

Retinopathy of prematurity in a tertiary care hospital: incidence and risk factors

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Abstract

Objective: To study the incidence and risk factors predisposing to retinopathy of prematurity (ROP) in Bapuji child Health Institute NICU. **Design:** Prospective cohort observational study. **Setting:** Infants admitted to a neonatal intensive care unit of Bapuji child Health Institute NICU in a period of two years. **Methods:** Preterm infants with birth weight < 1500g and gestation <34 weeks were screened for ROP at 4 weeks after birth or 31-33 weeks post conceptional age, whichever was later. Infants with birth weight >1500g and gestation >34weeks were screened only if they had additional risk factors. Those found to have high risk ROP had laser photocoagulation. **Results:** The incidence of ROP in the 200 infants who were screened was 13.5%. No ROP was found in infants weighing >2000g or with a gestational age more than 36weeks. Risk factors predisposing to ROP were oxygen therapy ($P=0.04$), apnea [$p=0.001$], ventilation [0.001], anemia [0.001], blood and blood product transfusion [0.001]. **Conclusion:** One third of the infants with ROP needed laser photo coagulation, the outcome of which was good. Risk factors predisposing to ROP were oxygen therapy, apnea, ventilation, blood transfusion, exchange transfusion.

Key words: Birth weight, Gestational age, Oxygen therapy, Prematurity, ROP.

Introduction

Retinopathy of prematurity (ROP) is a disorder of the developing retinal blood vessels in the premature infant retina. The key pathological change in ROP is peripheral retinal neovascularisation. This may regress completely or leave sequel from mild myopia to bilateral total blindness. Severe retinopathy of prematurity (ROP) can lead to retinal detachment and permanent visual loss. As acute ROP worsens, characteristic changes occur in the blood vessels of the posterior retina. Plus disease is considered to be present when the vascular changes are so marked that the posterior veins are dilated and the arterioles tortuous [1].

The condition was first described by Terry in 1942 as retrolental fibroplasia [2]. As developing countries

began to adopt modern neonatology techniques in the 1980s and 1990s, increasing the survival of preterm neonates, ROP began to emerge in middle-income countries (the 'third epidemic'), where it can account for as much as 60% of childhood blindness [3].

The 'first epidemic' of ROP took place in the 1940s and 1950s, affected larger premature infants, and was associated with unmonitored oxygen supplementation [3,4]. In India, with the development of neonatal intensive care units, premature infants with extremely low birth weights are surviving and are at highest risk of developing ROP [5].

Over 22% of childhood blindness in India is attributable to Retinal etiologies and "Retinopathy of Prematurity-ROP" is the commonest, and more preventable of these causes. The incidence of ROP in India estimated to be 47.27% according to Charan R et.al [6].

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The control of blindness in children is considered a high priority within the World Health Organization's (WHO's) VISION 2020- The Right to Sight programme [7]. Data on childhood blindness in India are incomplete, but applying an estimated prevalence of 0.7 (± 0.3) per 1000 children to the under-16 population provides an estimate of 218 000 ($\pm 92 000$) blind children [8].

Retinopathy of prematurity (ROP) is an important cause of preventable blindness in children [9]. This study intends to determine the incidence and risk factors of ROP in level 3 neonatal care centre.

Methodology

Study was carried out in a period of two years. A total of 200 babies were screened in the present study. Babies of gestational age ≤ 34 weeks and birth weight ≤ 1500 gms OR babies of birth weight between >1500 gms or >34 weeks with other risk factors like Oxygen therapy, Ventilation, Exchange Transfusion, Blood products use, Hyperbilirubinemia, Apnea, Septicemia, CPAP admitted to Bapuji Child Health Institute and Research Centre NICU, Davangere were taken as source of data. Babies born at > 34 weeks of gestational age and >1500 gms without risk factors were excluded from the study.

Ethical clearance was obtained from the hospital ethics committee and informed consent of the parents was also obtained.

Results

In the present study out of 200 cases 27 cases were ROP positive and majority of cases of ROP occurred between 28 -30 weeks ($n=12, 24.5\%$) of gestation. In 31-33 weeks of gestation 10 (11.6%) cases were seen. In 34-36 weeks of gestation 5 cases (7.5%) of ROP were seen. As the gestational age decreased there is significant increase ($p>0.03$) in the incidence of ROP.

