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The Effect of Platelet Transfusions on the Mortality in Neonatal Intensive Care Unit

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Abstract

Background: Platelet transfusions (PTs) currently are the only available treatment to thrombocytopenic neonates at risk of bleeding. There is much evidence indicates that increasing number of platelet transfusions administered to thrombocytopenic neonates increasing the mortality rate, but this association is controversial.

Aims: The main aim of this study is to reveal if PTs increase the mortality in Neonatal Intensive Care Unit (NICU). Secondary outcomes include:

1. To identify most common causes and hemorrhagic manifestations of thrombocytopenic patients who received platelets.
2. Platelets count and mean platelets volume (MPV) changes after PTs.

Design: Retrospective cohort study.

Setting: NICU at maternity and children hospital.

Materials and Methods: Records review of all thrombocytopenic neonates who received PTs at any time during NICU stay from January 2006 till December 2014.

Statistical Analysis: Binary logistic regression.

Results: A total of 756 PTs were given to 150 thrombocytopenic patients. PTs didn't significantly increase the mortality (OR: 1.067, CI: 0.967-1.178). Giving platelets to thrombocytopenic neonates at risk of bleeding with necrotizing enterocolitis (NEC) ≥2 significantly decreased the mortality (OR: 0.16 CI: 0.033-0.85). Mechanical ventilation >2 days because of respiratory failure decreased the mortality (OR: 0.117, CI: 0.02-0.65). The most common cause of thrombocytopenia that led to PT was proven sepsis. The most common hemorrhagic manifestation was intraventricular hemorrhage (IVH). The median increment of platelets count after 162 PTs was 46.5. MPV after 126 PTs tended to decrease by a median of 0.74 fL (femtolitre).

Conclusion: Giving PTs to thrombocytopenic neonates at risk of bleeding didn't increase the mortality. PT may decrease the mortality in thrombocytopenic neonates at risk of bleeding with NEC ≥ 2.

Keywords: Platelets transfusion; Mortality; NICU; thrombocytopenia

Introduction

Thrombocytopenia is defined as a platelet count below the fifth percentile reference range for gestational age and postnatal age [1], it affects 22–35% of infants admitted to the NICU [2-4]. Causes of thrombocytopenia can be classified by several different methods including platelet size (i.e., large, normal, and small), mode of acquisition (congenital or acquired), early (<72 hours of age) or late (≥72 hours of age) onset, gestational age, or underlying pathologic mechanisms. Increased platelet destruction is the most common mechanism for neonatal thrombocytopenia.

PTs represent the only specific therapy currently available for most thrombocytopenic neonates, and most of them are given prophylactically to non-bleeding neonates. Risks of PTs include transmission of bacterial and nonbacterial infections, alloimmunization, febrile reactions, hemolytic reactions, allergic reactions and transfusion-related lung injury.

There is much evidence indicates that increasing number of PTs administered to thrombocytopenic neonates increasing the mortality rate. It is unknown if this increasing in mortality rate is due to direct toxic effect of platelets transfusion, but this association is not conclusive. The main aim of this study is to reveal if PTs increase the mortality rate in NICU taking in an account other comorbid factors. Secondary outcomes included:

1. To identify most common causes and hemorrhagic manifestations of thrombocytopenic patients who received PTs.

2. Platelets count and MPV changes after PTs.

Method and Materials

Retrospective cohort records study conducted at a maternity and children hospital for all thrombocytopenic babies who received PTs in the NICU from January 2006 till December 2014. Data included:

1. Patients' characteristics: Gestational age (GA), birth weight (BW), gender, place of delivery, mechanical ventilation because of respiratory failure more than two days.

2. Causes of thrombocytopenia that led to platelets transfusion: asphyxia, which is defined as Apgar score less than 5 at 5 minutes, small for gestational age (SGA), pregnancy induced hypertension (PIH) , proven sepsis, unproven sepsis (clinical sepsis with negative blood culture), fungal sepsis, immune causes, genetic causes, NEC ≥2, DIC, and unknown causes.

