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Original Articles

Blood Transfusion: A Risk Factor in Retinopathy of Prematurity

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Abstract

Background: Retinopathy of prematurity (ROP) is a retinal vascular disorder of preterm neonates resulting in visual impairement. Along with prematurity, very low birth weight and hyperoxia, role of blood transfusions in the occurrence of ROP has been strongly emphasized.

Objective: To determine the relationship of timing and volume of blood transfusion and other factors with the development of ROP in preterm very low birth weight (VLBW) newborn infants.

Methods: This was a prospective observational study. It was done among the premature (≤34 weeks) VLBW neonates admitted to SCABU and ICU of Dhaka Shishu Hospital. Neonates who fulfilled the inclusion criteria were followed up daily to record certain clinical factors and effect of blood transfusions. Among 93 discharged neonates subjected to have ophthalmological screening, 58 (62%) completed the examinations. After ophthalmological study, they were divided into "Normal group" (n=35) that included newborns without ROP, and "Abnormal group" (n=23) that included newborns with ROP. Comparative analysis of recorded clinical factors was done between the two groups.

Results: Blood transfusion during the first week of life (p=.002, OR 1.15; C.I. 1.01–1.32) and cumulative volume of transfused blood (ml/kg) (p=.002, OR2.8, CI: 1.65-4.41) were significantly associated with the development of ROP. All neonates with ROP have got one or more transfusions (p=.003; OR 2.11 95% CI.012-.676). Univariate analysis demonstrated that VLBW (p=.03; OR .93; 95% CI=.87-.91), duration of oxygen inhalation (p=.001; OR 28; 95% CI 4.85-17.81) and mechanical ventilation (p= .001; OR3.36; 95% CI2.5-5.52) has significant relationship with ROP.

Conclusion: This study showed that repeated blood transfusion resulting in large cumulative volume, transfusion in first week of life has significant association with ROP. Other risk factors are very low birth weight, prolonged oxygen inhalation and mechanical ventilation.

Keywords: *ROP, blood transfusion, preterm neonates.*

Introduction

Retinopathy of prematurity (ROP) is a multifactorial disease in which retinal blood vessels of premature infants fail to grow and develop normally, sometimes resulting in visual impairment and blindness[1,2]. ROP has been acknowledged as one of the major causes of blindness in infants and children in developed countries, and has emerged as a problem in developing countries as well. This is because of advancement in neonatology for which survival of premature and very low birth weight neonates have been increasing in the developing countries[3, 4].

Although supplemental oxygen therapy has been considered the main risk factor in the past, several recent studies have suggested a multifactorial basis for ROP development. The risk factors reported are very low birth weight, preterm gestational age, postnatal steroid, prolonged mechanical ventilation,

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repeated blood transfusion, and prolonged parenteral nutrition[5-7].

In recent years, the role of blood transfusions and iron intake as risk factors for ROP has been strongly emphasized[8,9]. Reports have provided conflicting views on the relative role that transfusions may play. Some studies suggest that anemia per se is a risk factor for ROP, whereas others contend that a high haematocrit ratio and frequent blood transfusions are important independent risk factors[4,10-12].

The usual explanation is that tissue (including retinal) oxygen levels are increased by transfusion owing to the reduced affinity of adult hemoglobin to oxygen as compared to fetal hemoglobin. An alternative hypothesis is that damaging effects of blood transfusion on the retina are mediated by an increase in free iron load which may react with various intermediates of oxygen generating highly reactive oxygen radical. Otherwise, protection against free iron is provided by ceruloplasmin and transferrin, but in preterm infants with gestational age lower than 34 weeks, the levels of these binding proteins are very low, and rapid saturation of transferrin occurs[8, 9].

On the theoretical basis that blood transfusions might be linked causally to ROP pathogenesis, we have conducted a prospective, observational study in which the relationship of volume of transfused blood and other factors with the development of ROP has been observed in preterm VLBW newborn infants.

