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To Study Nutritional Factors and Postnatal Growth as Predictors of Retinopathy of Prematurity in Neonates Weighing <1750g and/ or Gestation <34 Weeks.

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retinal vessels of premature infants. ROP remains one of the leading causes of childhood blindness worldwide. India and other developing countries are facing the third epidemic of ROP. Various risk factors for development of ROP include low gestational age, low birth weight, hyaline membrane disease, sepsis, shock, prolonged oxygen therapy, poor nutrition and weight gain and blood transfusions. Objective: To study nutritional factors and postnatal growth as predictors of ROP in neonates weighing <1750g and/ gestation <34 weeks. **Methods:** It is a prospective observational study conducted over one year (May 2017 to April 2018) in NICU, Department of Pediatrics, Govt. Medical College Amritsar, in collaboration with Department of Ophthalmology. All antenatal, perinatal and neonatal factors along with nutritional factors and postnatal growth mointoring were recorded. Screening for ROP was done by indirect opthalmoscopy at 4 weeks of postnatal age and followed up till retinal vascularization was complete. Data was analysed using univariate and multivariate regression analysis to evaluate risk factors. **Results:** Out of 79 babies screened 44 were found to have ROP of which 4 required treatment. Important risk factors found significant on univariate analysis were low birth weight (p=0.023) gestational age (p=0.003), duration of i/v fluid therapy (p=0.004), day of start of feed (p=0.032), day of attainment of full feed (p=0.005), relative weight gain at 4 weeks (p=0.041) and 6 weeks of life (p=0.04). On mutivariate logistic analysis, relative weight gain (g/kg/day) at 4 weeks of life was found to be an independent risk factor. **Conclusion:** Relative weight gain (g/kg/day) at 4 weeks of life was found to be an independent risk factor for development of ROP. This result may be regarded as providing emphasis on the importance of weight gain at an earlier postnatal age.

Keywords: ROP, nutritional factors, weight gain, growth monitoring.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retinal vessels of premature infants. ROP remains one of the leading cause of childhood blindness worldwide.[1] Among the preventable causes of blindness in children, which are 57%, ROP figures high in agenda.[2]

ROP was first described by Terry in 1942, which was previously known as Retrolental Fibroplasia with implication of oxygen therapy as the causative agent.[3] ROP had been reported to have two epidemics in the past, in developed countries. The first epidemic occurred in 1940-1950s and unmonitored supplemental oxygen was the principal risk factor.[4] The second epidemic occurred during 1970-1980s, despite careful monitoring of oxygen delivery to neonates. It was concluded that this epidemic was due to increased survival of very low birth weight babies.

India tops with the list with more than 3.5 million preterm births, highest in world.[5] ROP is a major health concern for India as well as other low and middle income countries. ROP is becoming a significant problem in developing countries and these countries are experiencing 3rd epidemic due to increased rate of preterm deliveries and NICU

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facility for these babies, but the lack of adequate resources and expertise to monitor blood gases and other variables is ultimately leading to increased ROP in these preterm babies.[6] Vision 2020 is a global initiative of the international agency for prevention of blindness where mission is the elimination of avoidable blindness by 2020.[7]

The global initiative for the elimination of avoidable blindness targets ROP for prevention and treatment in an effort to decrease the prevalence of childhood blindness. There is a consensus now on including ROP as a part of universal eye screening in babies under the government run national program known as Rashtriya Bal Swasthya Karyakaram (RBSK).

The incidence of ROP varies widely across different countries and is linked to the socioeconomic developments as well as the quality and accessibility oh health care facilities.[8] In India, ROP has been reported to occur in 22.7%- 51.9% of low birth weight infants.[9-12] The degree of prematurity is in itself the most consistent risk factor for ROP. Lower the birth weight and the gestational age higher is the risk for ROP. A number of other postnatal factors may contribute to the development of ROP.[13-17] These include use of supplemental oxygen, intraventricular hemorrhage (IVH), apnea, mechanical ventilation, sepsis, surfactant therapy, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), anemia, thrombocytopenia, administration of blood products, double volume exchange transfusions, growth factors, poor nutritional intake and low postnatal weight gain proportion by 6 weeks of life.

