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# Association Between Platelet Transfusion and Mortality Rate Among Preterm Neonates in the Eastern Province, Saudi Arabia

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## ABSTRACT

**Background:** Platelet transfusion is the main mode of management of thrombocytopenia. However, some studies link frequent and high-threshold platelet transfusions with an incremental increase of mortality rate. **Objective:** This study aims to assess the association between the frequency and the threshold of platelet transfusions, with the mortality rate among preterm neonates. **Methods:** A retrospective cohort study design was used. This study was conducted at maternity and children's hospitals in Al-Ahasa, Saudi Arabia. The sample size includes 154 preterm neonates, included in the study by the use of the convenience sampling technique. **Results:** There is a significant relationship found between the gestational age and the birth weight of the preterm neonates with the survival rates among both groups. In contrast, there is no significant relationship found between transfusion frequency, transfusion threshold, and the survival rates of the group which received platelet transfusion. **Conclusion:** The current study found that mortality is mainly associated with lower gestational ages, and not platelet transfusions. More studies are needed to fill the remaining gaps of knowledge, and to optimise platelet transfusion practices among preterm neonates.

**Keywords:** platelet transfusion, preterm neonate, preterm, platelet transfusion threshold, mortality rate

## 1. BACKGROUND

Platelet transfusion is the main therapy for neonatal thrombocytopenia (platelet count < 150,000/ $\mu$ L), aside from directly treating the underlying cause (1). Thrombocytopenia is one of the most common hematologic problems faced by neonates, especially those admitted to neonatal intensive care units (NICU), and those with lower gestational ages(2, 3). Theoretically, neonatal thrombocytopenia is correlated with a high risk of bleeding and mortality (4). Hence, platelet transfusions are needed to prevent the risk of haemorrhage and death. Neonatal platelet transfusion thresholds vary according to clinical conditions. More liberal transfusions are considered by many neonatologists when facing cases of unstable preterm neonates (5). However, due to the recognised risks of platelet transfusions, and the frequent identification of bleeding among the disease conditions, rather than of low platelet count, restrictive platelet transfusions for preterm neonates is recommended (1, 6). Theoretically, platelet transfusions at the high threshold (platelet < 50,000/ $\mu$ L) may reduce the risk of bleeding and mortality, though in practice this is not the case (4). There is a newly raised debate regarding the association between platelet transfusion frequency, threshold, and the elevation of mortality rates among preterm neonates. Through randomised control trials (RCT) research, it has been reported that the prophylactic high threshold platelet transfusion is significantly associated with a higher mortality rate, with major bleeding, or with both to a more extreme degree than with low threshold transfusions (platelet < 25,000/ $\mu$ L) (7). Overall, there is uncertainty as to whether the elevation of neonatal mortality rate is associated with platelet transfusions, or with other factors, such as the severity of their illnesses (8, 9). As a result, there are new approaches recently used as alternatives to platelet transfusion, such as the administration of thrombopoietic growth factors, and thrombopoiesis-stimulating agents, done in hopes of reducing the risks associated with platelet transfusions (9, 10). However,

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the medical responses to those new approaches has not been well recognised (11). Furthermore, studies regarding platelet transfusion practices and risk factors among neonates are too few; as such, this study aims to assess the association between the frequency and threshold of platelet transfusions, with mortality rates among preterm neonates, focusing on the Maternity and Children’s Hospital (MCH) in Al-Ahasa, Saudi Arabia.

## 2. OBJECTIVE

This study aims to assess the association between the frequency and the threshold of platelet transfusions, with the mortality rate among preterm neonates.

## 3. MATERIAL AND METHODS

The researchers of the current research conducted a retrospective cohort study in order to answer the research question. The investigators measured the exposure to platelet transfusions and the survival status of the participants, thereby aiming to assess the association between the frequency and threshold of platelet transfusions, and the mortality rates among preterm neonates at the Maternity and Children’s Hospital (MCH) in Al-Ahasa, Saudi Arabia. A cohort design in this study represents two groups - one is of the preterm neonates who received platelet transfusions, and the other also is of preterm neonates who did not receive platelet transfusion therapy. Those two groups were compared against one another in terms of survival status.

