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Original Research Article

Study of risk factors of neonatal thrombocytopenia

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ABSTRACT

Background: Neonatal thrombocytopenia (platelet count < 1.5 lac/µl) is the commonest haematological abnormality encountered in neonatal intensive care unit (NICU). Thrombocytopenia if not detected can result in devastating complications. Determining the risk factors of thrombocytopenia enables us to prevent the inevitable and irreversible complications. The present study highlights the pattern, severity and risk factors of neonatal thrombocytopenia in our hospital.
Methods: Prospective observational study was conducted on 200 neonates with thrombocytopenia admitted in NICU of our hospital. Maternal and neonatal risk factors were recorded. Neonates were grouped based on the severity of thrombocytopenia. The risk factors were compared with severity of thrombocytopenia.
Results: 200 neonates with thrombocytopenia were divided into three groups based on severity of thrombocytopenia. 81% of babies had moderate to severe thrombocytopenia. The most common maternal predisposing factors were pregnancy induced hypertension (PIH), premature rupture of membranes (PROM) and anemia.62.5% babies were low birth weight babies and they had severe thrombocytopenia. 56% babies had late onset neonatal thrombocytopenia and 44% had early onset thrombocytopenia. The most common neonatal risk factors were sepsis in 48.5% babies and birth asphyxia in 20% babies.
Conclusions: The severity of neonatal thrombocytopenia in our NICU was moderate to severe type. PIH, PROM and anemia were the commonest maternal risk factors. Preterm and low birth weight babies had severe thrombocytopenia. Sepsis and birth asphyxia were the commonest neonatal risk factors. Birth asphyxia was associated with early onset neonatal thrombocytopenia and sepsis was associated with late onset thrombocytopenia. Severe thrombocytopenia can be used as a prognostic indicator in sick neonates.

Keywords: Neonatal thrombocytopenia, Neonatal intensive care unit, Prematurity, Sepsis

INTRODUCTION

Thrombocytopenia (platelet count < 1,50,000/µL) is one of the most common haematological problems in neonatal intensive care units (NICUs).[1] The overall prevalence of thrombocytopenia in neonates ranges from 1 to 5% and is reported to be much higher in neonates admitted to neonatal intensive care units, ranging from 22 to 35%.[1] It is more common among extremely low birth weight neonates, preterm or sick neonates in NICUs. In contrast, only 2% of the normal neonates are thrombocytopenic at birth with Severe thrombocytopenia (platelet count < 50,000/L) occurring in less than 3/1000 term infants.[2]

Multiple disease processes can cause thrombocytopenia in neonates and these can be classified as early onset (<72 hours) and late onset (>72 hours) neonatal thrombocytopenia.[3] The important causes of thrombocytopenia in neonates are sepsis, birth asphyxia, prematurity, intra-uterine growth retardation,

hyperbilirubinemia, respiratory distress syndrome, meconium aspiration syndrome and low birth weight. Apart from platelet counts, bleeding manifestations depend on underlying ailments.[4]

Detection of thrombocytopenia is a useful initial assessment for sick neonates and it is considered as one of the complication of the disease process, but in some cases thrombocytopenia is detected accidentally. Though thrombocytopenia is so prevalent it is often ignored in the assumption that it will resolve spontaneously. However if it is not detected and managed properly can result in devastating complications.[4]

The paucity of studies from India and the increasing prevalence of this condition in our NICU, instigated us to determine the maternal and neonatal risk factors and severity of thrombocytopenia in the neonates admitted to NICU in our hospital, AVBRH, Jawaharlal Nehru Medical College, DMIMS, Sawangi, Wardha, Maharashtra, India. The aim of the study was to study the maternal and neonatal risk factors, pattern and severity of neonatal thrombocytopenia.

METHODS

A prospective observational study was done on 200 neonates with thrombocytopenia admitted in the neonatal intensive care unit of Department of Pediatrics of Acharya Vinoba Bhave Rural Hospital, Sawangi over a period of two years i.e August 2014 to July 2016. All newborns admitted in NICU (inborn/outborn) of AVBRH with or developed neonatal thrombocytopenia during the course of study period were included .Neonates whose parents or guardians who do not agree to be a part of study were excluded. Ethical clearance was obtained from institutional ethics committee.

