Original Article

Risk Factors of Threshold Retinopathy of Prematurity

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Objective: *To determine the risk factors which predispose to the development of threshold retinopathy of prematurity among patients of retinopathy of prematurity.* ***Methods:*** *The ROP clinic records of a 3 year period were retrospectively studied to identify babies with threshold ROP (T-ROP) and sub-threshold ROP (ST-ROP). Various antenatal and perinatal risk factors, neonatal morbidity and therapeutic interventions were compared between the 2 groups.* ***Results:*** *Of the total of 108 babies, 55 had T-ROP and 53 had ST-ROP. On univariate analysis, packed cell transfusions for anemia, double volume exchange transfusions (DVET), number of DVET, ventilation, gestational age ≤ 28 weeks and apneic episodes were significantly higher in the T-ROP group. On multivariate analysis, the administration of packed cells [OR 2.8, 95% CI 1.2, 6.6; (p = 0.014)] and DVET [OR 2.7, 95% CI 1.2, 6.5; (p = 0.022)] emerged as independent risk factors of T-ROP.* ***Conclusions:*** *Administration of blood products increases the risk of developing T-ROP among patients who have ROP. There is a need to exercise caution in the use of blood products in premature newborns.*

Key words: *Prematurity, Retinopathy.*

RETINOPATHY of Prematurity (ROP), a disease of the immature retina, has a well-described classification, diagnosis and line of management(1-4). About 50% of babies with Threshold ROP (T-ROP) develop an unfavorable visual outcome, whereas only about 5% of those with less severe forms of ROP do so(5). Despite treatment with cryotherapy or laser photo-coagulation, patients with T-ROP may have poorer visual outcomes than the rest(6,7). Risk factors of ROP include lower gestational age, lower birth weight, higher number of days on oxygen, more days in the intensive care unit, exposure to steroids, sepsis, artificial ventilation for more than 7 days, high volume of blood transfusions, exchange transfusions, surfactant therapy, and poor rate of postnatal weight gain(8-10).

Among high risk populations in India, the incidence of ROP is between 20 and 47.27% (11-14). The risk factors of ROP reported from various centers in India are anemia, duration of oxygen therapy, lower gestation and birth-weight, blood transfusion and clinical sepsis(11-13).

Despite the importance of T-ROP, few attempts have been made to identify risk factors among patients with ROP, that

predispose, them to develop T-ROP. The studies on this issue done so far have the following limitations: most studies have compared T-ROP with normal preterms rather than patients with some degree of ROP, some have been uncontrolled studies, some studies have included sub-group analyses or have looked at isolated risk factors(15-19).

The central purpose of any ROP screening program is the early identification and prompt treatment of T-ROP. Hence, if one could identify risk factors among patients with ROP that predispose to the development of T-ROP, it would have important therapeutic implications. With this intention we performed a case controlled study to identify the independent risk factors that are associated with the development of T-ROP among patients with ROP.

Materials and Methods

Ours is a tertiary care referral hospital with a Level III Neonatal Unit: According to our unit's protocol all babies born at a gestation of 32 weeks or less, or have a birth weight of 1700 g or less, or premature babies of any gestation who have received prolonged oxygen therapy ($\geq$ 30 days) are screened for ROP at 4-6 weeks post-natal age. The subsequent screening depends on the initial findings. Threshold ROP (T-ROP) is defined as Stage III ROP with plus disease, involving 5 contiguous or 8 non-contiguous cumulative clock hours in Zone 1 or Zone 2 of the retina.

We reviewed the ROP clinic records of a 3 year period, and identified patients who had ROP, and who had been followed up till complete resolution or till treatment was completed. They were designated as having either T-ROP or Sub-threshold ROP (ST-ROP) on the basis of the most severe grade of ROP they had ever reached. All forms of ROP which fell short of the definition of T-ROP were called ST-ROP. No patient with ST-ROP received treatment for ROP. They were al1 followed up till complete resolution. The T-ROP group constituted the cases and the ST-ROP group constituted the controls.

From the computerized neonatal database, the following variables were extracted-demographic data, antenatal and intranatal data, neonatal morbidity, interventions such as blood transfusions, double volume exchange transfusions, ventilation and phototherapy, and details of the mode, parameters and duration of ventilation.

Univariate analyses were performed for these variables. Students' *t*-test was used for continuous variables with normal distribution, Mann Whitney U test for variables with skewed distributions, and Chi square test with Yates correction and Fisher's exact test for categorical variables. All variables that had achieved significance on univariate analysis were identified, and the 6 most significant variables were subjected to a stepwise forward logistic regression analysis to determine the independent risk factors associated with T-ROP.