The preterm neonates were selected based on the following inclusion criteria: the status of being preterm neonates (gestational age < 37 weeks) admitted to NICU within the period of January 2019 to December 2020; of being preterm neonates who received platelet transfusions, assigned to be the exposed group; and being preterm neonates who did not receive platelet transfusions, assigned to be unexposed group. The exclusion criteria were being preterm neonates with congenital malformation, genetic disorders, comorbid diseases, and the preterm neonates who were admitted from other health care institutions.

The total number of admitted preterm neonates throughout 2019 and 2020 was 790. Thus, 60% of this number (474) was examined. Random sampling was completed through the use of a reliable website (<https://www.dcode.fr/random-sampling>). Out of this total number, only 77 received platelet transfusions. Therefore, every one of the neonates who received transfusions were chosen as the exposed group. In accordance with this, the same number of neonates with similar characteristics who did not receive platelet transfusions was selected as the unexposed group. Thus, the final number of the sample was 154 preterm neonates.

The obtained data were secondary data taken from the registry books and electronic systems of specific departments; namely, the Neonatal Intensive Care Unit (NICU), the blood bank department, haematology department, microbiology department, and the ultrasound department. The used data collection tool (Case Report Forms) was adopted and modified from Platelets for Neonatal Transfusion - Study 2 (PlaNeT – 2) (7). To use the PlaNeT – 2 tool, permission was acquired by the authors. The face and content validity of the tool have been secured. Moreover, the reliability of the tool was tested. The Cronbach’s alpha was .733.

## 4. RESULTS

Upon data completion and validation, the data was transported from the data collection sheet to the statistical software, IBM SPSS software package version 25.0, for analysis. Qualitative data were described using numbers and percentage. The significance of the obtained results was judged to be at the 5% level. The utilised tests were the Chi-squared test for categorical variables, which was used to compare the results between the two groups, as well as either Fisher’s exact test, or the Monte Carlo correction, the latter of which was used as a correction for the chi-squared test, when more than 20% of the cells showed an expected count less than 5.

The sample was divided into two groups of equal numbers (n = 77). The first group consisted of preterm neonates who were treated with platelet transfusions, whereas the second group included preterm neonates

Demographic Data	Received platelet transfusion (n =77)		Did not receive platelet transfusion (n =77)	
	No.	%	No.	%
Gender				
Male	38	49.4	38	49.4
Female	39	50.6	39	50.6
Gestational Age				
Late preterm (34-36 weeks)	8	10.4	8	10.4
Moderate preterm (32-33 weeks)	4	5.2	4	5.2
Severe preterm(31-28 weeks)	31	40.3	31	40.3
Extremely preterm ( GA<28 weeks)	34	44.2	34	44.2
Birth weight				
Low birth weight (BW <2500 g)	5	6.5	13	16.9
Very low birth weight (BW<1500 g)	22	28.6	36	46.8
Extremely low birth weight (BW< 1000 g)	49	63.6	28	36.4
Normal birth-weight (2500 g - 4000 g)	1	1.3	0	0.0
Mode of delivery				
Spontaneous Vaginal Delivery (SVD)	38	49.4	24	31.2
Cesarean Section (C/S)	39	50.6	53	68.8
Number of gestations (Single_ multiple _birth)				
Single	62	80.5	56	72.7
Twin	13	16.9	17	22.1
Triplet	2	2.6	3	3.9
Quadruplets	0	0.0	1	1.3

