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Original Research Article

A study on role of thrombocytopenia in retinopathy of prematurity

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) is one of the causes of avoidable blindness in India. Globally ROP is estimated to affect more than 50,000 infants annually and in India, every year, 500 children are estimated to become blind from ROP. Many a times, lack of trained professionals and lack of timely referral are found to be setbacks in ROP diagnosis and treatment in developing nations. The aim of the study was to study if thrombocytopenia is a risk factor for retinopathy of prematurity and does supplemental oxygen with thrombocytopenia increases the risk of ROP.
Methods: It was a retrospective case control study done in a tertiary care hospital. Data was collected from 177 preterm admitted to NICU over a period of 3 years from March 2015-2018.
Results: A total of 177 preterm admitted to the NICU was included in this study. 77 had ROP and were taken as cases, while 100 were controls. Out of the cases, 55.6% had thrombocytopenia (OR-2.47, p value: 0.003). 89% (n =69) of cases had significant oxygen exposure (OR-8.65, p value 0.0001; 95% CI: 2.00-10.75). Oxygen exposure and thrombocytopenia coexisted in 57% of cases, with 4 times increased risk of ROP (OR-4.51, p value: 0.0001).
Conclusions: Thrombocytopenia is a significant risk factor for retinopathy of prematurity in preterm. The presence of thrombocytopenia with significant oxygen exposure tends to accentuate the risk further. Future prospective studies with long term follow up are warranted to establish other risk factors.

Keywords: Oxygen exposure, Retinopathy of prematurity, Risk factors, Thrombocytopenia, Vascular endothelial growth factor

INTRODUCTION

Retinopathy of Prematurity (ROP) is one of the causes of avoidable blindness in India.[1] It is a multifactorial vaso-proliferative retinal disorder. Globally, ROP is estimated to affect more than 50,000 infants annually. In India, every year, 500 children are estimated to become blind from ROP. The recent advances in neonatal care have led to an increase in the survival of low birth weight infants, hence resulting in a rise of ROP incidence.[2]

The National Neonatology Forum (NNF) guidelines recommend the first screen to be performed not later than 4 weeks of age or 30 days of life in infants ≥28 weeks of gestational age. And they must be screened by the third week of life to enable diagnosis of AP-ROP. Infants <28 weeks or <1200 grams birth weight should be screened early at 2-3 weeks of age, to enable early identification of aggressive Retinopathy of prematurity (AP-ROP).[3]

The clinical spectrum of ROP varies from spontaneous regression to bilateral retinal detachment and total blindness.[4] Increasing rates of preterm births and better survival rates but lack of uniform quality of neonatal care and delays in diagnosis have led to increasing ROP blindness. Blindness from ROP is a rare event in developed countries, while it's an ongoing pandemic in India, that needs standard protocols for screening and prompt treatment. Many times, lack of trained professionals and lack of timely referral are found to be

setbacks in ROP diagnosis and treatment in developing nations.

Pathogenesis of ROP is explained as two stages where the first stage involves an initial insult in the form of hyperoxia, followed by retinal hypoxia, and then finally vascular proliferation. The disease process is mediated by alterations in local Vascular Endothelial Growth Factor (VEGF) and systemic Insulin-like Growth Factor 1 (IGF1). The hypoxia in avascular retina normally induces VEGF secretion, which stimulates growth. However, for the action of VEGF, sufficient serum levels of IGF 1 is required, which is lacking in preterm infants. Due to lack of various maternal sources and endogenous secretion of IGF 1 in preterm infants, VEGF fails to bring about the retinal growth. With time, endogenous production of IGF 1 increases and permit VEGF activity, resulting in proliferative retinopathy. In the second stage, the decrease in oxygenation and upregulation of VEGF, leads to neovascularization. These newly formed vessels are fragile and permeable causing bleeding and edema and also fibrovascular proliferation that can lead on to retinal detachment.[5]