Method of collection of data

At admission the parents and/or the guardian were informed about the study and written consent was obtained. A detailed history inclusive of maternal obstetric history, birth history, perinatal events with a focus on history suggestive of bleeding and its type in the newborn was obtained as per the proforma. Information regarding a number of conditions that have been implicated by past studies to be associated with neonatal thrombocytopenia was prospectively recorded e.g history of PIH, gestational diabetes mellitus, premature rupture of membranes, anemia, history of drug intake in the mother was asked for.

Gestational age of all neonates was determined based on the New Ballard's scoring system till 14 days of life. In neonates beyond 14 days, birth records were studied to know about the gestation. Growth assessment at birth or admission by recording birth weight to detect intrauterine growth restriction was based on growth charts. All the neonates underwent necessary blood investigations as complete blood count, platelet count, peripheral smear study, blood culture and Septic screen. Blood was collected in sterile EDTA bulbs by venepuncture after taking all aseptic precautions and transferred to Central Laboratory of our hospital, the time lag between collection and estimation was usually 10 to 15 minutes.

CBC was obtained from an automated haematology analyser. The automated haematology analyser used in our laboratory was sysmex kx-21. Peripheral smear study, blood cultures were done using standard laboratory methodology. Low platelet counts were cross verified by peripheral smear study. Quantitative determination of CRP was done by latex turbidimetry using SPINREACT CRP- TURBILATEX. Micro ESR was done using micropipette and value more than day of life+3 mm/1st hour was considered positive.

A septic work up inclusive of absolute neutrophil count, total WBC count, micro ESR, C reactive protein was done on all patients. If any two of the above mentioned were positive then the neonate was labelled as having septicemia. In most of the cases with severe thrombocytopenia investigations such as prothrombin time (PT), aPTT were done by automated CL analyser. Platelet counts were repeated every 24 hours in babies with severe thrombocytopenia and every 48hrs in those with moderate thrombocytopenia.

Due to lack of laboratory facility, tests for platelet allo immunization were not conducted on all suspected cases as per recommendations. All diagnoses were based on standard diagnostic criteria laid down in indexed medical literature. All the neonates were managed according to standard NICU protocol as per recent recommendations in the medical literature.

The next step was to group the neonates, based on their lowest platelet counts as follows

Definition of the various groups

- Group 1/mild thrombocytopenia 1- <1.5lacs/ μL
- Group 2/moderate thrombocytopenia 50,000 to <1 lac/ μL
- Group 3/severe thrombocytopenia <50,000/μL

The pattern of onset of neonatal thrombocytopenia was classified as early if it developed <72 hours of birth and late onset if presented after 72 hours. Maternal and neonatal risk factors were analysed with respect to severity of thrombocytopenia. The data so collected was recorded in the case proforma, tabulated and statistically analysed.

Statistical analysis

Statistical analysis was done using description and inferential statistics using chi square test, one way ANOVA test, student's t-test. Software used for analysis

was SPSS 17.0 version, graphpad, prism 6 version and EPI-INFO 6 version.

'P' value below 0.05 was considered significant.

RESULTS

200 newborns with thrombocytopenia admitted in our NICU were divided into 3 groups based on their platelet counts. (Table 1) Out of 200 babies, 112 (56%) were male babies and 88 (44%) were females. We found a larger proportion of male babies (1.27:1 male to female ratio). Male gender was associated with moderate and severe thrombocytopenia, however it was statistically not significant (p value 0.23). Among maternal risk factors, PIH (pregnancy induced hypertension) was the commonest cause. 27 (13.5%) babies had PIH as the maternal risk factor followed by PROM in 15 (7.5%) babies, Anemia in 11 (5.5%) babies, oligohydramnios in 8 (4%) babies and eclampsia in 6 (3%) babies. All these risk factors were associated with severe thrombocytopenia. Among all these factors, association of PROM and anemia with severe neonatal thrombocytopenia was statistically significant (P value 0.0022 and 0.01).

Table 1: Distribution of babies in to 3 groups according to severity.

Groups	Severity	N = 200	Percentage
Group 1	Mild (1- <1.5lacs/µl)	38	19%
Group 2	Moderate (50,000-<1 lac/µl)	87	43.5%
Group 3	Severe (<50,000/µl)	75	37.5%

Table 2: Distribution of patients in three groups according to their maternal risk factors.

