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To Determine The Incidence And Risk Factors Of Retinopathy Of Prematurity In Tertiary Care Centre

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Abstract

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Introduction

The first study on ROP was done in 1942 by Terry. He described ROP as histologically a fibrovascular proliferation of embryonic hyaloid system in the immature retina which was named as retrolental fibroplasia.[1] The modern name was coined by Heath in 1951.[2] ROP is bilateral proliferative retinopathy affecting premature infants with low birth weight.[3]

The reported incidence of ROP in the Western world ranges from 21% to 65.8%, whereas in India, the incidence of ROP varies from 38% to 51.9% among low birth weight babies.[4] In developing countries, the incidence of ROP is rising with the improvement of the survival rates of extremely premature infants.[5] The importance of ROP lies in its frequency and in prevention of blindness due to this condition, given that, once diagnosed and treated, it is unlikely to develop into complete loss of vision.[6]

The pathogenic process involved in causation of ROP is multifactorial.[7] It is attributed to many possible risk factors like prematurity, low birth weight (LBW), oxygen therapy, sepsis, apnea, blood transfusion, among others.[6]

This study aims to determine the prevalence of ROP in a government tertiary care center in India and associated risk factors leading to development of ROP.

Method: The study was carried out in NICU at Rajindra Hospital, Patiala. The study was approved by the institutional review board and followed tenets of declaration of Helsinki. Informed consent was obtained from parents of the neonates who enrolled for the study. This was a cross-sectional observational study conducted for the period of 12 months. Babies born at <37 weeks of gestation and/or having birth weight <2000 grams were screened for incidence and risk factors of ROP.

Screening: Infants with GA less than 37 weeks or BW less than 2000 grams were screened for ROP. The timing of the first ophthalmological examination based on GA at birth was as follows:

GA at birth in weeks	Age at initial examination in weeks	
	Post menstrual age	Chronological age
22	31	9

23	31	8
24	31	7
25	31	6
26	31	5
27 to less than 37		4

Pupils were dilated with phenylephrine 2.5% and tropicamide 1%. These were added twice in both eyes at 15 minutes interval one hour before the time of examination. Wire speculum was inserted to keep the eyelids apart. Screening of ROP was done by experienced ophthalmologist by indirect ophthalmoscopy in NICU. The observations were recorded and the results obtained were statistically analysed.

Results: Among the 360 subjects screened, 99 had ROP (27.5%) and ROP was absent in 261 subjects (72.5%), the incidence of ROP being 27.5%. Among cases having ROP, 59.60% were males and 40.40% were females. The mean birth weight of cases having ROP was 1446.08± 213.15. The mean gestational age of the cases having ROP was 32±1.93 wks. Of all the stages of ROP, stage 2 was the most common and constituted 70.1% of the total number of cases of ROP followed by stage 1 constituting 20.2% cases and stage 3 constituting 9.09% cases. No case of Stage 4 and Stage 5 were detected. Also, among cases having ROP, 16.16% (16 cases) had plus disease. Of all the zones of ROP, zone II (71 cases) was found to be most commonly involved followed by zone III (18 cases) and zone I (10 cases). Maximum cases (50 cases) of ROP were seen in stage 2 zone 2.

Among neonatal risk factors; birth weight (p-value=0.037), gestational age (p-value=0.002), mechanical ventilation (p-value=0.008), duration of O_2 therapy (p-value=0.001), apnea (p-value=0.036), RDS/HMD (p-value=0.003), hypotension (p-value=0.001), sepsis (p-value=0.022) and BT administration (p-value=0.017) were statistically significant risk factors for the occurrence of ROP. None of the maternal risk factors were found to be statistically significant in our study (p-value>0.05).