Platelets have various action in our body including pro and anti-angiogenic regulation. Platelets also store, transport and deliver angiogenic factors like VEGF and IGF 1. Hence plays a key role in pathogenesis of ROP. Risk factors such low gestational age, low birth weight and prolonged oxygen exposure has been well studied. However, there are very few studies on other risk factors, although literature has mentioned about various other risk factors predisposing to ROP.[6] Numerous clinical and demographic risk factors for ROP as cited in various literatures include prolonged mechanical ventilation, sepsis, necrotizing enterocolitis and thrombocytopenia. Current treatment for severe retinopathy of prematurity focuses on laser therapy and visual rehabilitation, and potential new treatment strategies include targets within oxidative pathways, erythropoietin, and anti-VEGF agents.[7] Majority of ROP risks are well established and is based on low Birth weight and low Gestational age, however there are "outliers" which continue to confound ophthalmologists and neonatologists.[8] An evidence-based deeper knowledge of the determinants of ROP risk would enable to have effective screening guidelines and prevent under diagnosis of ROP. Jensen et al, in their study states that platelets act as vascular endothelial growth factor scavengers, thereby limiting neovascularization in ROP.[3] Aim of this study was to study thrombocytopenia as an independent risk factor of retinopathy of prematurity and does thrombocytopenia with hyperoxia increase the risk of retinopathy of prematurity.

METHODS

Source of data was preterm neonates admitted in Father Muller Hospital NICU during the period of study, who fulfill the inclusion criteria was taken into consideration.

Method of collection of data

Study design was retrospective case control study. Study period was over a period of 1 year from March 2017-18. Study population was preterm neonates admitted in Father Muller Hospital NICU during the period of study, who fulfill the inclusion criteria was taken into consideration. Sampling technique was time bound study. Includes all neonates fulfilling the inclusion criteria, during the study period was taken into consideration

Collection of data

All preterm admitted in NICU, who had ROP (any stage) was taken as cases and those babies with no ROP as controls. Under each group, those with thrombocytopenia (Platelet count <1,50,000 cumm/L) and without thrombocytopenia was considered. And each group was further evaluated based on the level of oxygen exposure as mentioned by the flow chart below. who had thrombocytopenia (Platelet count <1,50,000 cumm/L) anytime during their stay in NICU was taken as cases, while those who did not have thrombocytopenia was the controls (Figure 1).

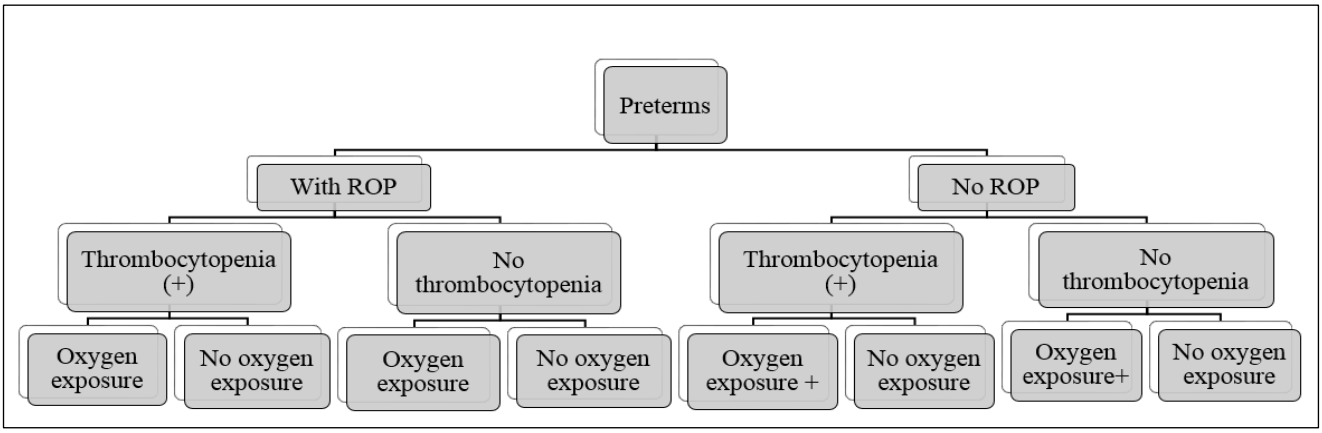

Figure 1: Flowchart-methodology.

