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Effect of Platelet Transfusion on Retinopathy of Prematurity- Hospital based Prospective Study

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Abstract :Retinopathy of prematurity (ROP) is an important preventable cause of blindness in developing and developed countries. Over all incidence of ROP is 66% and in 2015 ROP among low birth weight infants in India was reported to ranges between 38-51.9%.Throbocytopenia was found to be one of the important risk factor for ROP in earlier studies, as it leads to incomplete scavenging of vascular endothelial growth factor (VEGF) which in turn results in excessive proliferation of retinal vessels. OBJECTIVE: To assess the effect of platelet transfusion in the development of retinopathy of prematurity among the preterm infants admitted in tertiary care centre.MATERIAL AND METHODOLOGY: A prospective cohort study was conducted a period of 18 months among Preterm infants'≤34 weeks who were screened for ROP. Follow up was done as per early treatment of ROP guidelines and regression/progression in the stage of ROP was monitored.RESULTS: Among 136 infants 72 were females. Very low birth weight infants predominantly contributes to 53.7% (n=73) of the study population. Mean birth weight was 1473±309 grams. The mean gestational age among the study group was 32.30 weeks±1.71. The incidence of ROP was found to be 25%. Stage 2 ROP is predominantly seen and contributes to 70.5% in ROP infants. The ROC curve of thrombocytopenia shows that with a cut off value of 30,000/micro litre specificity was 70.6% and sensitivity was 74.7%. Platelet transfusion if given for platelet count less than 40000/micro litre was found to be a protective factor in the development of ROP with an odds ratio of 3.671(95% CI, 1.215-11.097).

Key words : ROP , Prematurity , Platelet transfusion

INTRODUCTION

A proliferative retinopathy of immature retina in preterm infants is due to inadequate vasculogenesis at the time of birth.[1,2] Increased survival of preterm infants due to advances in neonatology and improved awareness regarding the retinopathy of prematurity (ROP) screening contributes to more incidence of ROP.[3]ROP is an important preventable cause of blindness in developing and developed countries.[4] Identifying and screening at risk premature infants performed by an experienced ophthalmologist remains the most important strategy in the management of ROP.[5]Over all incidence of ROP is 66%. Out of this moderately severe ROP contributes to 18% and severe ROP contributes to 6%.[3] In India the incidence of ROP was reported in many studies. In 2015 Praveen et al reported the occurrence of ROP in low birth weight infants ranges between 38-51.9%.[6]ROP develops due to multiple

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risk factors like prematurity, low birth weight, oxygen exposure, hypoxia, intraventricularhemorrhage, surfactant therapy, blood transfusion, thrombocytopenia and sepsis.[6] The degree of prematurity has inverse relationship with ROP incidence and severity; hence infants born less than 28 weeks of gestation have more incidence and more severity than the higher age group.[7] Similarly 50% infants weighing less than 1250 grams at birth show evidence of ROP and 10% of the infants develop sever ROP.[8]Number of attempts has been made to minimize the risk factors in the development of ROP. Throbocytopenia was found to be one of the important risk factor for ROP in earlier studies, as platelets control the angiogenesis of retinal vessels by scavenging of growth factors of ROP like vascular endothelial growth factor (VEGF). Thrombocytopenia leads to incomplete scavenging of VEGF which in turn results in excessive proliferation of retinal vessels.[2] Spontaneous regression of ROP by correcting the thrombocytopenia with platelet transfusion was reported in literature as a case report and retrospective case control study. Hence further studies are required to find out the association of platelet transfusion with retinopathy of prematurity.[9] Early recognition by regular screening, timely follow up and early treatment as per standard guidelines are the keys in effective management of ROP. With this background we planned a study to evaluate the association of ROP and platelet transfusion. We also studied the proportion of ROP among the hospitalized premature infants ≤34 weeks of gestational age and clinic-epidemiological correlates like oxygen administration, sepsis, surfactant administration, antenatal steroid administration, packed red blood cell transfusion, platelet transfusion, mechanical ventilation and maternal risk factors among the study subjects.