**Table 1. Distribution of the studied preterm neonates according to their demographic data**

	Received platelet transfusion (n =77)				Did not receive platelet transfusion (n =77)			
	Survive (n =47)		Died (n =30)		Survive (n =62)		Died (n =15)	
	No.	%	No.	%	No.	%	No.	%
<b>Medical Diagnosis</b>								
<b>Admission Diagnosis</b>								
Preterm, & Respiratory distress	15	31.9	3	10.0	49	79.0	1	6.7
Preterm, Low birth weight	1	2.1	0	0.0	0	0.0	0	0.0
Preterm, Low birth weight, & Respiratory distress	8	17.0	5	16.7	2	3.2	1	6.7
Intrauterine growth restriction,	5	10.6	3	10.0	1	1.6	2	13.3
Extremely preterm, Extremely Low birth weight, & Respiratory distress	14	29.8	19	63.3	10	16.1	11	73.3
Others	4	8.5	0	0.0	0	0.0	0	0.0
c	11.300* (0.027*)				29.067* (<0.001*)			
<b>Chief Complaint</b>								
Intraventricular hemorrhage (IVH) & Sepsis	2	4.3	7	23.3	2	3.2	0	0.0
Gram negative sepsis	5	10.6	0	0.0	2	3.2	0	0.0
Gram positive sepsis	1	2.1	0	0.0	0	0.0	0	0.0
Necrotizing enterocolitis (NEC)	1	2.1	0	0.0	0	0.0	0	0.0
Grade I IVH	19	40.4	12	40.0	46	74.2	14	93.3
Grade II IVH	2	4.3	0	.0	2	3.2	0	0.0
Grade III IVH	6	12.8	7	23.3	5	8.1	0	0.0
Grade IV IVH	9	19.1	4	13.3	4	6.5	0	0.0
other diagnosis	0	0.0	0	0.0	1	1.6	1	6.7
Respiratory distress syndrome (RDS)	2	4.3	0	0.0	0	0.0	0	0.0
c	12.845 (0.062)				3.812 (0.701)			
<b>Mother Data</b>								
<b>Medical diagnosis</b>								
None	45	95.7	29	96.7	62	100.0	15	100.0
Diabetes Mellitus	2	4.3	0	0.0	0	0.0	0	0.0
Hypertension	0	0.0	1	3.3	0	0.0	0	0.0
c	2.367 (MCp=0.292)				-			
<b>Antenatal Complication</b>								
None	31	66.0	22	73.3	46	74.2	12	80.0
Premature Rupture of Membranes (PROM)	1	2.1	1	3.3	3	4.8	0	0.0
Abruption Placenta	1	2.1	0	0.0	3	4.8	0	0.0
Breech presentation	3	6.4	3	10.0	0	0.0	2	13.3
Pre-eclampsia (PET)	7	14.9	2	6.7	7	11.3	0	0.0
Emergency Cesarean Section (C/S)	1	2.1	0	0.0	1	1.6	0	0.0
Other	3	6.4	2	6.7	2	3.2	1	6.7
c	3.195 (0.906)				8.805 (0.109)			

**Table 2. Relationship between the survival status with the medical diagnosis of the preterm neonates and with the mother's data.  $\chi^2$ : Chi square test MC: Monte Carlo \*: Statistically significant at p  $\leq$  0.05**

who did not receive platelet transfusions. The 77 preterm neonates in the transfusion group received a total of 296 platelet transfusions.

Table 1 clarifies the sample characteristics. The most common admission diagnoses for the preterm neonates who received platelet transfusions were extremely preterm birth, extremely low birth weight, and respiratory distress (42.9%) - whereas the most common admission diagnoses among the group who did not receive platelet transfusion were preterm birth and respiratory distress (64.9%). Regarding the chief complaint, the most common chief complaint in both groups was of a grade I intraventricular haemorrhage (IVH). By explor-

ing subjects' mother's data, the statistics showed that there was no medical history or antenatal complications among most mothers in both groups. Concerning the frequency of platelet transfusion, most of the subjects received platelet transfusions between 1 and 3 times (59.7%). Regarding the survival status across the two groups, the survival rate among the group who received platelet transfusion was more than half (61%), and the mortality was 39% - whereas for the other group the survival rate was 80.5%.

Concerning the relationship between survival status and demographic data of the study's sample, there was a significant relationship between gestational age and

birth weight of the preterm neonates with survival status in the group who received platelet transfusions;  $\chi^2$  (MCp) = 10.120 (0.012), 11.565 (0.002), as well as with the group who did not receive platelet transfusions;  $\chi^2$  (MCp) = 22.877 (< 0.001), 26.175 (< 0.001) respectively. Thus, as gestational age and birth weight decreases, the mortality rate increases. However, there was no significant relationship between the gender, the mode of delivery, and the number of gestations with survival status among the preterm neonates in both groups. The relationship between the medical diagnosis of the preterm neonates, their mothers' data, and the survival status is represented on Table 2.

Concerning the relationship between the platelet transfusion frequency of the group who were treated with platelet transfusion and survival status, there was no significant relationship found ( $\chi^2$  (MCp) 3.921 (0.398)). Moreover, the relationship between the pre-transfusion platelet count (the threshold) with survival status was studied. The statistical analysis showed that there was no significant relationship between the platelet transfusion threshold and survival status.