Inclusion criteria

- All preterm with ROP admitted in NICU for various reasons.

Exclusion criteria

- Babies not fulfilling the criteria for the study.

RESULTS

Out of 177 preterm included in study, 77 had ROP and were taken as cases, while 100 were controls. 46% of preterm were females while 54% were males (Figure 2).

Thrombocytopenia and ROP

Among 177 preterms, 79 of them had thrombocytopenia. 55.6% of babies who had thrombocytopenia later developed retinopathy of prematurity, while 44% had no ROP (Table 1).

The odd's of developing ROP in presence of thrombocytopenia being 2.47. p value: 0.003 with 95% Confidence Interval (CI): 1.34-4.55. pearson's correlation coefficient being 8.63.

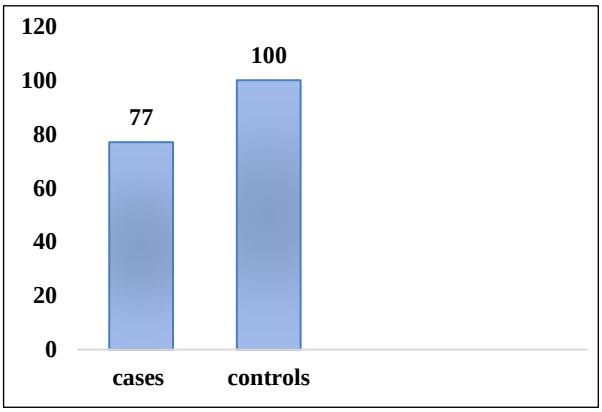

Figure 2: cases-Rop; Controls-No ROP.

Table 1: Thrombocytopenia and retinopathy of prematurity.

	Thrombocytopenia absent	Thrombocytopenia present	Total
Cases (ROP)	33	44	77
Controls (No ROP)	65	35	100
Total	98	79	177

Oxygen exposure and ROP

Among the 77 cases who had ROP, 89% (n=69) of cases had significant oxygen exposure (Table 2) compared to 65% (n=65) of controls. Only 10% (n=8) of cases who had ROP, did not have oxygen exposure.

Table 2: Oxygen exposure and retinopathy of prematurity.

	No oxygen exposure	Oxygen exposure present	Total
Cases	8	69	77
Controls	35	65	100
Total	43	134	177

The Odds of developing ROP in presence of oxygen exposure was 8.65 with a significant correlation coefficient and highly significant p value 0.0001 (95% CI: 2.00-10.75) (Table 2).

Effect of Oxygen exposure and thrombocytopenia on ROP

Among cases who had ROP, 57% (n=44) had both risk factors before the development of ROP.

While among the controls who did not develop ROP, 35% (n=35) had exposure to both risk factors (Table 3). Comparing the cases and controls, who had been exposed to oxygen and had thrombocytopenia before developing ROP. Cases showed a 4-fold increased risk for developing ROP. With a positive correlation coefficient and a significant. Odds ratio: 4.51 (95% CI: 2.33-8.71) p value: 0.0001 (95% CI: 2.00-10.75). Pearsons correlation: 14.33.

Table 3: Oxygen exposure and thrombocytopenia on retinopathy of prematurity.

	No thrombocytopenia / Oxygen exposure	Oxygen exposure/ Thrombocytopenia present	Total
Cases (ROP)	33	44	77
Controls (No ROP)	65	35	100
Total	98	79	177

DISCUSSION

Considering the role of platelets as scavengers of VEGF3, thereby preventing neovascularization, Jensen et al, studied the association of thrombocytopenia and severity of ROP and found significant association of low platelet count during the period of poor retinal growth and hence severity of ROP.