Maternal factors		Group			Total	⨯2-value	p-value
		Group 1	Group 2	Group 3			
PIH	Yes	6 (15.79%)	9 (10.34%)	12 (16%)	27 (13.5%)	1.99	0.36, NS
	No	32 (84.21%)	78 (89.66%)	63 (84%)	173 (86.5%)		
Eclampsia	Yes	2 (5.26%)	1 (1.15%)	3 (4%)	6 (3%)	2.69	0.26, NS
	No	36 (94.74%)	86 (98.85%)	72 (96%)	194 (97%)		
PROM	Yes	0 (0%)	6 (6.90%)	9 (12%)	15 (7.5%)	10.25	0.0022, S
	No	38 (100%)	81 (93.10%)	66 (88%)	185 (92.5%)		
Anaemia	Yes	0 (0%)	4 (4.60%)	7 (9.33%)	11 (5.5%)	9.14	0.010, S
	No	38 (100%)	83 (95.40%)	68 (90.67%)	189 (94.5%)		
Oligo	Yes	1 (2.63%)	3 (3.45%)	4 (5.33%)	8 (4%)	0.75	0.68, NS
	No	37 (97.37%)	84 (96.55%)	71 (94.67%)	192 (96%)		

Table 3: Distribution of patients in three groups according to their etiology (neonatal factors).

Etiology		Group			Total	⨯2-value	p-value
		Group 1	Group 2	Group 3			
Sepsis	Yes	8 (21.05%)	39 (44.83%)	50 (66.67%)	97 (48.5%)	42.90	0.0001, S
	No	30 (78.95%)	48 (55.17%)	25 (33.33%)	103 (51.5%)		
Birth asphyxia	Yes	8 (21.05%)	19 (21.84%)	13 (17.33%)	40 (20%)	0.87	0.64, NS
	No	30 (78.95%)	68 (78.16%)	62 (82.67%)	160 (80%)		
RDS	Yes	2 (5.26%)	9 (10.34%)	3 (4%)	14 (7%)	3.48	0.17, NS
	No	36 (94.74%)	78 (89.66%)	72 (96%)	186 (93%)		
NNH	Yes	15 (39.47%)	16 (18.39%)	8 (10.67%)	39 (19.5%)	24.23	0.0001, S
	No	23 (60.53%)	71 (81.61%)	67 (89.33%)	161 (80.5%)		
MAS	Yes	5 (13.16%)	4 (4.60%)	1 (1.33%)	10 (5%)	12.59	0.0001, S
	No	33 (86.84%)	83 (95.40%)	74 (98.67%)	190 (95%)		

Babies with low birth weight (<2.5 kg) constituted 125 (62.5%) of total babies and babies with birth weight ≥2.5 kg constituted 75 (37.5%) of total babies with neonatal thrombocytopenia. Low birth weight was significantly associated with moderate to severe thrombocytopenia (P value 0.007). According to gestation, 84 (41%) were preterm, appropriate for gestation babies, 4 (2%) were pre term, small for gestation babies, 95 (47.5%) were full term, appropriate for gestation and 17 (8.5%) were full term, small for gestation babies. Full term babies had moderate thrombocytopenia and preterm babies had severe neonatal thrombocytopenia which was statistically

significant (P value 0.014) According to onset of neonatal thrombocytopenia, 88 (44%) babies had early onset neonatal thrombocytopenia and 112 (56%) babies had late onset neonatal thrombocytopenia. Late onset neonatal thrombocytopenia was more common and it was associated with moderate to severe neonatal thrombocytopenia, however it was statistically not significant (P value 0.958).

Among multiple neonatal risk factors, sepsis was the most common cause of neonatal thrombocytopenia and was found in 97(48.5%) babies. Birth asphyxia was present in 40(20%) babies, RDS (respiratory distress syndrome) in 14(7%) babies, NNH (neonatal hyperbilirubinemia) in 39(19.5%) babies and MAS (meconium aspiration syndrome) in 10 (5%) babies. Sepsis was associated with severe neonatal thrombocytopenia and it was statistically significant (P value 0.0001). Birth asphyxia was associated with moderate neonatal thrombocytopenia; however it was statistically not significant (P value 0.64). NNH and MAS were associated with mild to moderate neonatal thrombocytopenia and it was statistically significant (P value 0.0001). Out of 97 babies with sepsis, 64 (57.14%) babies significantly had late onset neonatal thrombocytopenia (P value 0.007). Out of 40 babies with birth asphyxia, 27 (30.68%) babies significantly had early onset neonatal thrombocytopenia (P value 0.001).