3. Clinical manifestations of thrombocytopenia included: Cutaneous bleeding, defined as bruising or petechial or oozing from previous venipuncture sites, gastrointestinal bleeding, defined as gross blood per rectum (not Guaiac only and not identified as NEC or as a streak of blood from a rectal fissure), pulmonary hemorrhage, defined as endotracheal tube bleeding associated with desaturation and chest X-ray infiltrates, intraventricular hemorrhage (IVH) was diagnosed by ultrasound and graded by using the system of Papile et al. [5]. Other hemorrhages included hematuria and intra-abdominal bleeding.

4. Number of (platelets, packed red blood cells [PRBC], fresh frozen plasma [FFP]) transfusions.

5. Number of mortalities, whether during or after PTs.

6. Platelet counts and mean platelet volumes (MPVs) within 24 hours of platelets transfusion. Our guideline for administering PTs to neonates at risk of bleeding in our NICU during this period were as follow:

1. Platelets counts <100, and symptomatic bleeding.

2. Platelets counts<50 in unstable patients.

3. Platelets counts <30 in stable patients.

The platelets were pooled, but not volume-reduced, leukoreduced or irradiated. The Platelets were transfused via a peripheral intravenous line over 30 to 60 minutes at a volume of 10 to 20 mL/kg body weight.

Statistical analysis

Means and SDs were used to express values in groups that were normally distributed, medians and ranges were used to express values in groups that were not. Univariate and multivariate binary logistic regression were used to determine the effect of different independent variables on the mortality (dependent variable).

Univariate variables with P-values of ≤0.25 and important variables were included in multivariate model. The final model specifies odds ratios (ORs) and 95% confidence intervals (CIs), P-values. Tests of the final model quality included, Omnibus test of mode coefficient, Nagelkerke R Square, Hosmer and Lemeshow test. SPSS version 18 was used for data analysis.

Results

A total of 756 PTs were given to 150 thrombocytopenic patients, mean BW: 1570 ± 880 grams ranged from 510 grams to 5000 grams. Mean GA: 31.8 ± 4.7 weeks, ranged from 25 to 42 weeks. Fifty one percent (77/150) were male. Seventy four percent (112/150) were preterm infants. Seventy nine percent (119/150) were inborn, eighty three percent (125/150) were ventilated. The most common cause of thrombocytopenia that led to PTs was proven sepsis (62%, 94/150), Figure 1.

The most common hemorrhagic manifestation was IVH (21%, 32/150), Figure 2. Forty four percent (66/150) of patients died in NICU, seventy seven percent (51/66) died during thrombocytopenia. The median increment of platelet counts after 162 PTs was 46.5 ranged from -26 to 391. MPV of 126 readings tended to decrease after PTs by a median of 0.74 fL (femtolitre) ranged from 11.8 to -7.8 fL. Total number of Packed Red blood cells (PRBC), Fresh frozen plasma (FFP) were (659 and 318) respectively.

Univariate binary logistic regression included 23 variables, fourteen of them included in multivariate logistic regression, Tables 1 and 2. PTs did not significantly increase the mortality (OR:1.067, CI: 0.967-1.178). None of the other variables significantly increased the mortality, in reverse, giving PTs to thrombocytopenic patients at risk of bleeding with NEC significantly decreased the mortality (OR:0.16, CI:0.033-0.85, P:0.03). Mechanical ventilation >2 days because of respiratory failure decreased the mortality (OR:0.117, CI:0.02-0.65, P: 0.014).

The final model predicted 78% of the outcome, P value of omnibus test of mode coefficient was 0.0001, P value of Hosmer and Lemeshow test was 0.51, which indicated a strong model. Nagelkerke R Square was 0.40, which indicated that 40% of the variability in mortality (dependent variables) was explained by the independent variables.