40% of cases between 740-1000 gm of birth weight developed ROP. 15.7% of newborns between 1000-1500 gm of birth weight developed ROP. 10.3% of newborns between 1500-2000 gm of birth weight developed ROP. No baby with birth weight > 2000 gm developed ROP. 18 newborns had birth weight less than 1500 out of total 27 newborns with ROP. 9 newborns had birth weight >1500 (table 1).

In 27 ROP positive newborns there were 18 male newborns and 9 female newborns. There was no significant difference in the distribution of ROP between male and female sex. In the study out of 160 newborns who received oxygen, 16.3% ($n=26$) of newborns developed ROP. 2.5 % ($n=1$) newborns who have not received oxygen developed ROP. In the present study there was a significance association of ROP with oxygen therapy with a p value of 0.04 (table 2).

13 (6.5%) out of 200 cases had apnea. Out of 13 cases 10 (76.9%) had ROP. In 27 ROP positive cases 10 (37.03%) had apnea. In this study highly significant association between apnea and ROP is seen (p value <0.001). 8(4.0%) out of 200

Method of Examination: All the babies were screened with RETCAM by expert ophthalmic technician. The initial examination was carried out at 4 weeks after birth or 31 to 33 weeks post-conceptual age, whichever was later.

A detailed history including birth weight, gestational age at birth, weight for gestation, problems during NICU stay and its management were recorded in a pre-structured proforma. The screening was done in NICU nursery under the guidance of the neonatologist. The baby was clothed and mummified and was fed and burped one hour prior to examination. Incubator dependent babies can be screened (and even treated) within the incubator itself through the slanting wall without disturbing the equilibrium of the infant.

The screening was done using RETCAM. Eyes were examined with an infant speculum, under topical anesthesia using 2% Proparacaine drops. The pupils were dilated by using 0.4% Tropicamide +1.25% Phenylephrine eye drops two or three times, till full dilatation occurred. Retinopathy was graded into stages and zones as per the ICROP classification. Infants with normal vascularization up to the periphery were not examined again. Those with ROP were examined every week till regression occurred or till they reached threshold for laser treatment.

Statistical analysis: Analysis was performed using SPSS version 10.0. Univariate analysis was conducted using Chi square test.

newborns received ventilation in which 6 (75%) had ROP. Out of 27 ROP positive cases 6 (22.2%) received ventilation (table 3). There is a highly significant association between ventilation and ROP with a p value of <0.001.

16 newborns (8.0%) out of 200 had anemia. Out of 16 newborns 15 (93.8%) developed ROP. Out of 27 ROP positive newborns 15 (55.5%) were found to be anemia (table 3). There is a highly significant association between anemia and ROP In the present study with a p value of <0.001.

15 newborns (7.5%) received blood and blood product transfusion. Out of 15 newborns 13 newborns (86.7%) developed ROP. Out of 27 ROP positive cases 13 newborns (48.1%) developed ROP. There is a highly significant association between both the variables with a p value of <0.001. Out of 200 newborns 10 newborns (5%) received exchange transfusion in which 6 newborns (60%) developed ROP. In total of 27 ROP positive cases 6 cases (22.2%) have received exchange transfusion (table 3). There is a highly significant association between exchange transfusion and ROP.

Table-1: Birth weight and ROP.

Birth Weight(gm)	Positive		Negative		Total	
	No.	%	No.	%	No.	%
740-1000	2	40.0	3	60.0	5	2.5
1000-1500	16	15.7	86	84.3	102	51
1500-2000	9	10.3	78	89.7	87	43.5
2000-2500	0	0.0	6	100.0	6	3.0
Total	27	13.5	173	86.5	200	100.0

Table-2 - Oxygen Therapy and ROP Outcome.

Oxygen	Positive		Negative		Total	
	No.	%	No.	%	No.	%
Given	26	16.3	134	83.8	160	78.0
Not given	1	2.5	39	97.5	40	22.0
Total	27	13.5	173	86.5	200	100.0

Table 3- Correlation between Apnea, Anemia and Blood or Blood Product Transfusion and ROP.