Materials and Methods

This prospective study has been conducted at Dhaka Shishu Hospital from July, 2006 to March, 2008. Inclusion criteria was neonates admitted in Special Care Baby Unit (SCABU) and Intensive Care Unit (ICU), born at 34 or less weeks of gestation and having birth weight ≤ 1500 gm. Neonates who had congenital anomalies, syndromic manifestations or suspected inborn errors of metabolism were excluded. Informed consent from the parents or legal guardians was obtained by study investigator before enrollment. Ophthalmological examinations were performed at Paediatric Ophthalomolgy Department of Bangladesh Eye Hospital.

For each patient data regarding perinatal, maternal and fetal problems, birth weight (whenever applicable), gestational age (from maternal recall of LMP or available ultrasonogram reports) were recorded. Duration of gestation has been confirmed by assessing modified new Ballard score. In addition, duration of oxygen therapy, duration of mechanical ventilation was noted. Age at first blood transfusion, and cumulative volume of blood transfusion was recorded. Daily clinical care was performed by attending neonatologist in accordance with hospital protocol.

At discharge, both of the parents and other family members were counseled regarding the importance of eye examination. A date of examination was fixed at 4 to 6 weeks of chronological age of the baby and at parent's convenience.

One paediatric ophthalmologist has examined all the cases. Pupils were made dilated with 1% phenylephrine and 0.5% tropicamide eye drop. The examination was performed about 20 to 25 minutes later using a binocular indirect opthalmoscope and +20D lense. After ophthalmological examinations they were divided into 'Normal group' that had normal findings on examinations (no ROP) and 'Abnormal group' that included newborns with abnormal findings (any stages of ROP).

Data managment and anlaysis was done by using the Statistical Package for the Social Science (SPSS, version: 12). Mean and standard deviation of the continous variables were seen. Comparative analysis of the variables was done between the "Normal" and "Abnormal" groups. During univariate analysis the categorical variable were tested with Chi-square (χ^2) and Fisher's exact test and for continuous variable Student's t test was done.

Results

During the study period of one year and nine months total premature (gestational aged" 34 weeks) neonates admitted in the SCABU and ICU were 162. At admission 129 neonates fulfilled inclusion criteria of which 36 (28%) died. Ninety three neonates were available at discharge and counseled for ROP screening. Eighty five neonates presented for first screening. There was a high drop out rate and only 62% (58 of 93) neonates could complete the required examinations. After ophthalmological examinations they were divided into 'Normal group' comprising 35(60%) neonates and 'Abnormal group' comprising 23(40%) neonates. Of the abnormal 23 neonates stage II ROP was seen in 13 neonates, stage III in 5 and stage IV in 5 neonates.

Among the 58, birth weight of 90% (52) neonates could be known. Of them 6(10%) neonates were in

extremely low birth weight (d"999 gm) group. Birth weight ranges from 750-1500 grams with a mean 1185± 186 gm. Mean gestational age was 30±2 weeks and 19% of the neonate had a gestation of 28 weeks or less (Table I).

Table-I

Baseline characteristics of the study neonates (n=58)

Variables	N (%)	Mean±SD
Gestational age (weeks)		
27- 28	11 (19)	
29-30	20 (34.5)	30±2
31-32	24 (41)	
33-34	3 (5.5)	
Birth weight (grams)		
750-999	6 (10)	
1000-1500.1	25 (43)	1185±186
1251-1500.1	21 (35)	
Sex		
Male	28 (48)	
Female	30 (52)	

Tables-II shows total volume of blood transfusion (ml/kg) in the study population. Twenty two percent (13) neonates did not get any transfusion. Those 13 neonates were found to have normal findings on ROP screening. Thirty neonates received blood transfusion >20 ml/kg. Two neonates had exchange transfusion for once (transfused volume 170 ml/kg) and two had twice (transfused volume 240 ml/kg).

Table-III shows the relationship of transfusion variables with the findings of ophthalmologic examinations. Among the abnormal 23, 18(78%) neonates were given transfusion in 1st week of their life which has significant relationship with the development of ROP. Mean cumulative volume of transfused blood was only 8±4ml/kg in normal findings group. On the contrary it was 37±5 ml/kg in the abnormal findings group. Mean blood volume in the abnormal group is large as the analysis included the four neonates who got exchange transfusion. Other than those four neonates, mean volume of transfused blood remains 25ml/kg. However, the relationship of volume of transfused blood and ROP remained significant (p=.002; OR 2.8; 95% CI 1.65-4.41).