DISCUSSION

Neonatal thrombocytopenia (platelet count <1.5lacs/µl) is one of the commonest haematological abnormality encountered in NICU but may be missed if not specifically looked for. If it is not detected and managed properly can result in severe complications. We have conducted a prospective observational study on 200 neonates with thrombocytopenia admitted in NICU of Acharya Vinoba Bhave Rural Hospital. The present study highlights the maternal and neonatal risk factors, pattern and severity of neonatal thrombocytopenia in a tertiary care hospital.

Demographic features

Out of 200 newborns with thrombocytopenia admitted in our NICU, subjects were divided into 3 groups based on their platelet counts. Moderate and severe thrombocytopenia together constituted 81% of total thrombocytopenic babies. In studies conducted by khalessi et al, Ghamdi et al and Gupta et al, mild thrombocytopenia was more common.[3,7,8] In a study conducted by Nandyal et al on 99 neonates, severe thrombocytopenia was present in 65.6% of babies and in Bonifacio et al study, severe thrombocytopenia was present in 51% of babies.[9] The results in our study were similar to studies conducted by Nandyal et al and Bonifacio et al. The high prevalence of moderate and severe thrombocytopenia in our study was probably because of higher proportion of septicemic babies in our NICU which is also a referral centre.[4]

In this study the proportion of male babies with thrombocytopenia was more as compared to female babies (Male:Female ratio 1.27:1).Similar results were seen in a study conducted by Basil et al in which proportion of male babies with thrombocytopenia was more than that of female babies (1.37:1).[10] The high proportion of male babies with thrombocytopenia in our study is probably due to high incidence of sepsis among male babies. Khalessi N et al, Sheikh MA et al, Chandra A et al, Antoniette BWM et al, Schuchat A et al, Kuruvilla KA et al noted that the incidence of neonatal sepsis was higher in males than female neonates.[7,12-15] This is probably due to the fact that the factors regulating the synthesis of gamma globulin are situated on the X-chromosome and male has only one X-chromosome.[12]

Maternal risk factors

In this study, PIH was the commonest maternal risk factor. 27 (13.5%) babies had PIH as the maternal risk factor and it was associated with severe thrombocytopenia.In studies conducted by khalessi et al and patil et al, the percentage of babies with PIH as maternal risk factor was 17.7% and 72.17%.[7,16] The thrombocytopenia associated with PIH is almost always mild to moderate and caused by decreased platelet production as the main mechanism and decreased concentrations of circulating megakaryocyte progenitors. In this study, PIH was associated with severe thrombocytopenia. Other maternal risk factors in our study were PROM in 15 (7.5%) babies, anemia in 11 (5.5%) babies, oligohydramnios in 8 (4%) babies and eclampsia in 6 (3%) babies. All these risk factors were associated with severe thrombocytopenia. Among all these factors, association of PROM and anemia with severe neonatal thrombocytopenia was statistically significant. In a study conducted by Oren et al, an association has been documented between PROM and thrombocytopenia which was similar to results in our study.[17] PROM in mother is a cause of early onset neonatal sepsis eventually leading to neonatal thrombocytopenia.

Neonatal factors

In our study, out of 200 babies, 125 (62.5%) were low birth weight babies and 75 (37.5%) were babies with birth weight ≥2.5kg. Low birth weight babies significantly had severe thrombocytopenia and babies with birth weight ≥2.5kg had moderate thrombocytopenia. Our results were similar to studies conducted by khalessi et al in which 59.1% babies with thrombocytopenia were low birth weight babies.[7] Studies conducted by Charoo BA et al and Robert and Murray1 also state that neonatal thrombocytopenia was more common among low birth weight babies.[18] Gupta AK et al stated that LBW babies showed statistically significant

thrombocytopenia due to their limited ability to compensate for accelerated destruction of platelets.[19] Placental transport of IgG from maternal to fetal circulation increases with maturity and this transport is hampered in low birth weight babies which make them more prone for sepsis.[27]

In this study, 84 (41%) were preterm, appropriate for gestation babies, 4 (2%) were pre term ,small for gestation babies, 95 (47.5%) were full term, appropriate for gestation and 17 (8.5%) were full term, small for gestation babies. Full term babies had moderate thrombocytopenia and preterm babies had severe neonatal thrombocytopenia which was statistically significant.

