Lead Article

Early Fall in Platelet Count: A True Reminder of Outcomes in Preterm Neonates

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Abstract

Background and Aim: Thrombocytopenia is an independent risk factor of morbidity and mortality among preterm neonates. Severe thrombocytopenia is usually of acquired varieties and results from consumptive thrombocytopenia. The objective of our study was to determine the incidence of > 30% fall in platelet count in preterm neonates and to assess the mortality rate and length of hospital stay (LOS) among the survivors.

Materials and Methods: This was a prospective observational study conducted in a tertiary care NICU. All preterm neonates admitted on day 1 of life to the NICU were considered for the study. The platelet count determined on day 1 was taken as the baseline value. Subsequently, platelet counts were determined twice before the end of week 1. The neonates were classified into 4 groups based on the level of fall in the platelet count. Group 1 neonates had normal platelet counts with no platelet decline, group 2 neonates had normal platelet count with > 30% decline in platelet count from baseline, group 3 neonates had thrombocytopenia with no platelet decline, and group 4 neonates had thrombocytopenia with > 30% decline in platelets from baseline.

Results: A total of 130 preterm neonates were included in this study, of whom 16.92% (*n* = 22) stayed in the hospital for > 30 days. Most of these neonates belong to group 4, followed by group 2. Among these neonates, 8.46% (*n* = 11) had gram-positive bacterial infection, 3.85% (*n* = 5) had gram-negative

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bacterial infection, and 32.31% (*n* = 42) had fungal infection. The overall mortality was 19.23% (*n* = 25), and the highest mortality was noted in group 4.

Conclusion: A fall in platelet count in the first 7 days of life is an early predictor of mortality, LOS, and sepsis.

Key Words: Fungal sepsis, mortality, gestational age, birth weight, thrombocytopenia, neonatal resuscitation, length of hospital stay

Introduction

The most common hematologic problem in neonates is thrombocytopenia (platelet count < 150 × 10^9/L). The prevalence of thrombocytopenia in NICU settings ranges from 18% to 35%,[1] and the overall prevalence of thrombocytopenia in neonates is 1% to 5%.[1,2] It commonly occurs in extremely low-birth-weight neonates (birth weight [BW] ≤ 1000 g), preterm neonates (gestational age [GA] < 37 wk), and sick neonates in a NICU.[2]

In term neonates, the prevalence of thrombocytopenia is much less at birth, accounting for about 2%. The prevalence of severe thrombocytopenia (platelet count < 50 × 10^9/L) is < 3/1000 in term neonates.[1]

Neonatal thrombocytopenia is caused by various feto-maternal and neonatal factors. Therefore, the causes are diverse and include immune, inherited, and acquired disorders. Neonatal thrombocytopenia is classified into early and late, based on the time of its onset. Causes of severe thrombocytopenia include impaired megakaryocytopoiesis or consumptive thrombocytopenia, especially in septicemic preterm neonates.[1]

Neonatal thrombocytopenia is an independent risk factor of neonatal mortality and various major morbidities such as intraventricular hemorrhage, disseminated intravascular coagulopathy, and necrotizing enterocolitis. Although mild-to-moderate thrombocytopenia resolves on its own without any sequelae, thrombocytopenia should be detected at the earliest, as it may be a symptom of underlying disease and an obvious risk factor of hemorrhage.[1,3]

Materials and Methods

Study design

This hospital-based, prospective, observational study was conducted at Sri Dharmasthala Manjunatheshwara (SDM) College of Medical Sciences and Hospital (Dharwad, Karnataka, India). The study lasted for 1 year, from December 1, 2015, to November 30, 2016.

Inclusion and exclusion criteria

A total of 130 preterm neonates with GA < 37 weeks (36^{+6} wk), inborn or outborn, who needed NICU admission on day 1 of life, and who survived for 7 or more days were included in the study. Preterm neonates who had thrombocytopenia at admission to the NICU, those who had alloimmune thrombocytopenia, neonates who were discharged or died before 7 days of life, neonates who received blood product transfusion during the first 7 days of life, and neonates whose mothers were on medications such as aspirin and warfarin were excluded from the study.

Study procedure

The GA of the enrolled neonates was assessed by modified Ballard scoring. Data regarding BW and sex of the neonate, use of antenatal corticosteroids, and mode of delivery were documented.