Results

A total of 108 subjects with ROP with complete antenatal and neonatal records were identified. Of them, 55 had T-ROP and 53 had ST-ROP. Patients in the two groups had comparable mean gestational ages, mean birth weights, appropriateness for gestational age, sex distribution, antenatal care, mode of delivery and birth asphyxia (*Table 1*). A comparison of the neonatal morbidity showed that the incidence of hypoxic ischemic encephalopathy, sepsis, fungemia, jaundice, hypoglycemia, polycythemia, necrotising enterocolitis, apnea, hyaline membrane

disease, respiratory distress due to any cause, and chronic lung disease (at 28 days chronological age) were not significantly different in the two groups.

Among the therapeutic interventions, however, the administration of packed red cells for anemia and double volume exchange transfusion (DVET) for jaundice or sepsis were significantly more common in the T-ROP group (p = 0.03 and 0.04 respectively). The incidence of extreme prematurity (£ 28 weeks) and ventilation showed a trend towards an increase in the T -ROP group but did not achieve statistical significance. An attempt was made to quantify the impact of some of these variables. It was found that the number of double volume exchange transfusions performed was higher in the T-ROP group, while the number of packed cell transfusions given showed a trend towards an increase in the T-ROP group. The lowest hematocrit was not different between the two groups. The respiratory support required was subjected to detailed analyses. Although the frequency of ventilation was higher in the T-ROP group, there were no significant differences in the maximum value of the following parameters: FiO_2, Positive Inspiratory Pressure, Positive End Expiratory Pressure and PaO_2; and in the durations of oxygen administration, Continuous Positive Airway Pressure adminstration, and mechanical ventilation respectively.

On the basis of the univariate analysis the following variables were selected for forward stepwise multivariate logistic regression analysis: (*a*) Packed cell transfusions for anemia, (*b*) Number of packed cell transfusions, (*c*) DVET, (*d*) Number of DVET, (*e*) Ventilation and (*f*) Gestational age £28 week. Of these, only the administration of packed cell transfusions for anemia [Adjusted Odds Ratio 2.8, 95% Confidence Interval 1.2, 6.4; (p = 0.016)] and DVET [Adjusted Odds Ratio 2.7, 95% Confidence Interval 1.2, 6.6; (p = 0.019)] emerged as independent risk factors of T-ROP.

Discussion

There is paucity of data regarding the

TABLE I–*Comparison of Antenatal and Perinatal Risk Factors.*

Parameter	T-ROP* (n = 55)	ST-ROP** (n = 53)	p value	Odds ratio [95% C.I.]
Gestation in weeks (mean ± SD)	29.82 ± 1.93	30.47± 2.01	0.09	–
Birth weight in grams	1201.75	1250.11	0.38	–
(mean ± SD)	± 267.83	±296.93		
Gestation £ 28 weeks	18 (32.7)	9 (17)	0.06	2.38[0.96-5.92]
Males	32 (58.2)	34 (64.1)	0.53	0.78 [0.36–1.69]
Appropriateness for gestational age	42 (76.4)	34 (64.1)	0.37	1.81 [0.78–4.17]
Antenatal care received	49 (89.1)	46 (86.8)	0.71	1.24 [0.39–3.97]
Birth asphyxia	16 (29.1)	22 (41.5)	0.18	0.58 [0.26-1.28]

Figures in parentheses are percentages
*T ROP: Threshold Retinopathy of Prematurity; ** S TROP: Sub Threshold Retinopathy of Prematurity

TABLE II–*Comparison of interventions and respiratory parameters between T-ROP and ST-ROP.*

Parameter	T-ROP (n = 55)	ST-ROP (n = 53)	p value	Odds ratio [95% CI]
Blood transfusion given	38 [69.1]	26 [49.0]	0:03	2.32 [1.06-5.09]
Number of blood transfusions (median, inter-quartile range)	1 {0,3}	0 {0,2.5}	0.06	–
Lowest hematocrit (median, inter-quartile range)	30 {18, 34}	33 {20, 36}	0.12	–
DVET	25 [45.5.]	14 [26.4]	0.04	2.32 [1.03-5.21]
Number of DVET(median, range)	0 {0,6}	0 {0,1}	0.04	–
Ventilation	35 [63.6]	25 [47.2]	0.08	1.96 [0.91-4.23]
CPAP	23 [41.8]	17 [32.1]	0.32	1.52 [0.69-3.34]
Oxygen administration	40 [72.7]	30 [56.6]	0.12	2.04 [0.34-2.84]
Duration of oxygen administration in days (median, inter-quartile range)	24 {0, 108}	0 {0,92}	0.21	–
Maximum FiO_2 (median, inter-quartile range)	21 {21,50}	21 {21, 47.5}	0.85	–

Figures in curved brackets [ ] are percentages; *T-ROP: Threshold Retinopathy of Prematurity, ** ST-ROP: Sub Threshold Retinopathy of Prematurity

additional risk factors among patients with ROP that predispose to the development of T-ROP(15-19). All the common known risk factors in the development of ROP were included by us in our study. Of them, on multivariate analysis, only two factors emerged as independent predictors of T-ROP.