Vinekar et al, showed that a platelet count of <1,00,000 was associated with severe disease.[4] In the retrospective cohort of nine consecutive Indian infants with Aggressive Posterior Retinopathy of Prematurity (APROP) with similar stage and plus disease as the index case, the mean platelet count before laser treatment was compared with 21 age- and birth weight-matched control subjects. They suggested that premature infants who develop retinopathy of prematurity in the setting of low platelet counts may lack the function of either delivering the optimal level or incompletely scavenging the excess of vascular endothelial growth factor A present in APROP, hence leading to severe ROP.

Elizabeth Harnett stated that the effect of lower saturation on mortality was unclear and no consensus exists on optimal oxygen levels to reduce the risk of ROP and assure overall infant health.[7]

In this retrospective case control study, there was a significant association of retinopathy of prematurity with thrombocytopenia and oxygen exposure. The incidence of developing ROP being two to four-fold higher in the presence of these risk factors. In a retrospective 1:1 matched case control study done by Jensen et al, with 91 cases and controls, 25% of cases had thrombocytopenia. Sancak et al, found 71.6% of cases with thrombocytopenia and they had significant association between thrombocytopenia and development of retinopathy of prematurity.[8] This was comparable with this study where 57% of the cases had thrombocytopenia and had significant association with retinopathy of prematurity.

Many studies were conducted worldwide since 1951 and has established oxygen as a risk factor for ROP. A prospective cohort study (TR-ROP) conducted in 69 Neonatal Intensive Care Units (NICUs) in Turkey, to evaluate the prevalence, risk factors and treatment of retinopathy of prematurity (ROP).[9] They studied 6115 infants, of which 27% had any stage of ROP and established total days on oxygen as an independent risk factor for ROP (Odd's-1.023; CI 1.014 to 1.032; p<0.001). In this study authors found the incidence being 89% in cases, with Odd's ratio of 8.65 with highly significant p value 0.0001(95% CI: 2.00-10.75).

In this study authors tried to analyze the risk of developing ROP, when both risk factors existed together, that is, thrombocytopenia and oxygen exposure. The risk increased 4 times. Odds ratio: 4.51 (95% CI: 2.33-8.71) p value: 0.0001 (95% CI: 2.00-10.75). Pearson's correlation: 14.33.

The limitations of this study were thrombocytopenia irrespective of etiology was considered. Retrospective study, further prospective studies are needed to establish the severity of ROP and its association with thrombocytopenia.

CONCLUSION

Analysis of correlation between risk factors and the development of ROP, showed a significant influence of platelet counts as well as supplemental oxygen therapy in development of ROP. Oxygen supplementation with thrombocytopenia had a fourfold increased risk of developing ROP. Thrombocytopenia alone had a twofold increased risk of retinopathy of prematurity.

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REFERENCES

1. Azad R. Prevention of Blindness Due to Retinopathy of Prematurity: A National Movement. Ind J Pediatr. 2014;81:1373-5.
2. Smith LEH. Pathogenesis of retinopathy of prematurity. Seminars Neonatol. 2003;8:469-73.
3. Jensen AK, Ying GS, Huang J, Karp K, Quinn GE, Binenbaum G. Thrombocytopenia and retinopathy of prematurity. J AAPOS. 2011;15(5):447-50.
4. Dutta S, Raghuveer T, Vinekar A, Dogra MR. Can We Stop the Current Epidemic of Blindness From Retinopathy of Prematurity? Ind Pediatr. 2016;53 Suppl 2:S80-4.
5. Fierson WM, Capone A. Telemedicine for Evaluation of Retinopathy of Prematurity. Pediatr. 2015;135(1):e238-54.
6. Casteels I, Cassiman C, Van Calster J, Allegaert K. Educational paper: Retinopathy of prematurity. Eur J Pediatr. 2012;171(6):887-93.
7. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. N Engl J Med. 2012;367(26):2515-26.
8. Port A, Chan R, Ostmo S, Choi D, Chiang MF. Risk factors for retinopathy of prematurity insights from outlier infants. Graefes Arch Clin Exp Ophthalmol. 2014;252(10):1669-77.

9. Bas AY, Demirel N, Koc E, on behalf of the TR-ROP Study Group, et al. incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. Bri J Ophthalmol. 2018;102:1711-6.

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