The mortality rate among these preterm neonates was calculated, and the length of hospital stay (LOS) among the survivors was analyzed. The prevalence of sepsis was determined based on positive blood

culture result. Serial platelet counts were done. Blood was drawn under aseptic condition and sent to the laboratory. The platelet counts were determined using a platelet count analyzer (Sysmex XN1000 Fully Automated Hematology Analyzer, Sysmex Corporation, Kobe, Japan), which was followed by rechecking and confirmation on peripheral smear by the pathologist.

Platelet count along with other routine investigations was done on day 1 of life, and this platelet count was taken as the baseline value. Subsequently, the platelet counts were determined twice before the end of week 1 and repeated if the neonate became sick or any new symptoms were noticed.

To analyze the prognostic value of the platelet decline with and without thrombocytopenia, the neonates were classified into 4 groups as follows:

Group 1: Normal platelet count with no platelet decline

Group 2: Normal platelet count with > 30% decline in platelet count from baseline

Group 3: Thrombocytopenia with no platelet decline

Group 4: Thrombocytopenia with > 30% decline in platelets from baseline

Statistical analysis

The data were analyzed using SPSS software version 20.0 for Windows (IBM Corp, Armonk, NY, USA). *P* value < .05 was considered statistically significant.

Results

Totally, 130 neonates were studied. Of these 130 neonates, 83.8% (n = 109) had > 30% fall in platelet count (30 had no thrombocytopenia and 79 had thrombocytopenia).

Table 1 shows that both male and female neonates are equally affected in all the 4 groups, with slight female predominance in group 2.

The mean GA ranged from 31 to 33 weeks. We found a statistically significant association between BW and the incidence of thrombocytopenia (Table 2).

As shown in Table 3, the major risk factor for preterm delivery was preterm premature rupture of membranes (32.31%), followed by the spontaneous onset of preterm labor with no risk factors (20%). Severe pre-eclampsia and nonsevere pre-eclampsia were risk factors in 18.46% and 10% neonates, respectively. Oligohydramnios, antepartum hemorrhage, and anemia during pregnancy were risk factors in 6.92%,

Table 1. Comparison of the Neonates in the 4 Groups Based on Sex

Sex	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Group 4, *n* (%)	Total, *n* (%)
Male	9 (13.24)	13 (19.12)	5 (7.35)	41 (60.29)	68 (52.31)
Female	2 (3.23)	17 (27.42)	5 (8.06)	38 (61.29)	62 (47.69)
Total	11 (8.46)	30 (23.08)	10 (7.69)	79 (60.77)	130 (100.00)

$\chi^2 = 4.8353$; $P = .1842$.

Table 2. Comparison of Neonatal Characteristics Between the Study Groups

Neonatal Characteristic	Group 1	Group 2	Group 3	Group 4	*P*
n (%)	11 (8.46)	30 (23.08)	10 (7.69)	79 (60.77)	NA
Mean GA	33 wk	32 wk + 4 d	31 wk	32 wk + 2 d	.0107[a]
Mean BW, kg	1.71	1.61	1.23	1.45	.0114[a]

[a]$P < .05$.
BW, birth weight; GA, gestational age; NA, not applicable.

Table 3. Comparison of the 4 Groups Based on Maternal Risk Factors

Risk Factor	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Group 4, *n* (%)	Total, *n* (%)
No Risk Factor	1 (3.85)	10 (38.46)	4 (15.38)	11 (42.31)	26 (20.00)
PPROM	6 (14.29)	11 (26.19)	2 (4.76)	23 (54.76)	42 (32.31)
NSPE	1 (7.69)	1 (7.69)	2 (15.38)	9 (69.23)	13 (10.00)
Oligohydramnios	0 (0)	1 (11.11)	1 (11.11)	7 (77.78)	9 (6.92)
APH	0 (0)	2 (25.00)	0 (0)	6 (75.00)	8 (6.15)
MSAF	1 (100)	0 (0)	0 (0)	0 (0)	1 (0.77)
SPE	2 (8.33)	4 (16.67)	1 (4.17)	17 (70.83)	24 (18.46)
Anemia	0 (0)	1 (14.29)	0 (0)	6 (85.71)	7 (5.38)
Total	11 (8.46)	30 (23.08)	10 (7.69)	79 (60.77)	130 (100.00)

APH, antepartum hemorrhage; MSAF, meconium-stained amniotic fluid; NSPE, nonsevere pre-eclampsia; PPROM, preterm premature rupture of membranes; SPE, severe pre-eclampsia.

