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Original Research Article

Retinopathy of prematurity in multiple births versus single births preterm, extremely preterm infants

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ABSTRACT

Purpose: The purpose of the study was to compare the retinopathy of prematurity in preterm, extremely preterm infants between multiple and single births.

Materials and Methods: It was a hospital – based cross sectional comparative study conducted among preterm 28 - ≤37 weeks of gestational age, extremely preterm ≤ 28 weeks of gestational age at delivery of multiple and single births. Data on Gestational age, birth weight, birth order (single/multiple), Risk factors, Refractive status, and Treatment type were noted. Ophthalmological findings were performed routinely at 4 weeks and repeated later depending upon the severity.

Results: 49 infants were involved in this study; 22 were born as singletons and 27 as multiples. Our results show 2.0% of subject in stage 1, 18.4% in stage 2, 8.2% in stage 3, 2.0% in stage 4 substantially corresponds with the severity of retinopathy of prematurity due to lower gestational week and lower birth weight. Multiple birth infants statistically had 6.1% in stage 1, 18.4% in stage 2, 8.2% in stage 3, 2.0% in stage 4 retinopathy of prematurity than single birth infants. Risk factor results indicates necrotizing enterocolitis (33.3% in stage 2), oxygen (35.5% in stage 2 and 16.1% in stage 3), sepsis (37.9%, and 20.7% in stage 3), and continuous positive airway pressure (44.4% in stage 2 and 11.1% in stage 3) Compound hyperopic astigmatism was the most typical refractive error in both births. Laser treatment accounts for 18.1% in both groups.

Conclusion: This study showed a significant correlation with ROP development in multiple births.

1. Introduction

Retinopathy of prematurity (ROP) is proliferative retinopathy of the developing retina, which is characterized by abnormal neovascularization of the retina. It occurs in pre-mature infants with low birth weight who are exposed to a high concentration of oxygen and it is considered to be the leading cause of visual morbidity in children worldwide with the estimation of 15 million babies born preterm annually.[1] It is an avoidable and treatable cause of childhood blindness.

Preterm birth (PTB) is that the most important cause of neonatal vision problems and India is the biggest contributor to the global burden of PTB.[2] Classification of preterm birth is based upon gestational age: extremely preterm (< 28 weeks), Very preterm (< 32 weeks), Moderate preterm (32 to<34 weeks), Late preterm (34 to <37weeks).

In 1942, terry described it first as "retrolental fibroplasia".[3]The risk factors of ROP include, low gestational age and < 32weeks, low birth weight (<1500 g, especially <1250g), supplemental oxygen therapy, vitamin E deficiency, respiratory distress syndrome, asphyxia, shock and acidosis. The smaller a baby is at birth, the more chance to develop ROP but not all babies who are premature will

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develop ROP. An ROP epidemic occurred in the 1940s and early 1950s when hospitals used excessively high levels of oxygen in incubators to save the lives of premature infants.

In India, roughly, 1 in 1000 children is blind, and the incidence of ROP is recorded between 24% and 47%. Globally, more than 50,000 infants are getting affected by ROP per year.[4] Most studies say that low birth weight and low gestational week are responsible for the development of ROP. Premature births result in relative hyperoxia resulting in excessive blood vessel growth.[5]

A more recent study examined the ocular growth and refractive error development in premature infants (32- and 52-weeks postmenstrual age babies with or without ROP.[6] Impaired vision, large refractive error mainly myopia, strabismus, and blindness may occur following severe ROP.[7] Screening for early identification of retinal damages should be carried out preferably by the ophthalmologist for the early detection of this preventable blindness. Screening protocols are still insufficient in India and other developing countries. This study aims to compare the Severity, Risk factors, Refractive status in preterm, extremely preterm infants between multiple and single births which will be helpful in indication and timely intervention can be given.