Nutritional deficits and poor postnatal growth are major problems in preterm infants.[18,19] The metabolic rates of preterm infants are higher than in age-matched fetuses and, consequently, their nutrient and energy requirements are extremely high.[20] Poor nutritional intake during the first weeks of life was identified recently as a risk factor for severe ROP. VanderVeen DK et al,[21] demonstrated that infants with the lowest total energy intake during the first four weeks of life have an increased risk of severe ROP.

Poor postnatal weight gain emerged as a risk factor for severe ROP in preterm infants around the beginning of the new millennium. Both Wallace et al,[22] and Fortes Filho et al,[17] have reported that weight gain measured at 6 weeks after birth could be used as a predictor for severe ROP. Thus adequate weight gain during the first weeks of life may prevent the development of ROP.

With neonatal units having been equipped with the state-of-the-art technological background and highly qualified personnel providing optimum care of extremely immature newborns, ROP incidence is on a rise. By early detection and timely intervention, blindness due to ROP is preventable. So, the purpose of this study is to find nutritional factors and postnatal growth as predictors of ROP.

MATERIALS AND METHODS

This prospective study was conducted in the department of Pediatrics, Government Medical College, Amritsar in collaboration with department of Ophthalmology, Government Medical College, Amritsar from May 2017 to April 2018. One hundred and eighty two neonates of weight < 1750 g and/or <34 weeks were included in the study.86 babies who died before first opthalmological examination, 3 babies with congenital anomalies and 14 babies who left the study in between or did not complete the follow up were excluded from the study. Only 79 neonates fulfilling the inclusion criteria were screened and followed up for the presence ROP. The study was conducted after taking permission from the ethics committee, Government Medical College, Amritsar and informed consent was taken from parents/guardians. All neonates enrolled for the study were monitored daily and managed as per NICU protocol. The babies were weighed, gestational age was assessed, other clinical information was recorded which included the gender, mode of delivery, neonatal risk factors i.e. birth asphyxia, sepsis, apnea, NEC, BPD, hypoxic ischemic encephalopathy, pneumonia, patent ductus arteriosus (PDA), hyperbilirubinemia, seizures, meningitis, hyaline membrane disease (HMD) and treatment modalities given to babies were recorded i.e. any use and duration of supplemental oxygen, phototherapy, surfactant, exchange transfusion, blood transfusion, duration of intravenous fluids. Nutritional factors taken into account were day of start of feed, type of feed, day of attainment of full feed. Daily weight gain recording along with head circumference and length growth mointoring respectively on weekly basis was done.

Detailed eye examination of all the babies was conducted by a single ophthalmologist at 4 weeks postnatally or 32 weeks post-conceptional age whichever was earlier. Pupilary dilatation was achieved with a mixture of 2.5% phenylephrine and 0.5% tropicamide instilled 3 times before the scheduled examination. Topical anaesthetic 2% proparacaine was used. The examination was done using an indirect ophthalmoscope with 20 D lens or 28 D lens. The retinal findings were recorded as per guidelines of International Classification of Retinopathy of Prematurity (ICROP).[23] Follow up examinations were conducted until full vascularization of retina reached zone 3 or until full remission of ROP after Laser treatment.

The data from present study was systematically collected, compiled and statistically analysed using SPSS statistical package. Univariate analysis like Pearson chi square and Fishers exact probability test were applied to data. Risk factors were analyzed by multiple logisitic regression analysis to establish relationship with ROP.

RESULTS

This study was conducted in the department of Pediatrics in collaboration with Department of Ophthalmology, Government Medical College Amritsar. Out of 79 babies screened, 44 babies were found to have ROP of which 4 babies required treatment. The incidence of ROP in this study was 55.7% [Table 1]. Out of 44 babies with ROP, 16 babies (36.36%) were in stage 1, 24 babies (54.55%) were in stage 2 and 4 (9.09%) babies developed stage 3 [Table 2].

Table 1: Incidence of ROP.

ROP	No. of cases	%
Present	44	55.70
Absent	35	44.30
Total	79	100.00

Table 2: Stages of ROP.