6.15%, and 5.38% of the neonates, respectively. The factor with the lowest risk was found to be meconium-stained amniotic fluid (0.77%).

In our study, 21.54% (n = 28) required neonatal resuscitation at birth. A majority of these neonates belonged to group 4, accounting for 78.57% (n = 22), and none belonged to group 1 (Figure 1). We found a significant association between neonatal resuscitation and fall in platelet count.

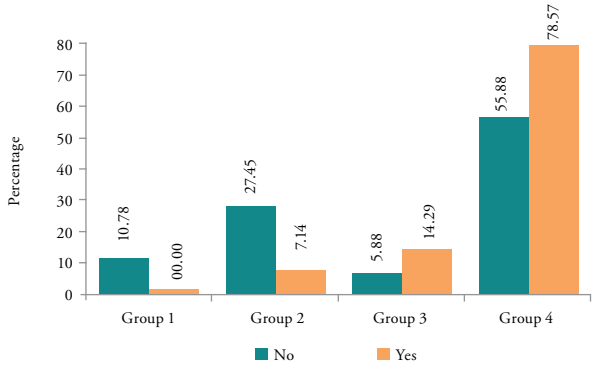

Figure 1. Comparison of the 4 Groups Based on Neonatal Resuscitation at Birth

Figure 2 presents a comparison of the 4 groups based on their status of sepsis. In our study, 58 neonates had culture-positive sepsis, of which fungal sepsis was the highest (42 [32.31%]). This was followed by polymicrobial sepsis (19 [32.75%]), gram-positive sepsis (11 [8.46%]), and gram-negative sepsis (5 [3.85%]).

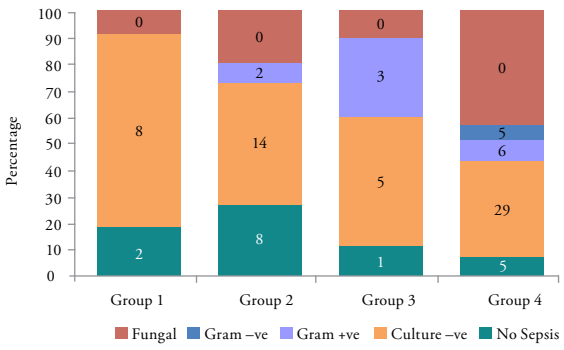

Figure 2. Comparison of the 4 Groups Based on Their Status of Sepsis

Staphylococcus aureus was the predominant organism in gram-positive sepsis and *Acinetobacter baumannii* in gram-negative sepsis. Among the neonates with fungal sepsis (n = 42), 34 belonged to group 4, 6 belonged to group 2, 1 belonged to group 1, and 1 belonged to group 3. Fungal sepsis is the most common culture-proven sepsis and has a significant association (P = .005) with a fall in platelet count and/or thrombocytopenia in preterm neonates.

As shown in Figure 3, 40.77% (n = 53) of the neonates did not require assisted ventilation after birth, and 59.3% (n = 77) of the neonates required assisted ventilation through continuous positive airway pressure (CPAP) and mechanical ventilation or both. CPAP was used in 31.54% (41 of 77 neonates). A majority of these neonates belonged to group 4 (28 of 41 neonates).

Of the 23.85% neonates (n = 31) who required mechanical ventilation, a majority of them belonged to group 4 (21 of 31 neonates) followed by group 2 (6 of 31 neonates).

Besides, 3.85% neonates (5 of 77 neonates) required both mechanical ventilation and CPAP (CPAP was either an initial mode of oxygen therapy or following extubation from a ventilator).

We found a significant association (P = .0447) between assisted ventilation and the incidence of thrombocytopenia, which shows that preterm neonates with respiratory compromise had a fall in platelet count, with or without thrombocytopenia.

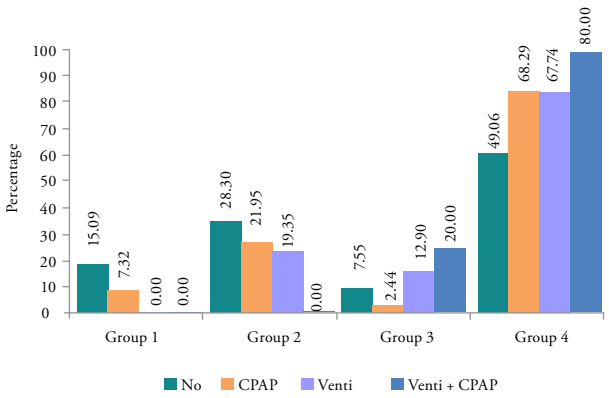

Figure 3. Comparison of the 4 Groups Based on Their Need for Assisted Ventilation After Birth

CPAP, continuous positive airway pressure; No, not requiring assisted ventilation; Venti, mechanical ventilation.