Our study generated 2 interesting findings. Firstly, those risk factors that have so far been considered to have the strongest associations with ROP (*i.e.*, degree of prematurity, birth weight, and oxygen therapy) could not predict the development of T-ROP among patients with ROP. Secondly, both the risk factors for T-ROP in our study involved the administration of blood products. Anemia, blood transfusions and DVET's have been implicated in the genesis of ROP. It has been hypothesized that the adult hemoglobin, being more capable of releasing oxygen to tissues, causes tissue-level hyperoxia(20-22). The hyperoxia in the tissues leads-on to free oxygen radical release and reflex vasoconstriction leading on to the familiar cascade of events that cause ROP(23,24). Although exposure to blood products was associated with T-ROP in our study, we found that the number of packed cell transfusions, the severtty of the anemia and number of DVET's did not emerge as significantly different between the two groups. Thus "dose responsiveness" to packed cell transfusions or DVET's could not be established, as far as the development of T-ROP is concerned. A prospective study design would be more suited to address the issue of the "dose" of transfusions and DVET.

We hypothesize that the hyperoxia related to adult hemoglobin is quantitatively different from the hyperoxia due to supplemental

Key Message

- Newborn infants with Retinopathy of Prematurity (ROP), have a greater risk of developing threshold ROP if they are exposed to packed cell transfusions or double volume exchange transfusions in the neonatal period.

oxygen administration, by virtue of the fact that the former is unquantifiable, uncontrollable and lasts as long as the transfused adult red cells are viable and circulating. Hence adult hemoglobin has the potential of causing persistent tissue-level hyperoxia, long after the administration of the blood product. ROP is a progressive disease, and one may speculate that T-ROP requires more persistent hyperoxia for its development than all the sub-threshold forms of ROP. Other possible factors that could tip the balance in favour of developing T-ROP could be the release of red cell breakdown products, including iron. These possibilities need further research.

Oxygen therapy in our unit is tightly regulated, and all the personnel working in the NICU are periodically educated about the relationship between hyperoxemia and ROP. The arterial oxygen saturation is continuously monitored by pulse oxymetry and regular arterial blood gases, with the intention of maintaining the pulse oxymeter saturation between 90 and 93% with outer limits of 88 and 95%. Our policy for administering packed cells consists of maintaining the hematocrit above 45 in babies with severe respiratory or hemodynamic compromise, above 40 in babies requiring respiratory or hemodynamic support, above 30 in babies who fail to thrive and above 20 in all babies. We perform DVET's for hyperbilirubinemia according to Cockington's charts, if the serum unconjugated bilirubin crosses 20 mg/dL or if it crosses 1% of the birth weight in grams in very low birth weight babies. DVET's are also performed for some specific indications in severe septicemia.

Unlike oxygen therapy, whose relationship with ROP has been rigourously studied, there is very little literature comparing various criteria for transfusions or DVET, evaluating their impact on ROP(25). It is possible that we are over-transfusing blood to our newborn patients.

Ours, being a case controlled study, had certain limitations. The data collection on the exposure parameters being retrospective, we were not able to study some risk factors in detail. Deaths among patients who may have otherwise been included in the study would introduce an unavoidable sample distortion bias. This bias would differentially exclude sicker and more premature patients, who are also more likely to develop T-ROP. There may have also been instances where indications for transfusions or DVET's deviated from the standard unit protocol, at the discretion of the treating physician, thus introducing an exposure selection bias.

Nevertheless, our study does raise three important issues. Firstly, among patients with ROP there appear to be additional risk factors for T-ROP, secondly these at-risk patients need a closer follow-up, and thirdly we need to consciously restrict transfusions and DVET's. There is a need for prospective randomized trials to evaluate the differences between various regimes of packed cell transfusion and DVET's, with respect to the incidence of ROP, particularly of T-ROP.

Contributors: SD planned the study, analyzed the data and wrote the manuscript, SN collected the data of ROP, AN supervised the drafting of the manuscript, MD performed all the interventions and recorded the data and AG supervised the interventions and drafting the manuscript.

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