Table-II

Cumulative volume of blood transfusion (n=45)

Volume (ml/kg)	N(%)
10-20	3 (22)
>20-40	25 (43)
>40	5 (9)
0	13 (22)

Comparison of certain clinical factors among normal and abnormal groups revealed that there is no significant difference in mean gestational age among normal and abnormal groups. Proportion of number of small for gestational age (SGA) neonates between the groups was also insignificant. Low birth weight had significant (p=.03; OR.93; 95% CI=.87-.91) relationship with abnormal findings on ophthalmological examinations. Male female ratio was similar in both the groups. Perinatal factors like multiple gestation, maternal pre-eclampsia or eclampsia and mode of delivery had no significant difference in the normal and abnormal groups. Duration of oxygen inhalation has very significant relationship (p= .001; OR 28; 95% CI 4.85-17.81) with occurrence of ROP. All the 6 neonates who were given mechanical ventilation developed ROP of any stage (p= .001; OR3.36; 95% CI2.5-5.52) (Table-IV).

Table-III

*Comparison of factors related with blood transfusion in study group**

Parameters	Normal (n=35)	Abnormal (n=23)	p value	Odds ratio (95% CI)
Got at least one Transfusion	22/35	23/23	.003	2.11 (.012-.676)
Got Blood transfusion in First week of life	3/35	18/23	.002	1.15 (1.01–1.32)
Cumulative volume of transfused blood (ml/kg)	8±4	37±5	.002	2.8 (1.65- 4.41)

*Mean ± SD, or ratio (%)

Table-IV

*Comparison of the risk factors in the study infants**

Parameters	Normal (n=35)	Abnormal (n=23)	p value	Odds ratio (95% CI)
Gestational age (weeks)	30±2	29±2	.329	-
SGA	5/35	6/23	.32	-
Birth weight (gm)	1258	1070	.03	.93 (.87-.91)
Male/Female	17/18	11/12	1.0	
Multiple gestation	11/35 (30)	7 /23 (30)	.720	-
Mother had PET	6/35 (17)	2/23 (8)	.573	-
Delivered by LSCS	15/35 (43)	6 /23 (26)	.523	-
Total hour of O_2 inhalation	54.54	141.41	.001	28 (4.85-17.81)
Mechanical ventilation	0	6	.001	3.36 (2.5-5.52)

*Mean ± SD, or ratio (%)

Discussion

ROP is an important cause of potentially preventable blindness in developed countries[13,14]. In developing countries it is emerging as an epidemic[15]. It has a well-known variation in the incidence as well as in associated risk factors among centers and among countries[16].

In our set up we do not have a well developed system for eye examination in preterm neonates. It is a limitation of this study that we could not perform eye examination during hospital stay due to lack of logistic support. Again, this was a follow up study. There was huge drop out (93 neonates were subjected to screening but examinations were completed by 58 neonates). For this reason we could not calculate the exact incidence of ROP. However, of the 58 neonates who completed all required examinations, rate of ROP occurrence was 40%. Bassiouny[6] from Oman reported an incidence of 34%, Maheshwari et al[16] from India found 27% incidence, and Grallo[17] from Italy showed an incidence rate of 37%. Our observation of rate of occurrence of ROP is similar to other studies.

In many studies of ROP, younger gestational age has been found to be a significant risk factor[5]. We did not find any significant relationship. We got only 11 (19%) neonates survived in the highest risk gestational age group (≤28 weeks) and almost 50% of our neonate had >30 weeks of gestation. Unlike developed countries we could save a few premature extremely low birth weight neonate who fortunately had a smooth clinical course and short duration of hospital stay. These factors may be responsible for gestational age not to be significant. There are other studies in developing countries who did not find significant relationship between gestational age and ROP[18-20]. Dutta et al[19] in India had found the degree of prematurity could not predict the development of severe ROP.

A good number of studies have proven the relationship between very low birth weight and occurrence of ROP[13,16,21,22]. Our study demonstrated the increased incidence of ROP in very low-birth weight babies which is comparable to most studies. Bassiouny et al[6] in Indonesia and Shah et al[2] in Singapore had similar findings of mean birth weight. It has been reported that infants who are born SGA may be more likely to develop ROP[16]. This finding could not be confirmed by the analysis of our data. Shah et al[2] in Singapore also did not demonstrate any significant relationship.

