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Original Article

Evaluation of therapeutic and prophylactic platelet transfusion practices in a neonatal intensive care unit

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Abstract

Aim: To investigate the causes of thrombocytopenia requiring platelet transfusion (PT), clinical factors influencing the decision to give PT, and the frequency of major hemorrhage post-PT in a neonatal intensive care unit (NICU).

Material and Methods: This retrospective cross-sectional study included neonates who underwent PT at least once in the NICU during a 4-month period. Demographic characteristics, postnatal age at time of PT, number of PTs, thrombocytopenia etiology, and occurrence of major hemorrhage were analyzed. PT threshold was <20x10^3/μL in group 1; 20x10^3/μL – 49x10^3/μL in group 2; and >50^3/μL in group 3.

Results: Thirty-seven (4.9%) of the 751 patients admitted to the NICU during the study period received PT. These 37 patients received a total of 133 PTs. The most common etiology of thrombocytopenia requiring PT was sepsis (83.5%), followed by NEC (9.8%). Of the 133 PTs, 7 were administered for early-onset thrombocytopenia and 126 for late-onset thrombocytopenia. All patients in group 1 (n=56) had severe thrombocytopenia only with no additional morbidity; patients in group 2 (n=72) had thrombocytopenia accompanied by severe morbidity and/or major hemorrhage, coagulopathy, or extremely low birth weight (ELBW); patients in group 3 (n=4) received PT due to thrombocytopenia and preoperative preparation, coagulopathy, or major hemorrhage. Seven of the 133 PTs (5.3%) were therapeutic and the other 126 (94.7%) were prophylactic. Existing major hemorrhage persisted after 6 of the 7 therapeutic PTs. Major hemorrhage occurred after only 1 prophylactic PT.

Conclusion: It was identified bacterial sepsis and NEC as the two most common clinical indications for PT. In general, prophylactic PT was not followed by major hemorrhage, whereas recurrent major hemorrhage occurred after therapeutic PT. Therefore, randomized controlled studies are needed to determine a safe PT threshold value based on a scoring system for predicting the risk of major hemorrhage.

Keywords: Thrombocytopenia; Newborn; Platelet Transfusion; Hemorrhage.

INTRODUCTION

Thrombocytopenia, defined as platelet count below 150x103/μL, is the most common hematologic condition in neonates treated in the NICU (1,2). Based on this definition, the incidence of thrombocytopenia in all neonates is about 0.12-0.24% (3,4). At least one measurement yields a platelet count under 150x10^3/μL in about 18-35% of all preterm and term neonates admitted to the NICU (5,6).

High-quality evidence is insufficient to establish a consensus regarding the management of thrombocytopenia. About 5-9% of neonates admitted to the NICU receive a platelet transfusion (PT) (7,8). PT can be given for therapeutic or prophylactic purposes. Prophylactic PT is generally used when platelet count falls below a designated threshold but there are no signs of hemorrhage. Prophylactic use aims to prevent severe hemorrhage, especially intracranial hemorrhage (ICH) in preterm infants (2).

The platelet threshold recommended by authorities for prophylactic PT varies (9-13). Today, guidelines based on expert opinion are typically used to guide prophylactic PT practices in different countries. It is important for specialists to know the PT protocols applied in their units and the associated outcomes in order to improve practices in this area of variability.

The primary aim of this study was to identify the causes of thrombocytopenia requiring PT and the secondary objectives were to investigate factors affecting the decision to give PT and the condition of major hemorrhage after transfusion.

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MATERIAL and METHODS

All neonates who were admitted to the Zekai Tahir Burak Women's Health Hospital NICU and received PT between January 1 and April 30, 2018 were included in this retrospective cross-sectional study, regardless of gestational and postnatal age. Ethical approval was obtained before the study from the Clinical Research Ethics Committee of Zekai Tahir Burak Women's Health Education and Research Hospital.