2. Materials and Methods

The comparative and cross-sectional study sample consisted of 49 neonates with birth weight less than 2300 gram and gestational age less than 37 weeks. The study had a total sample of 49 participants (n=49), out of which 27 participants were twin and 22 participants were single. The study adhered to the norms of the ethics committee and was initiated after approval by the Institutional Review board of Saveetha College of Allied Health Science (REF NO: SCAHS/IRB/2022/JULY/370). All participants parents were provided with informed consent and the entire steps and purpose of the study was explained. Neonates with birth weight less than 2300 grams and gestational age less than 37 weeks of single and multiple births were included. Neonates with cardiac respiratory, neurological or ocular anomalies (except ROP), babies with genetic disease and full-term babies were excluded.

Visual acuity assessment for up to three months was done on blink reflex and from 3 to 6-month visual acuity was measured by central steady maintained reflex. Retinoscopy was performed to measure the refractive status of a child and dilated fundus examination was done with indirect ophthalmoscopy.

2.1. Statistical software

Statistical significance was defined as 0.05 or less probability. We conducted statistical analysis and graph plotting using Sigma Plot 14.5 (Systat Software Inc., San Jose, USA).

3. Results

Their zones and stages of retinopathy were recorded along with the risk factors. Association between stages/zones with group (ex-preterm/preterm), Association between stages/zones with group (single birth/multiple birth) and Association between stages and risk factors was tested. The following tables support the analysis.

From the Table 1, it is evident that most of the Ex-preterm Infants (18.4%) are in the stage -2, 8.2% of the ex-preterm are in stage-3 and 2% of the ex-preterm Infant are in stage 4. It is also noted that the Infant in ex-preterm has reached the stage-4. It is found from the analysis that there is a close association between zones and group (ex-preterm/preterm) and it is evident that most of the ex-preterm Infants (24.5%) fall in the second zone.

Table 2, it is evident that there is no significant association between zones and group (Single birth /Multiple birth). It is found from the analysis that there is close association between stages and group (Single birth /multiple birth). It is noted that most of the multiple birth Infant (18.4%) have reached the stage 2.

Table 3, it is observed through the Chi-square values the risk factors: OXYGEN (10.63, p=.024), SEPSIS (9.61, p=.041), NEC (16.08, p=.003) and CPAP (9.15, p=.048) are having significant association with Stages in retinopathy. However LSCS, RDS, IUGR, NNJ, APNEA, HYPOGLC and IVF are not having significant association with the Stages in retinopathy.

3.1. Oxygen

It is noted that most of the Infants 35.5% who has risk factor of OXYGEN have reached the stage – 2 and 16.1% of the Infant reached stage 3.

3.2. Sepsis

It is noted that most of the infants 37.9% who has risk factor of SEPSIS have reached the stage– 2 and 20.7% of the Infant reached stage 3.

3.3. NEC

It is noted that most of the infants 33.3% who has risk factor of NEC have reached the stage2.

3.4. CPAP

It is noted that most of the infants 44.4% who has risk factor of CPAP have reached the stage2 and 11.1% of the Infant reached stage 3.

From Table 4, In the group of Ex-preterm infant, 18.4% of the infant are single birth and 22.4% of the infant is multiple birth. It is noted that in the group of Preterm categories, 26.5% of them are single birth, whereas 32.7% of them are multiple birth.

Table 1: Association between stage, zones and group (ex-preterm/preterm)

			Group		Total	Chi-Square
			EX-Preterm Gestational week < 27 and birth weight < 1500gms	**Preterm Gestational week 28-37 birth weight > 1500gms**		
Stage	0	Count	5	17	22	
		% of Total	10.2%	34.7%	44.9%	
	1.00	Count	1	3	4	
		% of Total	2.0%	6.1%	8.2%	
	2.00	Count	9	7	16	
		% of Total	18.4%	14.3%	32.7%	10.082* P=.026
	3.00	Count	4	2	6	
		% of Total	8.2%	4.1%	12.2%	
	4.00	Count	1	0	1	
		% of Total	2.0%	0.0%	2.0%	
Total		**Count**	**20**	**29**	**49**	
		% of Total	**40.8%**	**59.2%**	**100.0%**	
Zone	1.00	Count	7	0	7	
		% of Total	14.3%	0.0%	14.3%	
	2.00	Count	12	11	23	
		% of Total	24.5%	22.4%	46.9%	21.320** P=.000
	3.00	Count	1	18	19	
		% of Total	2.0%	36.7%	38.8%	
Total		**Count**	**20**	**29**	**49**	
		% of Total	**40.8%**	**59.2%**	**100.0%**	