## 5. DISCUSSION

Platelet transfusion is used as a treatment or prophylactic therapy for preterm neonates with cases of thrombocytopenia. However, platelet transfusion is assumed to elevate the mortality rate among neonates. Hence, the current study tested this assumption retrospectively by using a retrospective cohort design. The current study examined 154 preterm neonates, of which 77 were assigned to be in the study group, and 77 were assigned to the control group.

The frequency of platelet transfusion was investigated, and it was found that the most common number of transfusions was from 1 to 3 transfusions. This result was near to the results of Sparger et al. (19) who reported that the mean (SD) of platelet transfusions among their study sample was 4.3. Concerning the platelet transfusion threshold, the category of platelets < 100.000/ $\mu$ L was found to be the most dominant threshold for platelet transfusion, which matches what was reported by Sparger et al. (19). In contrast, a study conducted by Dogra et al. (20) found that platelet threshold between 20,000 and 50,000  $\mu$ L was the most common threshold for platelet transfusions. To our knowledge, platelet transfusion thresholds vary worldwide based on institutions' policies and procedures. Regardless, there is a lack of reliable evidence which guides clinical practices to identify the ideal thresholds for neonatal platelet transfusion (13, 14).

Neonatal transfusion triggers or thresholds vary according to clinical conditions, like gestational age at birth (5). Indeed, the more liberal transfusions are considered necessary by many neonatologists for unstable preterm neonates, whereas they prefer restrictive transfusions for term neonates (5). Jacquot et al. (21) reported that the risk of developing IVH forces many physicians to practice aggressive platelet transfusions (platelet count > 100.000/ $\mu$ L) in high-risk patients. The last two sugges-

tions justify why the transfusion threshold < 100.000/ $\mu$ L was the most dominant platelet transfusion practice in the current study.

Regarding the survival status of the two groups, the current study found that survival rates were higher than mortality rates among the two groups; either those who received platelet transfusions, or those who did not receive platelet transfusions. By investigating the demographic data of those who died, the data could determine the causes of death as relating to the gestational age. The results show that there was a significant relationship between both gestational age and birth weight with survival rates in both groups. As the gestational age and birth weight decreases, the mortality rates increase. The results showed that 44.2% of those who received platelet transfusion and died were extremely preterm neonates (GA < 28 weeks). This result is identical to the results reported by Jang et al. (23) and Pammi (24).

On one hand, the current study found that there was no significant relationship between transfusion frequency and survival rates. This result matches those of Al-safadi (15) and Dogra et al. (20). Likewise, Sola-Visner et al. (22) assumed that the association between platelet transfusions and mortality rates mainly reflects the seriousness of the underlying conditions, or of extreme prematurity rather, than the transfusions themselves (19). On the other hand, Kasap et al. (10) found that the mortality rate was significantly higher among the group which received platelet transfusions compared to the group which did not receive platelet transfusions ( $p$  < 0.001).

Concerning the relationship between the platelet counts before platelet transfusions (the threshold) with survival rates, there was no significant relationship found. This result is contrary to the findings of Curley et al. (9). Namely, Curley et al. (9) found that a prophylactic high threshold transfusion was significantly associated with higher mortality rates when compared to low threshold transfusions among preterm neonates.

Though the current study did not find a relationship between platelet transfusions threshold or frequencies with mortality rates, we cannot fully reject the association between platelet transfusion and mortality, as there are many suggestions that explain the reason behind the harmful effects of the current platelet transfusion practices for neonates (20). It has been suggested that neonatal platelets are hyporeactive when compared to adults' platelets, so it is unknown whether the transfusion of adult's platelets to neonates induces micro-thrombosis formation or not. Furthermore, platelets possess significant immunologic and inflammatory effects (7,20,21). As the exact causes developing adverse effects (such as death) of platelet transfusion has not been confirmed, restrictive platelet transfusions in preterm neonates are preferred over liberal transfusions.

## 6. CONCLUSION

Although platelet transfusion is common among preterm neonates, it remains a challenging procedure. There is an uncertainty about platelet transfusion prac-

tice among neonatologists regarding the platelet transfusion threshold and safety. The current study found that there was no significant association between platelet transfusion frequency, platelet transfusion threshold, and mortality rate, while mortality was mainly associated with the lower gestational ages. However, more studies are needed to fill the gap of knowledge and optimize platelet transfusion practice among preterm neonates.

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