MATERIALS AND METHODS

This Prospective cohort study was conducted atGovernment Lady Goshen hospital and Regional Advanced Pediatric Care Centre, aPaediatric block of Government Wenlock hospital, Mangalore .Preterm infants'≤34 weeks who were screened for ROP in Lady Ghoschen hospital and Regional advanced pediatric care hospital from September 2019 to February 2020 were included in the study after written informed consent from the parent or guardian. Infants who had congential abnormalities of the eye were excluded.History, risk factors, details regarding platelet transfusion and blood transfusion were recorded in the semi structured proforma. Gestational age was calculated by New Ballard Score. Pupils were dilated using Cyclopentonate and phenylephrine eye drops 3 times with 10 min interval before screening. Babies were screened by trained RETCAM technician and results were analyzed by an ophthalmologist. Follow up was done as per early treatment of retinopathy of prematurity guidelines. Regression/progression in the stage of ROP was monitored. The babies who had severe ROP were treated with LASER therapy and intravitrealBevacizumab.

Based on the severity, ROP has been described in five stages.[10]

Stage 1: It is defined by a demarcation line, which looks like a flat and white line commonly denoted as abnormal branching or arcading of retinal vessels that separates vascularised from the avascular retina.

Stage 2:Stage 2 is characterized by a ridge, which is increased in volume, length and width of demarcation line beyond the retinal surface.

Stage 3:Stage 3 is characterized by the existence of a ridge with growth of extra retinal fibro vascular tissue.

Stage 4:Stage 4 is characterized by subtotal retinal detachment: 1) Which involves macula 2)Not involving macula

Stage 5:Stage 5 is characterized by total retinal detachment: 1) with an open funnel 2) with a closed funnel

Outcome measures:

1. Progression/regression of ROP
2. Requirement of treatment

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Data analysis: Date collected were entered in excel spread sheet. SPSS version (statistical package for social science) 17.0 was used to do the analysis.Comparison between epidemiological correlates was done by chi square test, fisher exact test, and multiple regression analysis.P<0.005 was considered significant statistically.

The study was reviewed and approved by the institutional ethical committee

RESULTS AND ANALYSIS:

136 babies who satisfied the inclusion criteria were enrolled in the study.

Among 136 infants 72 (52.9%) were females and 64 (47.1%) were males. Female: male ratio was 1.125. Birth weight ranges from 800 grams to 2360 grams. Very low birth weight infants predominantly contributes to 53.7% (n=73) of the study population. Mean birth weight was 1473±309 grams. Birth weight of 1250 grams contributes to 25^{th} percentile, 1500 grams corresponds to 50^{th} percentile and 1700 grams corresponds to 75^{th} percentile.

The gestational age ranges from 26 weeks to 34 weeks. The mean gestational age among the study group was 32.30 weeks±1.71. Among the study population majority was contributed by infants born between 33 weeks to 34 weeks of gestation.

The incidence of ROP was 25% that is 34 infants out of 136 infants were diagnosed with ROP

On univariate analysis extremely low birth weight, gestational age less than 28 weeks, oxygen exposure, surfactant administration, packed red blood cell transfusion, thrombocytopenia were found to be statistically significant risk factors. On multiple regression only oxygen exposure was found to be significant risk factor for retinopathy of prematurity. (Table I and II)

Stage 2 ROP is predominantly seen and contributes to 70.5% in ROP infants.33 had ROP among 100 infants who had thrombocytopenia and 1 had ROP among the 36 infants who did not have ROP.

Out of 136 infants 40 received platelet transfusion (Table III). In platelet transfusion group 18 infants (45%) had ROP and 22(55%) did not have ROP (P=0.001). On multivariate analysis odds ratio for platelet transfusion was 3.671(95% CI, 1.215-11.097). (Table IV)

In this study platelet transfusion in earlier days of life and more number of platelet transfusions in infants was associated with less incidence of ROP. Platelet transfusion found to be a protective factor in the development of ROP in the present study.