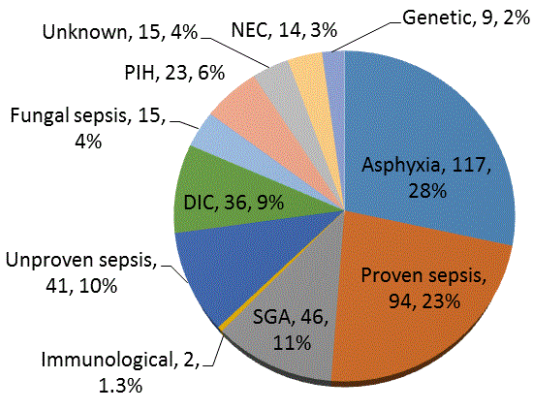

Figure 1: Causes of thrombocytopenia in 150 patients.

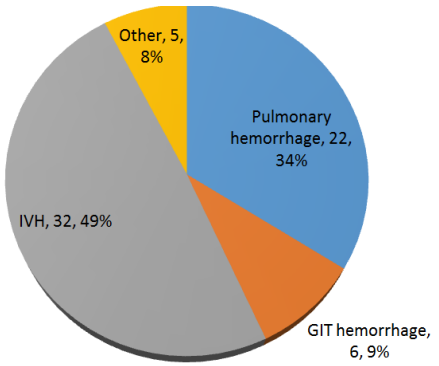

Figure 2: Clinical manifestations of thrombocytopenia in 150 patients.

variable	OR	P-value	95% C.I. for OR	
SEX	2.499	0.021	1.148	5.439
PTs	1.067	0.198	0.967	1.178
FFP	1.334	0.006	1.087	1.636
PRBC	1.05	0.409	0.935	1.179
IVH	0.444	0.095	0.171	1.152
Pulmonary hemorrhage	0.163	0.003	0.049	0.535
Cutaneous hemorrhage	0.428	0.162	0.13	1.405
Ventilations>2 days	0.046	0.003	0.006	0.355
DIC	0.205	0.002	0.077	0.547
NEC	0.138	0.075	0.016	1.221
Unproven sepsis	0.347	0.018	0.144	0.836
Proven sepsis	0.502	0.086	0.229	1.103
SGA	2.497	0.052	0.99	6.296
GA	0.926	0.072	0.851	1.007
BW	0.83	0.35	0.57	1.22
A/S	1.07	0.84	0.49	2.3
Fungal sepsis	0.88	0.82	0.3	2.58
genetics	1.01	0.97	0.26	3.95
Unknown causes	1.19	0.74	0.4	3.55
inborn	1.24	0.58	0.56	2.76
PIH	1.02	0.95	0.41	2.51
Immune causes	1.2	0.999	0.2	.4,2
Other	0.87	0.999	0.3	2.7
OR: odd ratio, 95% C.I.: 95% confident interval				

Table 1: Monovariate regression analysis.

variable	OR	P- value	95% C.I. for OR	
SEX	1.545	0.305	0.673	3.546
PLT	0.982	0.711	0.893	1.08
FFP	0.994	0.958	0.807	1.225
PRBC	0.963	0.63	0.825	1.124
IVH	1.646	0.389	0.529	5.116
Pulmonary hemorrhage	0.326	0.082	0.092	1.153
Cutaneous hemorrhage	0.583	0.466	0.136	2.49
Ventilations >2 days	0.117	0.014	0.021	0.653
DIC	0.333	0.064	0.104	1.065
NEC	0.169	0.031	0.033	0.853
Unproven sepsis	0.637	0.529	0.156	2.595
Proven sepsis	1.689	0.45	0.434	6.566
SGA	1.319	0.592	0.48	3.621
GA	0.985	0.722	0.908	1.069

Table 2: Multivariate regression analysis.

Discussion

Much evidence indicates that PTs is not entirely benign. Risks include transmission of bacterial and nonbacterial infections, alloimmunization, febrile reactions, hemolytic reactions, allergic reactions and transfusion-related lung injury [6-10], but the risk of increasing mortality is still controversial.