We have tried to find out the association between six perinatal factors and the development of ROP. Maternal eclamspsia or pre eclamptic toxaemia, mode of delivery, multiple gestation, small for gestational age was not significantly related with occurrence of ROP. Gitalisa et al[18] in their study did not find any association between maternal PET and ROP. Our study has revealed similar findings. Manzoni et al[15] in his study showed that vaginal delivery is a significant and independent predictor of severe ROP. In our study there was no difference in the occurrence of ROP and mode of delivery. Distribution of caessarian section was similar in both normal findings and abnormal findings group (12 and 14 respectively). We could not find any significant difference among the singleton or multiple gestation group. Rohit et al[21] also did not

demonstrate any difference between singleton and multiple birth.

Many studies[6,14,16-18] have poven the role of hyperoxia in the pathogenesis of ROP. In our study prolonged duration of oxygen inhalation (>140 hours) was significantly associated with abnormal examination findings. Mechanical ventilation has a strong association with the occurrence of ROP. In this study we had 8 (11.0%) neonates who got mechanical ventilation support and all of them developed at least stage 2 ROP. Shah et al[2], Shohat et al[20], Kim et al [22] and others[6,18] have got the similar result.

Blood transfusion may adversely influence the vascular development of retina, not only by increasing oxygen delivery to the retina, but also by overloading iron, which in turn increases free oxygen radicals[4]. The transfused adult haemoglobin increases oxygen delivery to the retina which may increase the risk of ROP[23]. Lackman[24] in his study has demonstrated that increased amount of free iron may catalyze fenton reactions, which produce free hydroxyl radicals from superoxide and hydrogen peroxide capable of damaging the retina.

Preterm sick neonates in our NICUs are often transfused with whole blood. Some times whole blood is transfused instead of plasma or platelet or any other blood product due to unavailability of that particular blood product. Our study has shown that the total volume of transfused blood is proportionately associated with the development ROP. We have found that neonates who developed ROP have got a mean of 37 ml/kg of blood transfusion and the normal group has got only 8 ml/kg. The association is significant. Sohat M[20], Inder TE[25] and Akkoyun I[26] in their study has shown that the number of blood transfusions received and/or the total volume of blood received by premature babies is a major determinant of ROP besides gestational age and birth weight. Our results are in full agreement with the previous studies.

Dani C[5] in his study has shown that transfusion of packed red cell >15 ml/kg increases the incidence of ROP. The author also found that transfusion of blood in the first week of life is related with ROP occurrence. Our study result also confirmed that transfusions during the first week of life act as a risk factor for the development of ROP.

We had four neonates who undergone double volume exchange transfusion and all four of them developed significant ROP. Dutta et al[19] reported the administration of packed cell and double volume exchange transfusions in the neonatal period acts as a major risk factors for the development of threshold ROP.

Conclusion

This study showed that blood transfusion in first week of life and repeated blood transfusion resulting in large cumulative volume are very significantly associated with occurrence of ROP. Other risk factors are very low birth weight, prolonged oxygen inhalation and mechanical ventilation. Our study suggests that a policy aimed at limiting the amount of blood transfusion to preterm infants could contribute to reducing the incidence of ROP.

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References

1. Early Treatment for Retinopathy of Prematurity Cooperative Group. The incidence and course of retinopathy of prematurity: Findings from the early treatment for retinopathy of prematurity study. Pediatrics 2005; 116: 15-23.
2. Shah VA, Yeo CL, Ling YLF, Ho LY. Incidence, risk factors of retinopathy of prematurity among very low birth weight infant in Singapore. Ann Acad Med Singapore 2005; 34: 169-78.
3. Valentine PH, Jackson Kalina RE, Woodrum DE. Increased survival of low birth weight infants; impact on the incidence of retinopathy of prematurity. Pediatrics 1989; 84: 442-45.
4. Brooks SE, Marcus DM, Gillis D, Pirie E, Johnson MH, Bhatia J. The effect of blood transfusion protocol on retinopathy of prematurity: a prospective randomized study. Pediatrics 1999; 104: 514-18.
5. Dani C, Reali MF, Bertini G. The role of blood transfusions and iron intake on retinopathy of prematurity. Early Hum Dev 2001; 62: 57-63.