*Significant at 5% level – Stage
**Significant at 1% level -Zone

Table 2: Association between zone, stages and group (Single birth /Multiple birth)

			Group		Total	Chi- Square
			Single birth	**Multiple birth**		
Stage	.00	Count	12	10	22	
		% of Total	24.5%	20.5%	45%	
	1.00	Count	1	3	4	
		% of Total	2.0%	6.1%	8.2%	
	2.00	Count	7	9	16	
		% of Total	14.3%	18.4%	32.7%	8.616* P=.027
	3.00	Count	2	4	6	
		% of Total	4.1%	8.2%	12.2%	
	4.00	Count	0	1	1	
		% of Total	0.0%	2.0%	2.0%	
Total		Count	22	27	49	
		% of Total	44.9%	55.1%	100.0%	
			Group		Total	**Chi- Square**
			Single birth	Multiple birth		
Zone	1.00	Count	2	5	7	
		% of Total	4.1%	10.2%	14.3%	
	2.00	Count	10	13	23	
		% of Total	20.4%	26.5%	46.9%	1.232 P=.540
	3.00	Count	10	9	19	
		% of Total	20.4%	18.4%	38.8%	
Total		Count	22	27	49	
		% of Total	44.9%	55.1%	100.0%	

*Significant at 5% level
**Significant at 1% level

Table 3: Association between risk factors and stages in retinopathy

		Stages in retinopathy										
		.00		1.00		2.00		3.00		4.00		Chi square
		N	N %	N	N %	N	N %	N	N %	N	N %	
LSCS	Yes	18	45.0%	3	7.5%	14	35.0%	5	12.5%	0	0.0%	4.91
	No	4	44.4%	1	11.1%	2	22.2%	1	11.1%	1	11.1%	p=.293
RDS	Yes	11	35.5%	4	12.9%	11	35.5%	4	12.9%	1	3.2%	4.86
	No	11	61.1%	0	0.0%	5	27.8%	2	11.1%	0	0.0%	p=.308
OXYGEN	Yes	11	35.5%	3	9.7%	11	35.5%	5	16.1%	0	0.0%	10.63*
	No	11	61.1%	1	5.6%	5	27.8%	1	5.6%	1	3.2%	p=.024
SEPSIS	Yes	9	31.0%	2	6.9%	11	37.9%	6	20.7%	1	3.4%	9.61*
	No	13	65.0%	2	10.0%	5	25.0%	0	0.0%	0	0.0%	p=.041
IUGR	Yes	4	44.4%	0	0.0%	5	55.6%	0	0.0%	0	0.0%	4.24
	No	18	45.0%	4	10.0%	11	27.5%	6	15.0%	1	2.5%	p=.374
NNJ	Yes	12	52.2%	2	8.7%	7	30.4%	2	8.7%	0	0.0%	1.92
	No	10	38.5%	2	7.7%	9	34.6%	4	15.4%	1	3.8%	p=.750
APNEA	Yes	5	33.3%	3	20.0%	6	40.0%	1	6.7%	0	0.0%	5.72
	No	17	50.0%	1	2.9%	10	29.4%	5	14.7%	1	2.9%	p=.223
HYPOGLC	Yes	5	55.6%	1	11.1%	3	33.3%	0	0.0%	0	0.0%	1.973
	No	17	42.5%	3	7.5%	13	32.5%	6	15.0%	1	2.5%	p=.741
NEC	Yes	1	33.3%	0	0.0%	1	33.3%	0	0.0%	1	33.3%	16.08**
	No	21	45.7%	4	8.7%	15	32.6%	6	13.0%	0	0.0%	p=.003
IVF	Yes	5	45.5%	1	9.1%	3	27.3%	2	18.2%	0	0.0%	0.839
	No	17	44.7%	3	7.9%	13	34.2%	4	10.5%	1	2.6%	p=.933
CPAP	Yes	3	33.3%	0	0.0%	4	44.4%	1	11.1%	1	11.1%	9.15*
	No	19	47.5%	4	10.0%	12	30.0%	5	12.5%	0	0.0%	p=.048