Stages of ROP	Stages			
	1	2	3	Total
ROP present	16	24	4	44
%	36.36%	54.55%	9.09%	100%

Out of 79 babies, 48 were males and 31 were females. The birth weight of the ROP babies ranged from 600-1700 g (mean 1198 ±218.906 g) while that of non-ROP babies ranged from 960-1800g (mean 1311 ±238.209 g). Low birth weight was significantly associated with ROP (p=0.023). The gestational age of the ROP babies ranged from 26-35 weeks (mean 30.75 ±1.57 weeks) while that of non-ROP babies ranged from 28-36 weeks (mean 31.65 ± 2.07 weeks). Lower gestational age was significantly associated with increased incidence (p = 0.003) of ROP.

Risk factors found significant on univariate analysis included birth weight (p=0.003), gestational age (p=0.003), i/v fluid therapy >10 days (p=0.004), day of start of feed (p=0.032), day of attainment of full feed (p=0.005), relative weight gain at 4 weeks (p=0.041) and 6 weeks of life (p=0.04) [Table 3].

Maternal risk factors like pregnancy induced hypertension, gestational diabetes, antepartum hemorrhage, antenatal steroids, anemia in mother were studied but none of the factors was found to be statistically significant. HMD, PDA, NEC, sepsis, pneumonia, meningitis, Intracranial hemorrhage, hyperbilirubinemia, birth asphyxia, seizures, shock, BPD, surfactant, phototherapy and exchange transfusion were not significantly associated with incidence of ROP. Type of feed, rate of head and length growth were not significantly associated with development of ROP.

On Multivariate logistic analysis of various risk factors which were significant on univariate analysis relative weight gain at 4 weeks of life was found to be an independent risk factor for ROP in this study [Table 4].

Table 3: Nutritional and Postnatal Growth Factors Found Significant on Univariate Analysis

Risk Factor	ROP				P value
	Present (n=44)		Absent (n=35)		
	No.	%	No.	%	
IV fluid duration >10days	21	77.78	6	22.22	0.004
Day of start of feed >2 days	27	67.50	13	32.50	0.032
Day of attainment of full feed >10 days	29	70.73	12	29.27	0.005
Relative weight gain at 4 weeks of life <10 g/kg/day	3	27.27	8	72.73	0.041
Relative weight gain at 6 weeks of life <10 g/kg/day	8	32.0	17	68.0	0.040

Table 4: Multivariate Analysis Of Risk Factors

	Adjusted Odds ratio	p-value	95% confidence interval
IV fluid duration	1.764	0.094	0.478-2.050
Day of start of feed	1.796	0.128	0.495-2.096
Day of attainment of full feed	1.351	0.418	0.237-6.517
Relative weight gain (g/kg/day) at 4 weeks of life	1.275	0.000	1.000-1.549
Relative weight gain (g/kg/day) at 6 weeks of life	1.620	0.185	0.238-4.810

DISCUSSION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the retina of premature infants. There is an alarming increase in the incidence of ROP in the developing countries including India, constituting what is referred to as third epidemic of ROP.

We screened 79 babies admitted to our NICU with birth weight <1750g and/or gestation <34 weeks. Out of these 44 babies were found to have ROP, 4 of whom required treatment and rest underwent spontaneous regression. Out of 44 babies with ROP, 16 babies (36.36%) were in stage 1, 24 babies (54.55%) were in stage 2 and 4 (9.09%) babies developed stage 3.

The overall incidence of ROP in the present study was 55.7%. Varughese S et al,[24] in 2001 screened 79 babies with gestation age less than 34 weeks and birth weight less than 1.5 kg found overall incidence to be 51.89%. Gupta et al,[25] in 2003 reported overall incidence as 21.7% and severe ROP as 5%.

Umamaheshwari B et al,[26] in 2016 screened 1366 babies who were ≤34 weeks and/or ≤1750g reported incidence of ROP and severe ROP to be 18.4% and 6.2% respectively.

Risk factors found significant on univariate analysis included low birth weight, gestational age, duration of i/v fluid therapy >10 days, day of start of feed after 2 days, attainment of full feed after 10 days, poor relative weight gain at 4 weeks (<10g/kg/day) and 6 weeks of life.