ROC curve for platelet transfusion:

ROC curve of platelet transfusion shows cut off for platelet transfusion in thrombocytopenia is <40000/micro litre, the specificity is 50% and the sensitivity is 84.5%. The area under the curve is 0.944, which implies the platelet transfusion if given for platelet count less than 40000/micro litre act as a protective factor in the development of ROP. (Figure I)

FOLLOW UP:

Out of these 136 infants, 34 infants had ROP. 9 babies had severe ROP which required treatment in the form of intra vitrealBevacizumab(1), laser photocoagulation(8). Of the 8 neonates who was treated with laser had persistent ROP for which vitrectomy was done. Post treatment babies were followed up till the completion of treatment. Remaining babies achieved complete vascularisation and underwent spontaneous regression of ROP.

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DISCUSSION

136 infants were screened for ROP out of which 34 infants had ROP. The incidence of ROP was found to be 25% in the present study. ROP is a well-known preventable cause of blindness and other visual morbidities. The advanced neonatal care and invention of tele machine to screen ROP contributes to early identification and increased diagnosis of ROP in infants. Literature was reviewed and the incidence of ROP was analyzed with the recent studies. Sumru et al[11]documented that preterm SGA was associated with more incidence of ROP.On analysis of risk factors gestational age ≤28 weeks (p=0.005), extremely low birth weight (P=0.000), oxygen therapy(0.000), surfactant administration(0.006), thrombocytopenia(0.000), packed red blood cell transfusion (0.000) were found to be statistically risk factors for ROP which was consistent with the previous studies.[11-14]Tao et al[15] studied the association of mean platelet volume and platelet count with ROP, high mean platelet volume associated with occurrence of type 1 ROP, large platelets are metabolically and enzymatically more active which results in release of more proangioenic and antiangiogenic materials from α granules. Thrombocytopenia leads to incomplete sequesteration of VEGF and results in more incidence of ROP.[15,16]

Thrombocytopenia was one of the most important risk factor for ROP in our study. Annie et al conducted explanatory case control study to find the association of thrombocytopenia in the development of ROP, they found thrombocytopenia (platelet count <150000/ micro litre) was closely associated with zone 1 ROP. But singles platelet count closely preceding laser treatment within a week of laser therapy was considered. 23 cases had thrombocytopenia out of the 91 cases (p=0.034), odds ratio is 2.38(95% CI, 1.04-5.43). In the present study the lowest platelet count was considered. Platelet count <150000/micro litre was considered for analysis of thrombocytopenia as a risk factor. 33/67 infants (49.2%) had ROP among the thrombocytopenic group and 1/35(2.8%) infants in non-thrombocytopenic group. Mean platelet count found in ROP cases was 54045/micro litre with standard deviation-±45446/micro litre.

In this study thrombocytopenia significantly contributes to development of ROP (P=0.000). Eliminating the association of other risk factors was done by multiple regression analysis. Odds ratio for thrombocytopenia and ROP was found to be 20.9(95% CI, 1.99-219.55).

In 2010 Vinekar el al[9] reported a case of spontaneous regression of aggressive posterior ROP with plus disease following correction of thrombocytopenia by platelet transfusion. It was found that newly transfused platelets serve anti-angiogenic factors which help in regression of ROP by effective sequesteration of VEGF. In the present study on analysis platelet transfusion played a protective role in the development of ROP. On multiple regression analysis odds ratio for platelet transfusion in early days of life (<5 days) showed less incidence of ROP (p=0.000). Infants who received 3 or more platelet transfusion showed less number of ROP than 1,2 platelet transfusion groups(p=0.004) which implies adequate correction of thrombocytopenia is necessary to reduce the risk of development of ROP. In this study, on analysis platelet transfusion was observed to have protective role on ROP incidence.

The incidence of ROP in this study is 25%. Prematurity, low birth weight, oxygen exposure, surfactant administration, thrombocytopenia were the statistically significant risk factors for the development of ROP while antenatal risk factors like PPROM, preeclampsia, PIH, GDM, antenatal steroid, gender did not influence the development of ROP. Thrombocytopenia is one of the most important risk factor for ROP. Platelet transfusion is found to be a protective factor in the development of ROP is our study. Adequate platelet transfusion in early days of life is associated with reduced incidence of ROP.

The limitation of this study was that it was conducted only in government hospitals of Mangalore and it does not reflect the overall incidence of ROP in the region. Further studies are required with larger number of neonates from multiple centres to confirm the protective role of platelet transfusion in the development of ROP.