Table 4: Single birth and multiple birth in retinopathy

			Group		Total
			Single birth	Multiple birth	
Group	EX- PRETERM Gestational week < 27 and birth weight < 1500gms	Count	9	11	20
		% of Total	18.4%	22.4%	40.8%
	PRETERM Gestational week 28-37 and birth weight > 1500gms	Count	13	16	29
		% of Total	26.5%	32.7%	59.2%
Total		Count	22	27	49
		% of Total	44.9%	55.1%	100.0%

Table 5: Association between refractive status and groups (single / Multiple Birth)

			Group		Total
			Single birth	Multiple birth	
Refractive Status	Myopia	Count	0	0	0
		% of Total	0.0%	0.0%	0.0%
	Hyperopia	Count	6	7	13
		% of Total	12.24%	14.3%	26.53%
	Astigmatism	Count	2	3	5
		% of Total	4.08%	6.1%	10.20%
	Compound Myopic astigmatim	Count	1	6	7
		% of Total	2.04%	12.2%	14.28%
	Compound Hyperopic astigmatism	Count	13	11	24
		% of Total	26.5%	22.45%	48.97%
Total		Count	22	27	49
		% of Total	44.9%	55.1%	100.0%

Table 6: Association between treatment and groups (single Birth/ Multiple Birth)

			Group	
			Single birth (n=22)	**Multiple birth (n=27)**
Treatment	Laser	Count	4	4
		%	18.1%	18.1%
	Avastin	Count	2	2
		%	9.09%	9.09%
	Accentrix	Count	1	1
		%	4.5%	4.5%

Table 5, it is found that the mostly compound hyperopic astigmatism is noted in both single 26.5% and multiple 22.45% groups. Table 6, Laser treatment accounts for 18.1%, in both single and multiple groups.

4. Discussion

Retinopathy of prematurity (ROP) is a proliferative retinopathy of the developing retina, which is characterized by abnormal neovascularization. Studies have shown that the rate of severe vision impairment is 26 times higher in infants weighing <1500g at birth than in infants weighing 2500 to 3499g. Thus, because multiple birth infants have a higher rate of prematurity and very low birth weight than singletons, they are believed to be at risk of more morbidity. However, it remains unclear whether the perinatal outcome of multiple- birth infants is worse than that of very low birth weight singletons.[8] There has been extensive research on ROP incidence in the past years, however there is yet no consensus regarding which risk factors are the more significant predictors of ROP.[9] This study investigated the severity of ROP in 49 preterm 28 - ≤ 37 weeks of gestational age, extremely preterm ≤27 weeks of gestational age at delivery of multiple and single births, there is statically significant difference was found regarding the severity of ROP between the groups. Extremely preterm infants of multiple births had a higher risk of ROP. It is observed that the risk factors: SEPSIS, NEC, oxygen, and CPAP are having significant association with stages in retinopathy. These risk factors more seen in multiple births. One of the studies conducted by Trivili et al., between 2008 and 2017 conducted that gestational age of premature infants ≤27 weeks of age showed advanced stage of ROP in comparison of gestational age of premature infants.> 27 weeks but ≤30 weeks of age.[10] Petricli LS et al., conducted a study between 2010 and 2016 in extremely premature infants who were ≤27 weeks of gestational age at birth and concluded that there was no difference between the groups in terms of multiple birth vs single births at ROP development and treatment.[11–16] Another study conducted by Boretea Cl et al., between 2017 and 2019. They concluded that logistic regression analysis of each risk factor revealed that ventilation treatment, surfactant treatment, CPAP treatment, GA and birth weight has a strongest correlation to ROP.[9]

5. Conclusion

The infants who were born in low gestational age and lower birth weight of multiple birth are more prone to develop severe stage of retinopathy.[13–15] Sepsis, oxygen, continuous positive airway pressure and necrotizing enterocolitis are risk factors has been linked to retinopathy of prematurity which was more seen in multiple births. The most frequent refractive error in both singleton and multiple births was compound hyperopic astigmatism. Laser treatment was mostly taken in both single and multiple birth.

6. Conflict of Interest

None.

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