Lower birth weight and gestation is a known risk factor for ROP. Multicenter Trial of Cryotherapy showed that lower the birth weight, the greater the risk of developing ROP especially at birth weights less than 750g.[27] In another study, in 2001 Dogra et al reported that 30.7% of babies with threshold ROP treated with cryotherapy were more than 1250 g and 15.3% were more than 1500 g at birth.[28]

In the present study, oxygen administration by oxygen prongs, CPAP and ventilator was not found to be significant. This was in contrast to study conducted by Gunn et al,[29] and Majid et al,[30] which showed results different from ours, showing the relation between oxygen duration and ROP as significant. The possible reason for the results in the present study could be the strict management of oxygenation that was done to reach target saturation.

In the present study, duration of i/v fluid was found to be significant risk factor for development of ROP. 23 babies (44.23%) who developed ROP received i/v fluids for less 10 days and 21 (77.73%) babies who developed ROP received i/v fluids for more than 10 days. In the present study day of start of feed and day of attainment of full feed were found to be statistically significant for the development of ROP. This was similar to study conducted by Kim J et al,[31] in 2015 who showed that the time to initial total enteral feeding and final total enteral feeding were longer in infants with ROP requiring treatment, than those with no ROP or ROP not requiring treatment. Whereas type of feed was found not to be a significant risk factor for the development of ROP.

In the present study, babies who had ROP mean of relative weight gain at 4 weeks of life in stage 1, stage 2 and stage 3 was 5.99±2.66 g/kg/day, 5.91±2.49 g/kg/day and 5.60±3.83 g/kg/day respectively. Babies who had poor relative weight gain at 4 weeks of life (<10g/kg/day) developed ROP than babies who had relative weight gain of ≥10g/kg/day which was similar to study conducted by Aydemir O et al,[32] and Kim J et al.[31] Similarly poor relative weight gain at 6 weeks of life was found to be a risk factor for the development of ROP which was similar to study conducted by Wallace et al,[22] and Allegaert et al.[33] Whereas rate of head and length growth were not found to be statistically significant for development of ROP.

On Multivariate logistic analysis of various risk factors which were significant on univariate analysis relative weight gain at 4 weeks of life was found to be independent risk factor for ROP in this study.

CONCLUSION

The incidence of ROP in the present study was 55.7%. Relative weight gain (g/kg/day) at 4 weeks of life was found to be an independent risk factor for developing ROP. Infants with poor weight gain in the early postnatal period could have high risk of developing ROP which may require treatment. Low energy intake during first 4 weeks of life lead to arrested vascularization due to poor nutrient supply to growing vessels. This result may be regarded as providing emphasis on the importance of weight gain at an earlier postnatal age. It can help to identify infants with poor postnatal course who are at a greater risk. Thus, ophthalmologists and neonatologists should take special care and pay attention to this group of patients while screening for ROP.

REFERENCES

1. Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008;84:77-82.
2. Dandona R, Dandona L. Childhood blindness in India. A population based perspective. Br J Ophthalmol. 2003;87:263-5.
3. Terry TL. Extreme prematurity and fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens. I. Preliminary report, Am J Ophthalmol 1942;25 : 203-04.
4. Clare Gilbert. Retinopathy of Prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Human Development 2008;84: 77-82.
5. Blencowe H, Cousens S, Oestergaard MZ. National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends 1990 for selected countries: a systematic analysis and implication. Lancet. 2012;379:2162-72.
6. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350:12-4.
7. Gilbert C, Foster A. Childhood blindness in the context of vision 2020 – the right to sight. WHO Bulletin 2001; 79: 227-32.
8. Gilbert C, Fielder A, Gordillo L. International NO-ROP Group. Characteristics of infants with severe retinopathy of prematurity in countries with low moderate and high. Amount of development: implications for screening programs. Pediactrics. 2005;115:518-25.
9. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophtalmol. 1995;43:123-6.
10. Gopal L, Sharma T, Ramchandran S. Retinopathy of prematurity: A study. Indian J Opthalmol.1995;43:59-61.
11. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity In Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J Opthalmol. 2007;55:331-6.
12. Jalali S,Matalia J,HussainA,Anand R. Modification of screening criteria for Retinopathy of prematurity in India and