ROP	Apnea				Anemia				Blood transfusion			
	Present	%	Absent	%	Present	%	Absent	%	Present	%	Absent	%
Positive	10	76.9	17	9.1	15	93.8	12	6.5	13	86.7	14	7.6
Negative	3	23.1	170	90.9	1	6.3	172	93.5	2	13.3	171	92.4
Total	13		177		16		184		15		185	

Discussion

Retinopathy of prematurity, first identified by Terry [2,10] in 1942, within a decade became the largest cause of childhood blindness in the United States [3] and a major cause of blindness throughout the technologically developed world. Terry's original reports designated the condition retrolental fibroplasia (RLF) on the basis of his impression that the primary change involved a proliferation of the embryonic hyaloids system that incorporated the retina. Owens and Owens [11] found that the hyaloids system was normal at birth and that RLF developed postnatally [11]. As the pathogenesis and clinical spectrum of manifestations became better

understood, the term retinopathy of prematurity was generally adopted.

The discovery of the relationship between supplementary oxygen and ROP in the 1950 [12,13,14,15] led to the practice of rigid curtailment of oxygen supplementation in the nursery, and a dramatic decrease in the incidence of ROP followed.

Our understanding of vascular development has advanced recently, both in general and with respect of the retinal circulation [16]. As a rule retinal vasculature

develops to meet retinal metabolic demand, with the exception of the foveal region, which has a very different vascular pattern [16], so that very early in development when the retina is thin it receives all its nutrients from the underlying choroid. The choroid is vascularized from about 6 weeks gestational age (GA) [17], but with increasing neural density and retinal thickness, the choroidal circulation alone cannot meet all the needs of the retina and a separate retinal circulation is required. Consequently at 14-15 weeks of gestation, retinal vascularization commences. This comprises two main- processes: vasculogenesis and angiogenesis [16]. Newly formed capillaries remodel and form a mature retinal vascular network with capillary-free areas [18], which in modern parlance indicates that retinal tissue responds to excess or lack of oxygen by trimming or inducing growth in its microvasculature so that oxygen supply matches the metabolic requirements of the retina [19].

Incidence of ROP In the present study is 13.5%. The incidence of ROP in the west has been reported to be 53-88.5% in babies with birth weight <1000 gm and 34.9-60.1% in <1500gm babies. In the present study the incidence seems to be higher in 28 to 30 weeks group. The incidence of ROP in other Indian studies range from 11.9% to 52%. In a study done by Sharma P et. al, (2009) [20] the incidence was 11.9% In other studies by Chaudhari S et.al,(2009) [21] and Varugheses (2001) et.al, [22], the incidence rates were 22.3%,52% respectively.

The major ROP risk factor is the degree of immaturity as measured by either birth weight or GA. Although these two parameters are highly correlated, this relationship is not linear as in intrauterine growth retardation. Furthermore, the assessment of GA, especially for the most immature neonate is prone to inaccuracy. As stated earlier both the incidence and severity of ROP are inversely related to birth weight and GA [23, 24] with the first being the more powerful predictor [25, 26].

In the present study the incidence of ROP is 13.5% in ELBW (<1000 gm) babies the incidence is 40%. In babies with birth weight 1000-1500 gm the incidence is 15.7%. In babies with birth weight between 1500 to 2000gm the incidence is 10.3%. In the present study, we would have missed 15 cases of ROP if we had used <30weeks criteria, as per American Academy of Pediatrics (AAP) updated recommendations. In western studies [20], the incidence of ROP has been reported to

be 53-88.5% in <1000gm babies and 34.9 to 60.1% in <1500 gm babies. In a study done by Vinekar et. al, 45% of the babies had threshold ROP at >1250gm birth weight [27]. There is a geographic variation in the incidence of ROP in babies born at even similar gestational ages. In the west ROP, at least the threshold variety is not seen in higher birth weight babies. In contrast ROP is seen in larger, bigger birth weight babies in Asia and other developing countries. In south India, threshold ROP has been seen in babies born with 2000 g birth weight. While partly this might reflect the failure of very small infants to thrive, other factors such as perhaps the quality of neonatal care that has led to a decline of ROP in the West is lacking here. Of note, a similar scenario existed in Lithuania, wherein ROP was seen in larger infants initially. However, the birth weights of babies with ROP have fallen quickly due to improvements in neonatal care. A similar swing in the pendulum could be expected to occur in India as well! Nevertheless, it is essential to realize that at least in the present scenario, the cutoff birth weight and the gestational ages of our babies that need to be screened for ROP need to be higher. In a study done by Chaudhary et.al [20], the incidence of ROP in 58 ELBW infants was 36.2%, in the 381 VLBW infants, it was 23.6% and was 11.4% in 105 infants weighing 1500-1999g. No ROP was seen in infants with birth weight \geq 2000g and gestational age more than 36 weeks.