Hospital blood center records were screened to obtain a list of patients for whom platelet suspensions were prepared for PT during the study period. Clinical and laboratory data were collected from patient medical records. These data included gestational age, birth weight, prenatal characteristics (preeclampsia, placental insufficiency, drug and disease history, intrauterine growth restriction [IUGR]), postnatal age at thrombocytopenia onset, clinical factors influencing decision to administer PT (stage 3-4 severe ICH, necrotizing enterocolitis [NEC], severe morbidities such as sepsis, extremely low birth weight [ELBW], invasive procedures, minor hemorrhage, active major hemorrhage, disseminated intravascular coagulation [DIC], preoperative/postoperative preparation], post-PT major hemorrhage (ICH, pulmonary hemorrhage), number of PTs administered, and interval between PT and post-PT platelet count. Patient files and laboratory data were reviewed for factors that may be related to thrombocytopenia etiology (neonatal alloimmune thrombocytopenia [NAIT], IUGR, small for gestational age [SGA], maternal immune thrombocytopenic purpura, sepsis, DIC, massive erythrocyte suspension transfusion, thrombus, etc.).

Thrombocytopenia that occurred in the first postnatal 72 hours was defined as early-onset and cases that occurred after the first postnatal 72 hours was defined as late-onset (2).

Three groups were formed based on the platelet count threshold used for PT: <20x10^3/µL (group 1), 20x10^3/µL - 49x10^3/µL (group 2), and >50x10^3/µL (group 3).

Statistical analyses

Shapiro-Wilk test was used to evaluate normality of data distributions. Descriptive statistics were expressed in median ± standard deviation and (minimum-maximum). Comparisons between groups were done using one-way ANOVA with Tukey's post hoc test. Statistical significance was accepted at p<0.05.

RESULTS

A total of 751 patients were admitted to the NICU during the study period and 37 (4.9%) received at least 1 PT. The analysis included 133 PTs administered to these patients. Demographic characteristics of the patients are given in Table 1.

Of the 133 PTs, 7 were administered for early-onset thrombocytopenia and 126 for late-onset thrombocytopenia. Etiologies of early-onset thrombocytopenia were non-immune hydrops, sepsis, asphyxia, and IUGR associated with placental insufficiency. The most common cause of late-onset thrombocytopenia was sepsis (83.5% of all cases), followed by NEC (9.8% of all cases). Eleven of the 113 sepsis cases were also diagnosed with DIC (Table 2). Sepsis was bacterial in all cases.

Table 1. Demographic characteristics of all patients

Gestational week at birth*	
24-30 (n = 17)	26.7 ± 1.6 (24.0–29.0)
31-37 (n = 17)	34.5 ± 1.8 (31.0-37.6)
≥ 38 (n = 3)	38.8 ± 0.7 (38.0-39.5)
Birth weight (g)	
24-30 weeks (n = 17)	811.8 ± 225.9
31-37 weeks (n = 17)	2036 ± 527.8
≥ 38 weeks (n = 3)	2830 ± 655.9
Male n,%	14 (37.8)
C/S n,%	29 (78.4)
Preeclampsia n,%	3 (8.1)
SGA n,%	9 (24.3)

*Data was expressed as mean ± SD (minimum-maximum); C/S, caesarian section; SGA, small for gestational age

Table 2. Etiologies of early and late thrombocytopenia requiring platelet transfusion

	Causes of thrombocytopenia n (%)	
Early thrombocytopenia	Non-immune hydrops	3 (2.3)
	Asphyxia + DIC	1 (0.8)
	Sepsis	2 (1.5)
	Placental insufficiency	1 (0.8)
Late thrombocytopenia	Sepsis	100 (75.2)
	NEC	13 (9.8)
	Sepsis + DIC	11 (8.3)
	Non-immune hydrops	1 (0.8)
	DIC*	1 (0.8)
Total		133 (100)

NEC, necrotizing enterocolitis; DIC, disseminated intravascular coagulation; *with multiple organ failure caused by hypoplastic left heart syndrome

Number of PTs administered to each patient was as follows: 1 PT to 16 patients (43.2%), 2 PTs to 7 patients (18.9%), 3 or more PTs to 14 patients (37.9%).