other middle income countries .Am J opthalmol. 2006;141:966-8.
13. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity (STOP-ROP). A randomised, controlled trial: primary outcomes. Pediatrics. 2000;105:295-310.
14. Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity :a metanalysis. Pediatrics. 2010;125:1483-92.
15. Karan P, Muttineni J, Angell L, Karmaus W. Retinopathy Of Prematurity and risk factors; a prospective cohort study. BMC Pediatr. 2005;5:18.
16. Dutta S, Narang S, Narang A, Dogra M, Gupta A. Risk factors of threshold Retinopathy Of Prematurity. Indian Pediatr.2004;41:665-71.
17. Fortes Filho JB, Bonomo PP, Maia M, Procianoy RS. Weight gain measured at 6 weeks after birth as predictors for severe retinopathy of prematurity: study with very low birth weight preterm babies. Graefes Arch Clin Exp Opthalmol. 2009;247:831-6.
18. Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. Arch Dis Child Fetal Neonatal. 2004;89:428-30.
19. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics. 2001;107:270-3.
20. Singer D, Muhlfeld C. Perinatal adaptation in mammals: the impact of metabolic rate. Comp Biochem Physiol A Mol Integr Physiol. 2007;148(4):780-4.
21. Vanderveen DK, Martin CR, Mehendale R, Allred EN, Dammann O, Leviton A. Early nutrition and weight gain in preterm newborns and the risk of retinopathy of prematurity. PLoS One. 2013;8(5):64325.
22. Wallace DK, Kylstra JA, Phillips SJ, Hall JG. Poor postnatal weight gain: A risk factor for severe retinopathy of prematurity. J AAPOS. 2000; 4:343-47.
23. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity. Arch Opthalmol. 2005;123(7):991-9.
24. Varughese S, Jain S, Gupta N ,Singh S, Tyagi V, Puliyel JM. Magnitude of the problem of retinopathy of prematurity. Experience in a large maternity unit with a medium size level-3 nursery. Indian J Opthalmol 2001;49:187-8.
25. Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of Prematurity - Risk factors. Indian J Pediatrics 2004;71:887-92.
26. Umamaheswari B. Screening based on incidence of severe retinopathy of prematurity in a tertiary care centre in India: are Indian infants different? Int J Contemp Pediatr. 2016;3(3):847-53.
27. Palmer EA, Flynn JT, Hardy RJ. Incidence and early course of retinopathy of prematurity. Ophthalmology 1991;98:1628–40.
28. Dogra MR, Narang S, Biswas C, Gupta A, Narang A. Threshold retinopathy of prematurity: Ocular changes and sequelae following cryotherapy. Indian J Ophthalmol 2001; 49: 97-101.
29. Gunn TR, Easdown J, Outerbridge EW. Risk factors in retrolental fibroplasia. Pediatrics 1980;65:1096.
30. Majid A, Gholam-Ali M, Hassan B, Zakiye Y, Shahin MN, Mojtaba A. Incidence and Risk Factors of Retinopathy of Prematurity in Mashhad, Northeast Iran: Iran Red Cres Med J 2013;15(3):229-33.
31. Kim J, Jin JY, Kim SS. Postnatal weight gain in the first two weeks as a predicting factor of severe retinopathy of prematurity requiring treatment. Korean J Pediatr. 2015;58(2):52-9.
32. Aydemir O, Sarikabadayi YU, Aydemir C. Adjusted poor weight gain for birth weight and gestational age as a predictor of severe ROP in VLBW infants. Eye. 2011; 25:725-29.
33. Vinekar V, Mangalesh S, Mallavapu M, Jayadev C, Sharma P, Shetty B. Regaining birth weight and predicting ROP-a prospective pilot study. Ann Eye Sci. 2017;2:50.
34. Allegaert K, Vanhole C, Casteels I, Naulaers G, Debeer A, Cossey V. et al. Perinatal growth characteristics and associated risk of developing threshold retinopathy of prematurity. J AAPOS. 2003;7(1):34-7.

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