

Incidence and complications associated with platelet transfusion in preterm newborns from 26 to 35 weeks in a third-level hospital in Mexico

Abstract

Introduction: Platelet transfusions are an important and vital part of neonatal intensive care units because they can stop serious complications such as massive and active bleeding, which can occur during surgical procedures or in infants diagnosed with thrombocytopenia. They are currently the second most common blood product transfusion.^{1,2}

Recent studies suggest that its excessive use may be associated with adverse effects, including a significant increase in mortality.¹⁻⁶ Higher incidence of bronchopulmonary dysplasia, sepsis, enterocolitis, and in one study reported in mice, pulmonary hypertension.⁷⁻⁹

Aim: To determine the incidence of platelet transfusions, and their impact on neonates in the neonatology service of the National Institute of Perinatology from 2019 to 2023 associated with long-term inflammatory diseases.

Materials and methods: This is a retrospective, descriptive, and multifactorial observational study. Locatable records of patients discharged from the Neonatology service of the National Institute of Perinatology from 2019 to 2023 will be used.

Results: were included, with a gestational age of 26 to 35 weeks of gestation, 54.3% were male, and cesarean section was predominant in 81.2%.

The most frequent pathologies in premature neonates were studied before and after platelet transfusion. Respiratory distress syndrome predominated prior to platelet transfusion, and late-onset sepsis was the most prominent cause of thrombocytopenia. Intraventricular hemorrhage occurred in 45.7% of our patients prior to platelet transfusion. During surgical procedures, 19.6% required platelet transfusion either during or prior to the procedure due to pre-existing thrombocytopenia.

15.9% presented active bleeding through endotracheal cannula, and 10% presented disseminated vascular intravascular coagulation.

Conclusions: Currently there is little evidence, so the use of protocols in each institution with restrictive indications for platelet transfusions to neonates constitutes the best preventive strategy.

Keywords: neonate, platelets, platelet transfusion, bronchopulmonary dysplasia, hemorrhage, inflammatory diseases

Introduction

Platelet transfusions are an important and vital part of neonatal intensive care unit management, as they can stop severe complications secondary to massive and active bleeding.^{1,2}

On March 4, 1908, the first blood transfusion was performed on a full-term newborn; since then, its use has steadily increased. Currently Platelet transfusions are the second most common blood product transfusion in neonates, used to prevent bleeding; however, much of the evidence on protocols and safety for their administration is based on adult patients with oncological or hematological pathologies, without a standardized protocol for newborns that considers the specific characteristics of this patient population.¹

In 1993, Andrew et al.¹⁻³ published the first clinical study on platelet transfusions in newborns, with the aim of investigating. This study aimed to determine whether early platelet administration in patients with platelet counts below 150,000 would reduce the

Volume 16 Issue 1 - 2026

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Received: January 7, 2025 | **Published:** January 23, 2026

incidence or extent of intracranial hemorrhage according to the Papille classification compared with initiating transfusion in patients with counts below 50,000. It included 152 preterm infants born before 33 weeks of gestation with birth weights between 500 and 1500 g. Patients with counts of 150,000 or below were monitored until day 7 with a maximum of 3 transfusions; the group with counts below 50,000 received no transfusions unless their platelet count decreased or they presented with signs of bleeding. Transfontanellar ultrasound was performed before treatment and on days 7 and 10. The incidence of new or increased intracranial hemorrhages was comparable between the two groups. However, an increase in the number of severe intracranial hemorrhages was observed in the 150,000 platelet group compared to the more restricted group.⁴⁻⁶

Years later, in 2019, two more trials were published, one by Kumar et al. in India and the other by Curley et al. in the UK, Ireland, and the Netherlands. These trials compared platelet counts and the use of restrictive versus free transfusion practices in premature infants. Both studies found that more liberal platelet transfusions, with a platelet

count greater than 100,000 in the first study and greater than 50,000 in the second, increased the risk of bleeding or the spread of hemorrhage. Therefore, the study concluded that limiting platelet transfusions was recommended. However, the exact platelet count threshold for platelet administration remains unknown, and there is considerable variation in clinical practice and among institutions.⁴⁻⁶

Platelet transfusions must be performed judiciously, as they are not without risk; because the cells come from adults, they can cause inflammatory reactions in newborns.^{7,8}