Many studies showed increasing mortality in neonates receiving PTs. Borges et al. showed that mortality was four times greater for premature infants who received PTs [11]. Christensen et al. found that the mortality rate among extreme low birth weight (ELBW) that received PTs was twice that of those who received no PTs in a cohort study [4]. Baer et al. Showed that the mortality rate increased in 494 thrombocytopenic patients who received platelets in a manner roughly proportional to the number of PTs they received in a regression analysis [12]. Del Vecchio et al. Showed that the overall mortality rate among NICU patients who received one or more PTs was 33 percent, compared with a mortality rate of 3 percent among NICU patients during this period who received no PTs [13]. Other study showed that the mortality rate increased in a step-wise manner according to the number of PTs received in 273 severely thrombocytopenic patients [14]. All of the previous studies except VL Baer et al. didn't use a regression analysis to determine if PTs were the direct cause of increasing the mortality taking into account other co-morbid factors. None of the previous studies concluded that PTs was solely the cause of increasing the mortality in NICU.

In contrast to the previous studies, Von Lindern et al. revealed no difference in the mortality rate in the subgroups of neonates with thrombocytopenia, although one third receiving PTs. There was no difference in mortality rate in neonates with and without thrombocytopenia [15]. Other study found that implementing a program to improve compliance with NICU transfusion guidelines increased compliance from 65% to 90%. Improved compliance with

transfusion guidelines of all blood products was accompanied by a significant reduction in transfusions given, with no change in the mortality rate [16]. Our study showed that giving platelets did not increase the mortality, taking into account the previous comorbid factors, this results will add to the controversy of the effect of PTs on the mortality.

Unexpectedly, the mortality decreased in neonates with NEC ≥2. Up to our knowledge, only one study examined the effect of PTs on the neonatal mortality in patients with NEC ≥2, which showed no change in the mortality with greater number of platelet transfusions in 46 infants with NEC ≥2 [17]. In our study, 14 neonates had NEC ≥2, which was the probable potential cause of thrombocytopenia that required PTs.

Interestingly, neonates who had been mechanically ventilated >2 days because of respiratory failure, had less mortality rate, this could be attributed to maintaining the airway of sick neonates with respiratory failure, which by itself is lifesaving. In our study, we did not take into account the temporal relationship between PTs and mechanical ventilation. To our knowledge, no study has revealed such an association in thrombocytopenic neonates who received PTs.

MPVs tend to decrease post PTs, this could be explained by platelet storage lesion which may make platelets older and smaller. Median increase in platelet count is 46.5. In general, administration of 10 to 15 mL/kg of platelet suspension will increase the platelet count by 30,000 to 100,000/micro L.

Neonatal sepsis was the most frequent disease at the time of PTs, which is in agreement with the findings of other studies [11,18,19]. Sepsis predisposes neonates to thrombocytopenia, with a rapid drop in the platelet count and slow recovery, in many cases, leading to multiple transfusions.

The most common hemorrhagic manifestation was intraventricular hemorrhage, this may be because 74% of the patients were preterm, and we considered any grade of IVH. We didn't consider the temporal relation between IVH and thrombocytopenia or platelets transfusion, therefore IVH could not be attributed to thrombocytopenia or platelets transfusion in our study. Although some studies reported that neonates receiving multiple platelet transfusions actually had a higher incidence of intraventricular hemorrhage, it is uncertain whether the observed association between PTs and IVH is a cause and effect relationship or, alternatively, is a chance finding [12,20].

Our study has limitations, first being retrospective. Second, we found occasional breach in platelets transfusion guidelines with no explanation. Third, we considered most but not all the factors that can affect the mortality. Further studies are needed to reveal whether PTs increase the mortality in NICU and whether it is beneficial in NEC patients. We conclude that giving platelets to neonates at risk of bleeding didn't increase the mortality in NICU. Giving PTs to thrombocytopenic neonate at risk of bleeding with NEC ≥2 might improve the survival.

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