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Table I: Univariate analysis of risk factors associated with ROP

Characteristics		ROP		χ^2	P value
		Present	Absent		
Sex	Male	12(18.75%)	52(81.25%)	2.519	0.113
	Female	22(30.56%)	50(69.44%)		
Birth weight	LBW	10(17.86%)	46(82.14%)	15.290	0.000
	VLBW	18(24.66%)	55(75.34%)		
	ELBW	6(85.71%)	1(14.29%)		
Gestational age	≤28 weeks	2(40%)	3(60%)	9.442	0.009
	29-32 weeks	24(40%)	36(60%)		
	33-34 weeks	10(14.08%)	61(85.92%)		
Premature rupture of membranes		6(42.8%)	8(57.2%)	2.654	0.103
Preeclampsia		7(29.2%)	17(70.8%)	0.270	0.603
Pregnancy induced hypertension		6(33.4%)	12(66.6%)	0.768	0.381
Gestational hypertension		1(20%)	4(80%)	0.069	0.792
Twin pregnancy		6(18.2%)	27(81.8%)	1.080	0.299
Antenatal steroids		18(32.2%)	38(67.8%)	2.590	0.108
Oxygen		33(34.7%)	62(65.3%)	15.934	0.000
Mechanical ventilation		7(38.8%)	11(61.2%)	1.366	0.243
Surfactant		11(47.8%)	12(52.2%)	7.692	0.006
Sepsis		23(31%)	51(69%)	3.201	0.74
Packed red blood cell transfusion		13(59%)	9(41%)	16.268	0.000
Thrombocytopenia		33(33%)	67(67%)	12.895	0.000

Table II: Multiple regression analysis of statistically significant risk factors

Characters		Odds ratio	95% CI		P value
			lower	Upper	
BW	LBW				0.237
	VLBW	15.857	0.649	387.517	0.09
	ELBW	16.129	0.563	462.247	0.104
Gestational age	≤28 weeks	1.663	0.207	13.351	0.632
	29-32 weeks	0.548	0.177	1.694	0.296
	33-34 weeks				0.406

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Oxygen exposure	20.159	2.382	170.591	0.006
Surfactant therapy	0.531	0.150	1.876	0.363
Packed RBC transfusion	0.417	0.087	1.994	0.273
Thrombocytopenia	20.921	1.993	213.519	0.11

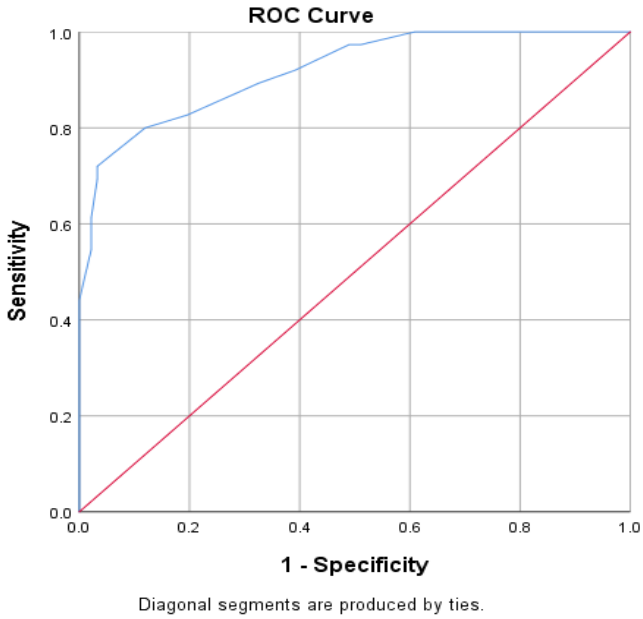
Table III: INCIDENCE OF THROMBOCYTOPENIA

Variables		Frequency	Percentage
Thrombocytopenia (N=136)	Present	100	73.5
	Absent	36	26.5
Platelet transfusion (N=136)	Done	40	29.4
	Not done	96	70.6

Table IV: Association of platelet transfusion and ROP

	ROP		Chi square	P value	Odds ratio	95% CI	
	Present	Absent				Upper	Lower
Platelet transfusion	18(45%)	22(55%)	12.089	0.001	3.671	1.215	11.097

Figure I: ROC curve for platelet transfusion



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