies like Maheshwari *et al*. (1996) and Hakeem *et al*. (2012) noted that post-natal sepsis was an independent risk factor for developing ROP [23, 24]. Unfortunately, we did not have this correlation in any of our study groups. Studies by Seiberth and Linderkamp (2000) and Kim *et al*. (2004) found that mechanical ventilation for any reason or the use of continuous positive airway pressure were risk factors for the development of ROP [22, 25]. We could not get this significance in our study. Congenital heart disease has been found to be a risk factor for ROP by Shah *et al*. [19]. Apnea of prematurity has been reported as a risk factor for developing ROP, in studies done by Shah *et al*. (2005), Shohat *et al*. (1983), and Kim *et al*. (2004) [19, 21, 25]. With regards to the risk factors, in our study, a low GA was noted to have the strongest association with the development of ROP ($p < 0.01$) in all 3 groups, in consensus with previous published research [6]. Newer studies like the G-ROP have studied the effect of poor postnatal weight gain and IGF – 1 as an indirect measure of poor weight gain and identified them as risk factors in the development of retinopathy. Further research is warranted into this topic [26].

Current guidelines in neonatal care advocate the use of titrated oxygen therapy in treatment of mechanically ventilated preterm infants. In our NICU setup as well, titrated oxygen therapy is used with strict monitoring of the SpO2 levels. This may be the reason our study did not find any association with exposure to oxygen therapy and the development of ROP, in contrast to previously published literature which implicates oxygen exposure as the main cause of disease development [27]. Neonatal sepsis in our study population, if clinically suspected, was treated early with empirical antibiotics. This early treatment and detection are probably the reason we did not find any association with sepsis and ROP, which is contradictory to previous studies like the ELGAN study [28]. Introduction of early enteral nutrition has been found to be highly beneficial for preterm neonates to improve early postnatal weight gain and decrease morbidity such as NE, BPD and ROP. In our NICU, early enteral nutrition with the mother's breastmilk is practiced routinely and is protective against the development of ROP [5, 17, 29].

Kangaroo care is also in practice at our NICU. It has been shown to significantly improve neonatal outcomes in all aspects, including good postnatal weight gain, decreasing the risk of BPD, NE, neonatal sepsis, requirement of oxygen and may thus have an indirect effect on decreasing the incidence and severity of ROP as well. Further research is warranted into this matter [30].

The study was limited due to the following factors: Due to the COVID 19 pandemic, once discharged from the NICU, parents were reluctant to bring the preterm babies to the hospital for follow up. The number of SGA births occurring was very less as compared to AGA births. By virtue of a smaller number of births and also loss to follow up due to COVID 19, the sample size in the SGA group could not be achieved. We were able to recruit 152 out of the 175 babies.

Conclusion

Management of ROP in the coming years is going to be an uphill battle due to the ever-increasing preterm population that is now surviving. A collaborative and multidisciplinary approach by the neonatologist and ophthalmologist is necessary to prevent visual disability for future generations. Future multicenter studies are warranted to validate the results of this research.

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