Table no. 1 show the baseline demographic risk factors of the neonates having ROP

Characteristics – demographic		ROP present	ROP absent	P value
Gender	Male	59(59.60%)	136(52.11%)	0.203
	Female	40(40.40%)	125(47.89%)	
Gestational Age (in weeks)	$\leq 27^{+6}$	3(75%)	1(25%)	0.002
	$28\text{-}33^{+6}$	74(33.03%)	150(66.96%)	
	$34\text{-}36^{+6}$	22(16.67%)	110(83.33%)	
Birth weight (in grams)	<1000	2(66.67%)	1(33.33%)	0.037
	1000-1499	67(31.16%)	148(68.84%)	
	1500-1999	30(21.13%)	112(78.87%)	

Table no. 2 show relationship between neonatal risk factors and ROP

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Neonatal Risk factors		ROP Present	ROP absent	P value
Oxygen Duration (in hours)	<6	0(0%)	36(100%)	0.001
	6-24	23(19.33%)	96(80.67%)	
	>24	76(37.07%)	129(62.93%)	
Mechanical Ventilation	Yes	54(35.06%)	100(64.94%)	0.008
	No	45(21.84%)	161(78.16%)	
Apnoea	Yes	50(33.33%)	100(66.67%)	0.036
	No	49(23.33%)	161(76.67%)	
Birth asphyxia	Present	50(32.47%)	104(67.53%)	0.068
	Absent	49(23.79%)	157(76.21%)	
Sepsis	Yes	86(30.28%)	198(69.72%)	0.022
	No	13(17.11%)	63(82.89%)	
Blood Transfusion (BT)	Yes	82(31.06%)	182(68.94%)	0.017
	No	17(17.71%)	79(82.29%)	
Hypotension	Yes	81(53.64%)	70(46.36%)	0.001
	No	18(8.61%)	191(91.39%)	
Intraventricular Hemorrhage	Yes	5(14.29%)	30(85.71%)	0.066
	No	94(28.92%)	231(71.08%)	
Necrotizing Enterocolitis	Yes	20(25.97%)	57(74.03%)	0.735
	No	79(27.92%)	204(72.08%)	
Respiratory distress Syndrome	Yes	64(36.57%)	111(63.43%)	0.003
	No	35(18.92%)	150(81.08%)	
Surfactant Administration	Yes	40(33.33%)	80(66.67%)	0.08
	No	59(24.58%)	181(75.42%)	
Neonatal Hyperbilirubinemia	Yes	53(27.04%)	143(72.96%)	0.831
	No	46(28.05%)	118(71.95%)	
Phototherapy administration	Yes	53(27.04%)	143(72.96%)	0.831
	No	46(28.05%)	118(71.95%)	
Exchange Transfusion	Yes	8(13.79%)	50(86.21%)	0.017
	No	91(30.13%)	211(69.87%)	

Table no. 3 shows relationship between maternal risk factors and ROP

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Maternal risk factors		ROP present	ROP absent	P value
Age of mother (in years)	≤20	7(7.07%)	20(7.66%)	0.935
	21-30	85(85.86%)	234(89.66%)	
	31-40	7(7.07%)	7(2.68%)	
Mode of delivery	NVD	59(59.60%)	153(52.11%)	0.867
	LSCS	40(40.40%)	108(47.89%)	
Pregnancy induced hypertension	Yes	16(16.16%)	60(22.99%)	0.203
	No	83(83.84%)	201(77.01%)	
Gestational diabetes Mellitus	Yes	4(4.04%)	27(10.34%)	0.057
	No	95(95.96%)	234(89.66%)	
Antepartum haemorrhage	Yes	8(8.08%)	41(15.71%)	0.06
	No	91(91.92%)	220(84.29%)	
Premature rupture of membranes	Yes	51(51.52%)	120(45.98%)	0.347
	No	48(48.48%)	141(54.02%)	
Steroid intake in mother	Yes	24(24.24%)	40(15.33%)	0.048
	No	75(75.76%)	221(84.67%)	