Recent studies suggest that its excessive use may be associated with adverse effects, including a significant increase in mortality, a higher incidence of bronchopulmonary dysplasia, sepsis, enterocolitis, and, in one study reported in mice, pulmonary hypertension.⁷⁻⁹

These findings prompt us to re-evaluate and study current platelet transfusion protocols in neonatal intensive care units to determine and balance benefits and risks, generating precise and non-excessive indications to improve short- and long-term outcomes.^{7,8} multiple systematic reviews report that a large percentage of neonates with thrombocytopenia can recover their platelet counts without platelet transfusion.^{2,7,8}

A high association between thrombocytopenia and bleeding, especially intraventricular hemorrhage due to prematurity, has been found in premature infants. Previously, it was common practice to transfuse infants with platelet counts even higher than those used in children or adults to reduce bleeding; however, it was found that multiple transfusions or prophylactic transfusions increase bleeding more in these patients than in newborns who did not receive platelet transfusions.^{1,2} This finding is described in PlaNeT-2, the largest randomized study of platelet transfusion in premature infants, which reported a significantly higher incidence of severe bleeding or death among infants with platelet counts below 50,000 compared to those with a platelet count below 25,000.^{1,2,8,10}

A randomized trial comparing prophylactic transfusions in neonates showed no benefit in maintaining a normal platelet count of 150,000/mm³ to prevent intraventricular hemorrhage in 152 preterm neonates.^{4,7,8,10}

Neonatal hemostasis differs from that in adults, which again leads us to consider the benefits and risks, since it is important to remember that all blood components are biological products that can carry risks and adverse events associated with their transfusion, such as circulatory overload, administration errors, infections, or inflammatory reactions due to differences in their function.⁷

Studies of platelets have shown that their functions extend beyond primary hemostasis, becoming involved in inflammatory and immunological processes.^{7,8}

The PlaNeT-2/MATISSE study showed a higher incidence of bleeding and mortality in patients receiving platelet transfusions in the on-demand group with higher platelet counts; however, although the causes of these mechanisms are unknown, several proposals exist based on the damage mechanisms observed in vitro in mice.^{5,7,10,11}

The first is that preterm infants generally receive larger volumes during transfusion compared to adults. Circa compares 15 ml/kg versus 5 ml/kg. Furthermore, volume expansion following platelet administration can induce hemodynamic changes that could contribute to a higher risk of hemorrhage by altering blood flow to the brain and germinal matrix of neonates.^{5,7,10}

Another difference is that there are structural developmental differences in platelets between adults and premature infants. Adult platelets are functionally hyperreactive, while neonatal platelets are hyporeactive.⁸

Platelets may be very similar in number, but their functional capabilities are lower, resulting in a particularly short bleeding time.^{7,8} Theoretically, the lifespan of neonatal platelets is longer to compensate for lower production. This review was prompted by the observation that many infants did not present with bleeding symptoms, including those with severe thrombocytopenia.^{7,8,10}

Developmental differences between platelets in neonates and platelets in adults

Among the differences between neonatal and adult platelets, it was found that adult platelets have different functions and exhibit higher levels of glycoprotein IIb/IIIa activation and P-selectin exposure, as well as greater aggregation in response to most agonists compared to neonatal platelets.^{1,7,8,10} *In vitro* studies were conducted in which adult human platelets were mixed with thrombocytopenic neonatal blood, generating a prothrombotic phenotype.¹⁰⁻¹²

Platelets are primary hemostatic cells and are essential for controlling bleeding. Previously, it was theorized that this was their only function, but after several studies, it has been shown that platelets are key in many non-hemostatic processes, including the inflammatory response to infections, vascular growth, tone and activity, and tumor biology,^{12,13} and immunoregulatory role.^{7,12,13}

This defense mechanism against infections occurs because platelets express pattern recognition receptors, including Toll-like receptors, through which they identify molecular patterns associated with damage and molecular patterns associated with pathogens.^{7,12,13} Signaling through these receptors triggers the production and release of inflammatory cytokines and antimicrobial molecules.⁷

Platelets have the ability to interact with immune cells such as neutrophils and monocytes. Upon activation, they express multiple ligands on their surface, releasing immune mediators. These platelet and leukocyte aggregates enhance platelet activation and increase the activation and mobilization of neutrophils and monocytes.^{7,12} The presence of higher levels of P-selectin in adult platelets could indicate a greater capacity to activate immune cells, which could trigger and increase systemic inflammation.^{1,7,12,13}