Thrombocytopenia etiologies and PT indications according to PT thresholds are summarized in Table 3. Platelet threshold for PT was <20x10^3/µL (group 1) in 42.1% of the patients, 20x10^3/µL - 49x10^3/µL (group 2) in 54.1%, and >50x10^3/µL (group 3) in 3.1%. No patients with platelet count >100x10^3/µL received PT. All patients in group 1 were given PT for severe thrombocytopenia regardless of other comorbidities. In group 2, PT was

administered due to comorbid coagulopathy (11 PTs), severe comorbidities (sepsis, NEC, hypoplastic left heart syndrome with multiple organ failure, severe asphyxia) (57 PTs), ELBW (1 PT), and active major hemorrhage (4 PTs for pulmonary hemorrhage, 1 PT for ICH). In group 3, 2 PTs were given due to active major hemorrhage (pulmonary hemorrhage), 1 PT for preoperative preparation, and 1 PT for DIC (Table 3).

Table 3. Causes of thrombocytopenia and clinic indications for PT according to the transfusion threshold

Transfusion threshold	Causes of thrombocytopenia	n(%)	Clinical indications for PT	n(%)
< 20.000/µL (Group I)	Sepsis	51 (38.3)	Severe thrombocytopenia	56(42.1)
	Non-immune hydrops	2 (1.5)		
	NEC	2 (1.5)		
	Sepsis + DIC	1 (0.8)		
20x10^3-50x10^3 /µL (Group II)	Sepsis	49 (36.8)	Concomitant coagulopathy	11 (8.3)
	NEC	11 (8.3)	Concomitant severe morbidity	56(42.1)
	Sepsis + DIC	8 (6.0)	ELBW	1 (0.8)
	Non-immune hydrops+DIC	2 (1.5)	Active major hemorrhage*	5 (3.7)
	DIC	1 (0.8)		
	Asphyxia	1 (0.8)		
	Placental insufficiency	1 (0.8)		
>50x10^3/µL (Group III)	Early sepsis	2 (1.5)	Active major hemorrhage	2 (1.5)
	Sepsis + DIC	2 (1.5)	Preoperative	1 (0.8)
			DIC	1 (0.8)
	Total	133(100)		133(100)

NEC, necrotizing enterocolitis; DIC, disseminated intravascular coagulation; ELBW, extremely low birth weight; IUGR, intrauterine growth restriction; *active major hemorrhage accompanied by severe morbidities

Of the 133 PTs, only 7 given to 3 patients (5.3%) were therapeutic (6 for active pulmonary hemorrhage, 1 for active ICH) and the remaining 126 (94.7%) were prophylactic (Table 3). Of the 3 patients who received therapeutic PT, the first was transfused during active ICH, and ICH grade was increased the day after transfusion. The second patient was given 3 PTs during active pulmonary hemorrhage, which also recurred after the transfusions. The third patient also received 2 PTs for active pulmonary hemorrhage, which recurred after the first transfusion but resolved after the second transfusion.

Four patients who received 27 prophylactic PTs had history of ICH. Only 1 of these patients exhibited post-PT major hemorrhage (pulmonary hemorrhage); platelet count was found to be within normal limits at the time of hemorrhage.

Mean intervals between PT and follow-up platelet count in groups 1, 2, and 3 were 20.6±7.1 hours, 21.1±8.2 hours, and 27.5±14.1 hours, respectively (p=0.27). In 76 cases (% 57.1% of all cases), follow-up platelet count was done 24 hours post-PT.

DISCUSSION

In our study, the most common etiology of thrombocytopenia requiring PT was sepsis, followed by NEC. Prophylactic applications accounted for 94.7% of all PTs. Existing major hemorrhage persisted after 6 of the 7 therapeutic PTs. Major hemorrhage occurred after only 1 prophylactic PT.

Differentiating between early and late onset provides a suitable diagnostic algorithm in the etiologic investigation of thrombocytopenia. Intrauterine infections or neonatal diseases associated with specific maternal conditions are common causes of early-onset thrombocytopenia. Early-onset thrombocytopenia associated with acute or chronic placental insufficiency is generally mild and self-limiting when megakaryopoiesis resolves with postnatal normalizing of tissue oxygenation (14). In our study, only 1 PT was administered for early-onset thrombocytopenia due to placental insufficiency. Infections and NAIT are the main etiologies of severe early-onset thrombocytopenia (<50x10^3/µL) (15). However, none of our patients were diagnosed with NAIT; early-onset thrombocytopenia requiring PT in our patients was attributed to bacterial sepsis and severe asphyxia and non-immune hydrops associated with DIC.