Indian Studies	Gestational age (weeks)	Birth weight (grams)	Incidence
Rekha S et al[9] (1991-1994)	28-38	710-1700	46%
Hungi B et al[10] (2011-2012)	<34	<2000	41.5%
Tekchandani U et al[11] (2013-2017)	<34	<1750	32.3%+
Goyal K et al[12] (2017)	<34	<1750	29.5%
Kaul S et al[8] (2018-2020)	<32	<1500	28%
Present study (2021-2022)	<37	<2000	27.5%

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The incidence of ROP varies in international studies due to difference in economic status, ethnicity, genetics, practice setting, screening programs and level of perinatal care at the respective institutions.

International Studies	Gestational age (weeks)	Birth weight (grams)	Incidence
Dani C et al[13] (Rome)	23-29	_	38%
Aplay A et al[14] (Turkey)	<34	_	32.1%
Abdel-Aziz SM et al[15] (Egypt)	<37	<2000	30.6%
Zarei M et al[16] (Iran)	<28	<1000	27.28%
Ahmedhussain HK et al[17] (Saudi Arabia)	<30	<1500	21.8%

Discussion:

Incidence Of Rop:-

In our study 360 subjects fulfilled the inclusion criteria, of which 99 had ROP and ROP was absent in 261 subjects, the incidence of ROP being 27.5%. Results were in accordance with study by **Kaul S et al[8]** who found the incidence of ROP to be 28%. The incidence of ROP in our study is low as compared to previous studies done on ROP in various parts of India. The higher incidence in previous studies can be attributed to low sample size and mainly inclusion of <1750 grams and <34 weeks babies in the study.

Sex Distribution:

In our study, we observed that among cases having ROP, 59.6% were males and 40.4% were females. Results were in accordance with study by **Le C et al[18]** who found that 59% cases having ROP were males. Also, studies by **Goyal K et al[12]** and **Patel SS et al[19]** observed statistically insignificant association between the occurence of ROP and gender on univariate analysis.

Gestational Age Distribution:

In our study, 4 subjects were having gestational age $\leq 27^{+6}$ weeks, out of which ROP was present in 3 cases (75%) and absent in 1 case (25%). 224 subjects were having gestational age 28-33^{+6} weeks, out of which ROP was present in 74 cases (33.03%) and absent in 150 cases (66.96%). 132 subjects were having gestational age 34-36^{+6} weeks, out of which ROP was present in 22 cases (16.67%) and absent in 110 cases (83.33%). Therefore, incidence of ROP was inversely related to GA in our study. This observation is similar to studies by **Patel SS et al[19]**, **Sundar KC et al[20]**, **Abdel-Aziz SM et al[15]** and **Abdel HA et al[21]** who found that the risk of ROP increased with decrease in gestational age. It can be attributed to the fact that underdeveloped retinas of preterm babies are predisposed to insults that interrupt neurovascular growth, resulting in ROP. Also, studies by **Patel SS et al[19]** and **Abdel-Aziz SM et al[15]** observed statistically significant association between the occurrence of ROP and gestational age like in our study.

Birth Weight Distribution:

In our study, 3 subjects were having birth weight <1000 g, out of which ROP was present in 2 cases (66.67%) and absent in 1 case (33.33%). 215 subjects were having birth weight 1000-1499 g, out of which ROP was present in 67 cases (31.16%) and absent in 148 cases (68.84%). 142 subjects were having birth weight 1500-1999 g, out of which ROP was present in 30 cases (21.13%) and absent in 112 cases (78.87%). Therefore, it can be inferred that for the same level of prematurity, lesser the birth weight more is the chance

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of developing ROP. This observation is similar to studies by **Patel SS et al**[19], **Sundar KC et al**[20], **Abdel-Aziz SM et al**[15] and **Abdel HA et al**[21] who found that the risk of ROP increased with decrease in birth weight. This can be due to more susceptibility for oxygen therapy, prolonged ventilation, sepsis and blood transfusion in very low birth weight infants which contribute to the development of ROP. Also, studies by **Patel SS et al**[19], **Vasavada D et al**[22] and **Abdel-Aziz SM et al**[15] observed statistically significant association between the occurrence of ROP and birth weight like in our study.