Although the degree of hyporeactivity of neonatal platelets might suggest a bleeding phenotype, studies have found shorter bleeding times in term neonates compared to healthy adults.⁷ Furthermore, preterm neonates have longer bleeding and closure times than term neonates, but still within the normal range for adults. This is explained by the fact that neonatal platelet hyporeactivity is well balanced by neonatal factors that promote and accelerate coagulation, such as high hematocrit, high mean corpuscular volume, and high concentrations of von Willebrand factor.⁷

One study compared the proteome of neonatal and adult platelets, finding approximately 170 different proteins involved in functions such as mitochondrial energy metabolism, fatty acids, and iron binding. Adult platelets, on the other hand, contained proteins related to platelet activation in the inflammatory and complement response. These differences support the hypothesis that platelets have different functions at different stages of development and that adult platelets are more immunoactive.^{13,15}

Effects of platelet transfusions in neonates

Given that adult platelets have a more hyperreactive and possibly more immunoactive function, a key question in the context of platelet transfusions to neonates has been whether transfused adult platelets impact neonatal hemostatic and immunological responses differently, and what the potential adverse effects are in these patients.¹⁵ Multiple studies have been conducted analyzing their function; one of them mixed umbilical cord blood from a full-term infant with thrombocytopenia with adult and neonatal platelets, demonstrating that adult platelets exhibited a significant shortening of their closure in response to collagen and epinephrine, with levels associated with a higher prothrombotic risk of cardiovascular events.¹⁶ This study supports the hypothesis that adult platelets, within the context of neonatal hemostasis, generate a prothrombotic phenotype by promoting microvascular thrombosis in critically ill neonates, worsening diseases characterized by tissue ischemia, such as enterocolitis.^{14–16}

To determine the inflammatory effect of platelet transfusion in neonates, a group of authors transfused adult platelets into 10-day-old mice and found elevated levels of inflammatory cytokines in plasma, including interleukin-6, two and four hours after the platelet transfusion, indicating that platelet transfusions can induce an inflammatory response in neonates.^{16,17}

Finally, Maurya et al. investigated whether the developmental stage of adult platelets transfused into neonates affects the monocyte phenotype, finding that transfusion of platelets with different developmental stages can alter the neonatal immune balance and lead to dysregulated immune responses, potentially increasing monocyte migration to inflamed tissues.¹⁸

The reasons for the increased risk of intraventricular hemorrhage when neonates are transfused more liberally or with a platelet count greater than 50,000 are unknown, but it has been hypothesized that they may be related to hemodynamic factors associated with the rapid infusion of a large volume over a short period.^{7,19}

Neonates in the PlaNeT-2 trial received 15 mL/kg of platelets over 30 to 60 minutes. This volume is approximately three times greater than the 5 mL/kg usually transfused to older children or adults, and it is possible that this rapid infusion causes hemodynamic changes leading to bleeding in the delicate vasculature of the germinal matrix.^{5,20}

Possible adverse effects

The PlaNeT-2 study also describes a major finding: an increase in bronchopulmonary dysplasia, with a higher incidence and association between the number of platelet transfusions and increased neonatal morbidity and mortality.^{5,7,20}

Bronchopulmonary dysplasia is the result of a complex, multifactorial process involving prenatal and postnatal factors.^{20–23} Its development is due to pulmonary inflammation and arrest of alveolarization, and depending on its severity, it is associated with prolonged hospitalizations, neurodevelopmental disorders, nutritional deficiencies, and pulmonary infections.^{20–23} According to studies by SIBEN, this occurs in 25–40% of preterm newborns, those born before 32 weeks of gestational age. While this morbidity cannot currently be avoided, its prevalence, incidence, and severity can and should be reduced.²³

Adult platelet transfusions are more pro-inflammatory when transfused into neonates than when transfused into adults. Almost

all infants who develop severe bronchopulmonary dysplasia have received transfusions, suggesting that, although understudied, they could be contributing factors to bronchopulmonary dysplasia.^{21,22}

The mechanisms are unclear; it has been hypothesized that this relationship could be linked to functional differences between neonatal and adult platelets, and the migration of monocytes to inflamed tissues such as the lung, generating pro-inflammatory effects from transfused adult platelets in critically ill neonates.^{22–24}

Ribeiro et al. found that transfusions of adult platelets to neonates potentially increased mortality and morbidity, including sepsis and necrotizing enterocolitis in premature infants.²⁵ In the study by Davenport et al., platelet transfusion was disproportionately associated with higher mortality rates, and severe neurodevelopmental problems were observed at two years of corrected age. This suggests the possibility that platelet transfusions may also affect the developing brain.²⁶

How much and who?