In the present study the incidence of ROP in babies with gestational age \leq 36 weeks is 3.5%. Incidence increased as the gestational age decreased. Prematurity is the single most important risk factor responsible for retinopathy of prematurity. As reported by Palmer, et.al, [20], incidence and severity of ROP was closely related to lower birth weight and lower post-conceptual age, as was seen in the present study. In a study done by Chaudhari S, et.al, the Incidence was 83% in 28-30 weeks, 32% in 31-33 weeks, and 13% in 33-36 weeks [20].

Campbell was the first to suggest that supplemental oxygen was the cause for the sudden increase in the numbers of infants developing ROP in the early 1940s. Saito et.al.,'s conclusion that extremely premature infants with fluctuating arterial oxygen probably have a higher risk of developing progressive ROP [28]. It was confirmed by Cunningham et.al, [29] and York et.al., [30]. Clinical implication from these four studies is that, with respect to ROP development, arterial oxygen levels are particularly critical within the first weeks after birth (probably 4-6 weeks). ROP may develop in

preterm infants who have never received oxygen and in premature infants with cyanotic heart-disease. Furthermore, some studies have suggested a relationship between neonatal hypoxia and ROP [31] and in an animal model retinal ischemia may lead to the same retinal changes as hyperoxia [32].

In the present study prolonged oxygen therapy was found to be a significant risk factor [$p=0.04$]. It is found that mean duration of oxygen was significantly higher in the ROP group. Study done by Rekha S et. al, [33] also have shown a similar significance with the duration of oxygen therapy. In a studies done by Chaudhari S et.al, [20], Gupta VP et. al, [34] oxygen was found to be significantly associated with ROP. Study done by Dutta S et. al, [35] has concluded that there was no significant association of ROP with oxygen therapy.

In the present study apnea found to be significant risk factor. [$p<0.001$]. In a study done by Agarwal¹⁵, et.al, in 2002 apnea came as a significant risk factor. In another study by Gupta VP et.al, [34] in 2004 apnea came as a significant risk factor. In another study by Chaudhary S et.al,[20] in 2009 apnea came as a significant risk factor. In the present study ventilation found to be highly significant risk factor [$p<0.001$]. In a study done in Iran by Mokhtari MB,et. al, mechanical ventilation came as a significant risk factor [36]. In a prospective cohort study by Karna P,et.al, from USA has shown that mechanical ventilation is a significant risk factor [32].

In the present study anemia found to be significant risk factor. [$p<0.001$] In another study by Rekha S et. al, [33] in 1996 anemia came as a significant risk factor. In a study done by LiLiu et. al, [39] from china, anemia was a significant risk factor.

In the present study there is a highly significant association between blood and blood products transfusion [$p<0.001$]. In a study done in Brazil by Pinheiro AM et. al, [36] there was a significant association between blood transfusion and ROP [$p=0.022$]. In a study done in Egypt by Abdel H.A.A. Hakeemet. al, [37] there was a significant association between blood transfusion and ROP [$p=0.03$]. In a study done in Iran by Mojginbayat-Mokhtari et. al, [38] there was a significant association between blood transfusion and ROP.

In the present study there is a significant association between double volume exchange transfusion and ROP.

In a study done by Dutta S et.al, in 2004, there was a significant association between double volume exchange transfusion and ROP [35].

Conclusion

ROP is a disorder of developing retinal blood vessels in the premature infant retina. ROP is the commonest and more preventable form of blindness. During the study period of 2 years 200 babies were screened for ROP in which 27 were found to be positive. Our incidence rate is 13.5%. ROP is found to be associated with the following risk factors in the present study Oxygen therapy, ventilation, anemia and exchange transfusion. Out of 27 positive babies for ROP 18 babies were <1500 gm and 9 babies were >1500gm. If we followed AAP guidelines we would have missed 9 babies. It suggests that we should screen large babies with risk factors.

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