As shown in Table 4, 22 neonates had a hospital stay of > 30 days, and most of these neonates belonged to group 4 (72.73%) followed by group 2 (18.18%).

Table 4. Comparison of the 4 Groups Based on Their LOS

LOS, d	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Group 4, *n* (%)	Total, *n* (%)
0–10	5 (11.63)	11 (25.58)	4 (9.30)	23 (53.49)	43 (33.08)
11–20	3 (8.82)	11 (32.35)	2 (5.88)	18 (52.94)	34 (26.15)
21–30	1 (3.23)	4 (12.90)	4 (12.90)	22 (70.97)	31 (23.85)
> 30	2 (9.09)	4 (18.18)	0 (0)	16 (72.73)	22 (16.92)
Total	11 (8.46)	30 (23.08)	10 (7.69)	79 (60.77)	130 (100.00)

χ^2 = 9.3759; *P* = .4034.
LOS, length of hospital stay.

Table 5 presents data about the mean LOS in each group. There was a significant association (*P* = .0394) between the mean LOS and decline in platelet count. Neonates in group 1 had the shortest LOS compared with that of other groups.

Table 5. The Mean of LOS in Each Group

Group	Group 1	Group 2	Group 3	Group 4
LOS, Mean, d	13.22	21.06	21.00	21.61
SD	9.83	11.77	12.40	13.38

P = .0394 (significant).
LOS, length of hospital stay; SD, standard deviation.

As shown in Table 6, 73.08% (*n* = 95) of the neonates were discharged. In group 1, 9 of the 11 neonates were discharged, and the other 2 neonates left the hospital against medical advice.

The overall mortality was 19.23% (*n* = 25). The mortality rate in groups 4, 2, and 3 was 64% (*n* = 16), 24% (*n* = 6), and 12% (*n* = 3), respectively. Hence, the mortality rate was significantly high in group 4 followed by that in group 2.

We compared the probability of death among the study groups, taking group 1 as the control. Group 2 showed the highest probability of 99.11 times compared with that of group 1, which is statistically significant (*P* = .0210). Group 4 had 42.09 times probability of death compared with that of group 1, which is statistically significant (*P* = .0430).

Table 6. Comparison of the 4 Groups Based on Clinical Outcomes

Outcome	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Group 4, *n* (%)	Total, *n* (%)
Discharge	9 (9.47)	23 (24.21)	4 (4.21)	59 (62.11)	95 (73.08)
DAMA	2 (20.00)	1 (10.00)	3 (30.00)	4 (40.00)	10 (7.69)
Death	0 (0)	6 (24.00)	3 (12.00)	16 (64.00)	25 (19.23)
Total	11 (8.46)	30 (23.08)	10 (7.69)	79 (60.77)	130 (100.00)

χ^2 = 13.9576; *P* = .0301 (significant).
DAMA, discharge against medical advice.

Table 7. The Probability of Death in Various Study Groups in Relation to That in Group 1 (Logistic Regression)

Variable	Category	OR	95% CI for OR		*P*
			Lower	Upper	
Group	Group 1		Reference		
	Group 2	99.11	1.98	4965.46	.0210[a]
	Group 3	21.42	0.62	737.53	.0900
	Group 4	42.09	1.12	1581.24	.0430[a]
GA	Group 1		Reference		
	Group 2	0.09	0.003	2.89	.1720
	Group 3	0.17	0.004	6.93	.3520
BW	Group 1 ELBW (< 1 kg)		Reference		
	Group 2 VLBW	0.011	0.002	0.086	.0001[a]
	Group 3 LBW	0.008	0.001	0.094	.0001[a]

[a]*P* < .05.
BW, birth weight; ELBW, extremely low birth weight; GA, gestational age; LBW, low birth weight; VLBW, very low birth weight.

To analyze the mortality in terms of GA, we considered the extremely preterm (GA < 28 wk) as a reference. The early preterm neonates (28–32 wk) in group 2 showed 0.09 times probability of death, and moderate-to-late preterm neonates (32–36 wk + 6 d) showed 0.17 times probability of death, with an insignificant *P* value.