Each hospital generally has its own transfusion guidelines and protocols, and it is vital to standardize them. The 2015 French guidelines recommend the use of single-donor, pediatric-processed, deplasmatized platelet concentrates, respecting the ABO blood group system. The recommended transfusion volume is 15 to 20 mL/kg with a transfusion time of 60 minutes.^{7,27–29} Transfusion is recommended for patients with a platelet count less than 25,000/mm³ without evidence of bleeding and without a surgical procedure, compared to patients with a platelet count of 50,000/mm³ who have evidence of bleeding in the last 72 hours and require a surgical procedure.^{7,27–29} Among premature neonates with a platelet count of 50,000/mm³, prophylactic transfusions resulted in a higher rate of death or severe hemorrhage compared to those with a platelet count of 25,000/mm³.^{3,27–29}

Problem statement

Given the potential complications and adverse events associated with imprudent platelet transfusion, it is vitally important to provide appropriate treatment according to each patient's platelet count.

Research question

What is the incidence of platelet transfusions at the National Institute of Perinatology and what are the complications associated with this practice?

Goals

General objective

Describe the factors associated with neonatal platelet transfusions in the Neonatology sub-directorate of the National Institute of Perinatology from January 1, 2019 to December 30, 2023.

Specific objectives

- (i) Describe the frequency of maternal thrombocytopenia secondary to preeclampsia associated with neonatal thrombocytopenia.
- (ii) To describe the frequency of bronchopulmonary dysplasia reported in association with platelet transfusions in neonates.
- (iii) Describe the frequency of clinical and biochemical data in patients with neonatal thrombocytopenia.
- (iv) Describe the treatment used in the management of neonatal thrombocytopenia.

(v) To determine the existence of an association between clinical, biochemical, and treatment variables.

Materials and methods

Research classification (type of study): This is a retrospective, descriptive, multifactorial observational study.

The records of patients discharged from the Neonatology service of the National Institute of Perinatology from 2019 to 2023 will be used.

Population universe

Newborns in the Neonatology service from January 1, 2019 to December 30, 2023.

Eligible population

Records of newborns diagnosed with thrombocytopenia who required platelet transfusion during their hospital stay.

Inclusion criteria

- Locatable and complete records of patients from the Neonatology service of the National Institute of Perinatology diagnosed with thrombocytopenia.
- Both sexes.

Exclusion criteria

Records of patients who have not been diagnosed with thrombocytopenia.

Elimination criteria

Incomplete patient records.

Place or site of study

Deputy Director of Neonatology of the National Institute of Perinatology, Isidro Espinosa de los Reyes.

Method

A list of patient records from the National Institute of Perinatology's blood bank and medical records department was requested for all patients discharged from the Neonatology service who received platelet concentrate transfusions as treatment. This list was supplemented with the Neonatology service's electronic statistics. The records were located in the medical records department, and the required data were reviewed. The form created for this purpose was completed, collecting demographic, clinical, hematological, and patient progress data. The data was then compiled into an Excel spreadsheet for processing.

Sample size

A convenience sampling will be carried out that will include all locatable cases of newborns discharged from the Neonatology service of the National Institute of Perinatology from January 1, 2019 to 2023.

Statistical analysis

In the first phase, a database was created using Microsoft Excel. This database was then exported to SPSS version 21, the statistical software used to analyze the information. The results of the study are presented in tables, charts, or graphs.

Descriptive statistics were performed on qualitative variables, expressed as frequencies and percentages. For quantitative variables, the mean and standard deviation were determined. A p-value < 0.05 was established to determine statistical significance.

Ethical considerations

The study was retrospective; given the nature of the study, informed consent was not required. Patient information will be kept confidential, and their identities will not be disclosed. No individual data will be included.

Results

138 patients were included, with a gestational age of 26 to 35 weeks, with an average weight of 1283 (± 592) g, the most frequent sex being male (54.3%).

The most common delivery method was cesarean section in 81.2% of cases, perhaps associated with the high prevalence of maternal comorbidity treated at INPer, the most frequent of which was preeclampsia with a total of 46 patients (33.3%).