Stage & Zone Of Rop Distribution:

In our study, we found that of all the stages of ROP, stage 2 was the most common followed by stage 1 and stage 3. No case of Stage 4 and Stage 5 were detected. Furthermore, zone II was found to be most commonly involved followed by zone III and zone I. Our study findings were in accordance with studies by **Ahmedhussain HK et al**[17] and **Tekchandani U et al**[11] who observed that maximum cases of ROP belonged to stage 2 and zone II of ROP. Also, in studies by **Ahmedhussain HK et al**[17] and **Abdel-Aziz SM et al**[15] no case of stage 4 and stage 5 of ROP were observed like in our study. This can be attributed to increased awareness of ROP screening and early screening of ROP leading to decreasing trend of end stage of ROP.

Relationship Of Risk Factors With Rop:

Ahmedhussain HK et al[17] showed statistically significant association between the occurrence of ROP and mechanical ventilation. This can be explained by the fact that in cases of ROP, free oxygen radicals are formed as a result of increased partial oxygen pressure, which is related to the amount of oxygen delivered during mechanical ventilation.[23]

Patel SS et al[19] and **Ahmedhussain HK et al**[17] showed a statistically significant association between occurrence of ROP and duration of O_2 therapy. This can be explained by the fact that increased PaO2 with relative retinal hyperoxia leads to vasoconstriction and decrease in growth factors, such as insulin like growth factor (IGF-1) and vascular-endothelial growth factor (VEGF). This leads to arrest of vascularization and capillary obliteration, which leads to decreased perfusion and subsequent retinal ischemia and hypoxia, further leading to ROP.[24].

Patel SS et al[19] showed statistically significant association between the occurrence of ROP and apnea. This can be explained due to the fact that apnea causes systemic hypoxia that leads to hypoxia of the retina and more O_2 therapy need which further contributes to occurrence of ROP.[15]

Kaul S et al[8] observed RDS was present in 76% of cases of ROP and was one of the most prevalent postnatal risk factor in the occurrence of ROP. This can be explained by the fact that children with RDS may need oxygen therapy or mechanical ventilator to support their breathing which contribute to the occurrence of ROP. Moreover, once the supplemental oxygen is removed, the avascular retina of preterm infants becomes hypoxic, thereby stimulating the overexpression of angiogenic factors that are responsible for vaso-proliferation observed in ROP.[25]

Yang CY et al[26] showed statistically significant association between the occurrence of ROP and hypotension. This can be explained by the fact that hypotension affects retinal perfusion and it leads to retinal ischemia which contributes to the occurrence of ROP.[27]

Goyal K et al[12] showed that presence of sepsis contributes to the risk of developing ROP. This can be explained due to the fact that sepsis causes secretion of endotoxins that effects retinal blood vessels and this may lead to ROP.[5]

Abdel-Aziz SM et al[15] found statistically significant association between the occurrence of ROP and administration of BT. This can be explained due to the fact that transfused adult RBCs are rich in 2,3 DPG and adult hemoglobin has less affinity for oxygen, thus it releases excess oxygen to retinal tissue.[28] Secondly, the iron load from transfusions may catalyze the formation of reactive oxygen species and accelerate oxidative damage, predisposing to ROP.[29]

Conclusion:

The safe implementation of oxygen therapy with appropriate monitoring, cautious use of mechanical ventilation, better antenatal and neonatal care, meticulous attention to hygienic procedures, control of sepsis and judicious use of blood transfusion products may reduce the prevalence of ROP. Also, timely retinal screening of high-risk preterm infants is important to prevent the development of advanced ROP.

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