BW plays an important role in mortality and probability of death rates. The BW of group 1 (< 1 kg) was taken as a reference. Group 2 (BW = 1.1–1.5 kg) had 0.011 times

probability of death compared with that of group 1. Group 3 (BW = 1.6–2.4 kg) had 0.008 times probability of death, which indicates a good prognosis of survival compared with that of group 1. BW and mortality showed a significant statistical association (Table 7).

From Figure 4 and Table 8, the area under the curve shows that as the GA and BW increase, the chances of survival are better, and the prognosis is good. Both the variables have a significant *P* value (.0001).

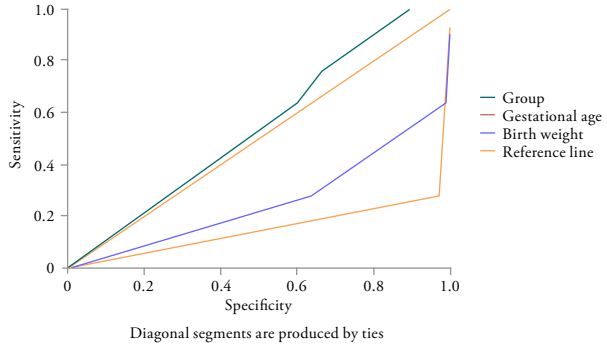

Figure 4. The ROC Curve Representing the Relationship Between Increased Chances of Survival and Increase in GA and BW

BW, birth weight; GA, gestational age; ROC, receiver operating characteristic curve.

Table 8. Area Under the ROC

Test Result Variable(s)	Area	SE	*P*	95% CI	
				Lower Bound	Upper Bound
Group	0.545	0.060	.4890	0.427	0.662
GA, wk	0.259	0.062	.0001[a]	0.137	0.381
BW, kg	0.159	0.056	.0001[a]	0.048	0.269

[a]*P* < .05.
BW, birth weight; GA, gestational age; ROC, receiver operating characteristic curve.

Discussion

In our study, we found a significant association between the fall in platelet count in preterm neonates and increased morbidity and mortality. These findings corelate with the results of a study by Rastogi et al,[3] which concludes that a > 30% fall in platelet count in preterm neonates is linked with an increased LOS, morbidities, and mortality, with or without thrombocytopenia. As this fall in platelet count occurs before symptom onset, it can serve as a predictor of prolonged LOS.

The results of our study are in agreement with that of Elmoneim et al,[4] which shows that an early fall in platelet count without thrombocytopenia is an effective predictor of increased morbidity, LOS, and mortality.

Our study suggests a strong correlation between the fall in platelet count (with or without thrombocytopenia) and fungal sepsis in preterm neonates. With the fall in platelet count, an increase in the incidence of bacterial sepsis was also observed; however, the association was not of statistical significance. These findings are similar to the results of a study by Rastogi et al,[3] which reports a significant association between the increased risk of fungal sepsis in preterm neonates and the fall in platelet count, with or without thrombocytopenia. In our study, we found a statistically significant association between the decline in platelet count (with or without thrombocytopenia) and gram-negative bacterial sepsis. Compared with Rastogi et al's[3] study, the incidence of sepsis was higher in our study. Sepsis itself is known to enhance platelet destruction and cause thrombocytopenia.[5] But, the role of a specific organism and type of infection in the development of thrombocytopenia are not clearly known.[6]

In our study, 25 (19.23%) neonates died. A majority of the deaths were noted in group 4, where the neonates had a fall in platelet count and thrombocytopenia (*P* = .0430; significant). Compared with a study by Andrew et al,[7] the mortality rate was high in our study. However, the findings of our study are similar to that of a study conducted by Elmoneim et al,[4] which reports increased mortality in neonates with a fall in platelet count along with thrombocytopenia.

Limitations

- The sample size of our study was small. Hence, further studies with a larger sample size are needed to substantiate the results.
- We could not collect the platelet transfusion data of all neonates.
- We could not estimate the mean platelet volume, a marker of production or destruction of platelets, in all neonates.

Conclusion

In addition to thrombocytopenia, the early fall in platelet count is also an effective predictor of outcomes in preterm neonates. A > 30% fall in platelet count is indicative of increased LOS, morbidities, and mortality.

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