6. Bassiouny MR. Risk factors associated with retinopathy of prematurity: A study from Oman. J Trop Pediatr 1996; 42: 355-58.

7. Louis CB, Michael S, Rose AJ, William CF, Jhon TF. ROP in multiple gestation pregnancy. American J Ophthalmol 1998; 125: 197-203.

8. Hesse L, Eberl M, Schlaud C, Poets F. Blood transfusion, iron load and retinopathy of prematurity. Eur J Pediatr 1997; 156: 465-70.

9. Cooke RWI, Clark D, Hickey DM, Weindling AM. The apparent role of blood transfusions in the development of retinopathy of prematurity. Eur J Pediatr 1993; 152: 833-36.

10. Sacks LM, Schaffer DB, Anday EK, Peckham GL. Retrolental fibroplasia and blood transfusion in very low-birth-weight infants. Pediatrics 1981; 68: 770-74.

11. Aranda JV, Clark TE, Maniello R, Outerbridge EW. Blood transfusion (BT): possible potentiating risk factor in retrolental fibroplasia. Pediatr Res 1975; 9: 362.

12. Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet 1997; 350: 12-14.

13. Wheatley CM, Dickinson JL, Mackey DA, Craig JE, Sale MM. Retinopathy prematurity: recent advances in our understanding. Arch Dis Child Fetal Neonatal Ed 2002; 87: F 78-82.

14. Manjoni P, Farina D, Maestri A, Giovannozzi C, Leonessa ML, Arisio R, et al. Mode of delivery and threshold retinpathy of prematurity in preterm ELBW neonates. Acta Pediatrica 2007; 96: 221-26.

15. Gibson DL, Sheps SB, Schechter MT. Retinopathy of prematurity: a new epidemic? Pediatrics 1989; 83: 486-92.

16. Maheshwari R, Kumar H, Paul VK, Singh M, Deorari AK, Tiwari AK. Incidence and risk factors of retinopathy of prematurity in a tertiary care newborn unit in New Delhi. Natl Med J Ind 1996; 9: 211-14.

17. Grallo JE, Jacobson L, Broberger U. Perinatal factors associated with retinopathy of prematurity. Acta Paediatr 1993; 82: 829-34.

18. Gitalisa AA, Elvioza, RS Sitorus. Screening for retinopathy of prematurity at Cipto Mangunkusumo Hospital, Jakarta, Indonesia – a preliminary report. Acta Medica Lituanica 2006; 13: 165-70.

19. Dutta S, Narang S, Narang A, Gogra M, Gupta A. Risk facros for threshold retinopathy of prematurity. Indian Pediatr 2004; 41: 665-71.

20. Shohat M, Resiner SH, Krikler R, Nissenkorn I, Yassur Y, Ben-Sira I. Retinopathy of prematurity: incidence and risk factors. Pediatrics 1983: 72; 159-63.

21. Charan R, Dogra MR, Gupta A, Narang A. The incidence of retinopathy of prematurity in a neonatal care unit. Indian J Ophthalmol 1995; 43: 123-26.

22. Kim TI, Sohn J, Pi SY, Yoon YH. Postnatal risk factors for ROP. Paediatr and Perinatl Epidemiol 2004; 18: 130-34.

23. Clark C, Gibbs JAH, Maniello R, Outerbridge EW, Aranda JV. Blood transfusion: a possible risk factor in retrolental fibroplasia. Acta Paediatr Scand 1981; 70: 535-39.

24. Lackman GM, Schnieder C, Bohner J. Gestational age dependent reference values for iron and selected proteins of iron metabolism in serum premature human neonates. Biol Neonate 1998; 74: 208-13.

25. Inder TE, Clemett RS, Austin NC, Graham P, Darlow BA. High iron status in very low birth weight infants is associated with an increased risk of retinopathy of prematurity. J Pediatr 1997; 131: 541-44.

26. Akkoyun I, Sibel O, Gursel Y, Berkan G, Aylin T, Deniz A, et al. Risk factors in the development of mild and severe retinopathy of prematurity. J Am Association Ped Ophthal Strab 2006; 10: 449-53.