Late-onset thrombocytopenia (after postnatal 72 hours) may herald a severe disease, especially if there is a rapid drop in platelet count. The most common causes are bacterial or fungal sepsis and NEC (16). Our study evaluated only thrombocytopenic neonates that received PT. The most common cause of thrombocytopenia requiring PT was bacterial sepsis. This is consistent with the knowledge that bacterial sepsis has a severe

course and frequently necessitates PT (17). Our study showed that the second most common reason for PT was NEC, reflecting its etiological ranking in late-onset thrombocytopenia.

It has been reported that 5-9% of neonates admitted to the NICU undergo PT (7,8). In our study, the frequency of PT among neonates admitted to the NICU during the study period was 4.9%. Del Vecchio et al. evaluated multiple PT applications in a neonatal unit and reported that 59% of the neonates who received PT were exposed to more than one transfusion (8). Similarly, we determined that 56.8% of the patients who received PT during the study period had at least 1 and 37.9% had 3 or more transfusions.

PTs are given to prevent or treat hemorrhage. In most cases, non-hemorrhage neonates are treated with prophylactic PT when their platelet count falls below a certain thresshold, with the intention to prevent major hemorrhage and particularly ICH in preterm infants (18). However, there is insufficient evidence related to the transfusion threshold that will best protect the patient with thrombocytopenia. Current practice is heterogeneous and based primarily on expert opinion (19-24). The transfusion thresholds used in Canada and America are higher compared to those used in Europe (25). The Turkish Neonatal Society (TNS) recommends PT for all neonates with platelet count <20x10^3/µl; neonates with platelet counts of 20x10^3/µl - 49x10^3/µl who are ELBW, have comorbid coagulopathy or severe comorbidity, minor hemorrhage, or are scheduled for an invasive procedure; and neonates with platelet counts <50x10^3/µl who have active/major hemorrhage, are being prepared for surgery, or develop DIC (13). Our findings indicate that the PT thresholds used in our center are consistent with TNS recommendations.

It is not clear whether a more liberal transfusion threshold prevents hemorrhage, but it definitely increases exposure to donor blood products (25). In our study, major hemorrhage (pulmonary hemorrhage) occurred after only 1 prophylactic PT (0.08%). However, since we did not have a thrombocytopenic control group that was not given PT, we do not have the necessary data to draw a definitive conclusion regarding the effectiveness of prophylactic PT in the prevention of hemorrhage. Analysis of the therapeutic PTs revealed that the major hemorrhage that precipitated PT also persisted after transfusion. This finding points to the influence of factors other than thrombocytopenia in the occurrence of major hemorrhage.

The TNS recommends conducting platelet counts at least twice, once at 1 hour and again at 24 hours after PT, to assess its effectiveness (13). We found that the mean interval between PT and follow-up platelet count did not vary based on the patients' initial platelet counts. In most cases, platelet count was done 24 hours post-PT. Considering that only 1 patient developed major hemorrhage following prophylactic PT and this patient had platelet count within normal limits when this new hemorrhage occurred, an interval of 24 hours seems safe for these patients. However, the new major hemorrhage following therapeutic PT in our series indicates that platelet counts should be done more frequently to avoid the thrombocytopenia that causes hemorrhage.

Limitations of this study are that it is retrospective and there is not a thrombocytopenic control group that did not have PT. Moreover, because not all of the patients' files had records regarding the presence of minor hemorrhage, we could not establish a data set on this topic in our study. The study was cross-sectional and thus our analysis did not include outcomes from beyond the study period.

CONCLUSION

In conclusion, in this study we identified bacterial sepsis and NEC as the two most common clinical indications for PT. The threshold platelet counts we used for PT are concordant with those recommended by the TNS. In general, prophylactic PT was not followed by major hemorrhage, whereas recurrent major hemorrhage occurred after therapeutic PT. Therefore, randomized controlled studies are needed to determine a safe PT threshold value based on a scoring system for predicting the risk of major hemorrhage.

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