In contrast to other studies, we had more number of full term babies with thrombocytopenia, this was probably because of proportionately more number of full term admissions than preterm admissions in our NICU during the study period. This is also because of the fact that most of the term neonates in our study were sick and septicemic in relation to their premature counterparts since many normal pre-terms were admitted for preterm care and their respective platelet counts may not reflect upon that of the normal term neonates.

However the preterm babies in our study had severe thrombocytopenia. Prematurity it is a risk factor for thrombocytopenia due to decreased platelet production and when this was associated with sepsis the increased consumption of platelets further contributed to severe thrombocytopenia. In studies conducted by Nandyal et al, Charoo BA et al, prematurity was associated with severe thrombocytopenia.[4,10,18]

Among multiple neonatal risk factors, sepsis was the most commonest cause of neonatal thrombocytopenia which was found in 97 (48.5%) babies and was associated with severe neonatal thrombocytopenia. The percentage of sepsis among thrombocytopenic babies in nandyal et al study was 22.2%, Gupta et al study was 42% and khalessi et al study was 24.1%.[4,3,7] In studies conducted by Patil et al, Basil and Zaccheaus et al, sepsis was associated with severe thrombocytopenia which was similar to the results in our study.[10,16,21] Septicemia leads to thrombocytopenia due to both decreased production and increased consumption of platelets and hence results usually in severe thrombocytopenia.

Birth asphyxia was present in 40 (20%) babies, NNH in 39 (19.5%) babies, RDS in 14 (7%) babies and MAS in 10 (5%) babies. Birth asphyxia was associated with moderate to severe neonatal thrombocytopenia. Neonates with birth asphyxia have impaired megakaryopoiesis and platelet production. In studies conducted by Nandyal et al and Gupta et al, birth asphyxia was associated with severe thrombocytopenia which was similar to present study.[3,4] NNH and MAS were associated with mild to moderate neonatal thrombocytopenia and it was statistically significant (P value 0.0001). In Gupta et al study and Nandyal et al study, NNH and MAS were associated with mild thrombocytopenia which was similar to our study.[3,4]

Another study conducted by Boskabadi et al on incidence of thrombocytopenia in idiopathic hyperbilirubinemic newborns also showed that 86.4% of babies with NNH had mild thrombocytopenia.[22] In a study conducted by Khera et al on incidence of thrombocytopenia following phototherapy in hyperbilirubinemic neonates, an association of phototherapy as a cause of thrombocytopenia in hyperbilirubinemic neonates was established.[23] Zieve et al demonstrated effects of high intensity white light on human platelets in vitro. Maurer et al and pishwa et al observed in their studies that neonates exposed to phototherapy had decreased platelet counts and increased platelet turn over.[25,26]

CONCLUSION

Neonatal thrombocytopenia is a common clinical entity in NICU and a prognostic marker of many disease conditions in neonates. The severity of neonatal thrombocytopenia in our NICU was moderate to severe type. Late onset neonatal thrombocytopenia i.e onset of thrombocytopenia after 72 hours was more common than early onset neonatal thrombocytopenia. Low birth weight babies were more prone to severe thrombocytopenia. Preterm babies had severe thrombocytopenia whereas term babies had moderate thrombocytopenia.

The most common maternal predisposing factors were pregnancy induced hypertension (PIH), premature rupture of membranes (PROM) and anemia. Sepsis and birth asphyxia were the commonest neonatal factors associated with thrombocytopenia followed by neonatal hyperbilirubinemia, respiratory distress syndrome and meconium aspiration syndrome. Sepsis was associated with late onset thrombocytopenia and birth asphyxia was associated with early onset thrombocytopenia.

Severe thrombocytopenia can be used as a prognostic indicator in sick neonates. But to generalize this statement and apply to all neonatal admissions, more studies are required in this regard with similar results. Neonatal thrombocytopenia is a treatable and reversible condition. Hence it is important to identify neonates at risk and initiate appropriate therapy to prevent severe bleeding and potentially significant morbidity. Babies born to mothers with PIH and PROM and those with sepsis, birth asphyxia, and other risk factors should be closely monitored for thrombocytopenia and early intervention should be done to control them.

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