Regarding the newborns, the majority required advanced resuscitation (73.9%), probably associated with pathologies such as intrauterine growth restriction and maternal history of preeclampsia with severe symptoms that can cause fetal distress (Table 1).

Table 1 Demographic characteristics of the population

Variable	n= 138
Gestational age (SDG+)	30 of 2.8
Weight (G +)	1283 of 592
Sex (n/%)	
Male	75 (54.3%)
Female	63 (45.7%)
Via birth (n/%)	
Delivery	26 (18.8%)
Caesarean section	112 (81.2%)
Maternal pathology (n/%)	
Systemic arterial hypertension	32 (23.2%)
Preeclampsia	46 (33.3%)
Maternal thrombocytopenia	46 (33.3%)
Advanced resuscitation (n/%)	
Yeah	102 (73.9%)
No	36 (26.1%)

In patients with thrombocytopenia who received platelets, the main comorbidities were analyzed before and after transfusions, the most frequent (before and after transfusions) being bronchopulmonary dysplasia (61.15%) followed by late sepsis (49.74%) and in third place necrotizing enterocolitis with 12.35%, the rest of the diseases studied are shown in Table 2.

Table 2 Morbidity associated with platelet transfusion

Variable	Prior to platelet transfusion	Following platelet transfusion	p
Respiratory distress syndrome (n/%)			
Yes	87 (86.72%)	1 (0.72%)	683238
No	1 (1.28%)	49 (49.28%)	
Necrotizing enterocolitis (n/%)			
Yes	48 (58.65%)	23 (12.35%)	<0.0001

Table 2 Continued...

No	66(55.35%)	1 (11.65%)	
Bronchopulmonary dysplasia (n/%)			
Yes	11 (35.85%)	86(61.15%)	<0.00001
No	40 (40.75%)	1 (25.85%)	
Early sepsis (n/%)			
Yes	30(43.40%)	22 (8.60%)	<0.0001
No	85 (71.60%)	1 (14.40%)	
Late sepsis (n/%)			
Yes	39 (54.26%)	65 (49.74%)	<0.0001
No	33(17.74%)	1(16.26%)	
Pulmonary arterial hypertension (n/%)			
Yes	20 (30.3%)	14 (3.7%)	<0.00001
No	103 (92.7%)	1 (11.3%)	
Retinopathy of prematurity (n/%)			
Yes	13 (24.75%)	15 (3.25%)	<0.00001
No	109 (97.25%)	1 (12.75%)	
Intraventricular hemorrhage (n/%)			
Yes	40 (52.04%)	23 (10.96%)	<0.00001
No	74 (61.96%)	1 (13.04%)	

Regarding the indications for transfusion, 19.6% of patients received a transfusion prior to a surgical procedure; in this group, the average platelet count before the event was 49,000. 15.9% received a transfusion due to active bleeding from an endotracheal tube with a platelet count of 48,000, and 10% presented with disseminated intravascular coagulation with a platelet count of 49,000.

Regarding the timing of transfusions, the following was found:

- (i) 95% of patients were transfused every 8 hours.
- (ii) 2% every 12 hours
- (iii) 2% had a single transfusion during their hospital stay
- (iv) The predominant transfused volume was 10 ml/kg of weight

The time at which the transfusion was performed:

- (i) Bolus 93.5%
- (ii) 10 minutes 3.6%
- (iii) 15 minutes 1.4%
- (iv) 30 minutes 1.4%

Discussion

In the present study, it was observed that most mothers presented with severe preeclampsia, which, according to the literature, is a risk factor associated with morbidity due to the hypoxic intrauterine environment to which the baby is subjected. This is a risk factor that increases morbidity and mortality, as well as the risk of thrombocytopenia in newborns.²

In this study, most patients were premature infants with lower gestational age and low birth weight, significantly increasing the risk of transfusion and the number of transfusions per patient. Thrombocytopenia in these patients can have a multifactorial origin, beginning with intrauterine factors such as infections in the cervicouterine tract, preeclampsia (not necessarily with platelet involvement in the mothers), sepsis, autoimmune origin, or active bleeding.³⁻⁵

The risk of bleeding increases with lower gestational age, so one of the variables analyzed was intraventricular hemorrhage, which,

although it had a statistically significant value, did not result in transfusions for this cause in patients.⁷

The literature reports that when a patient presents with thrombocytopenia and active bleeding simultaneously, platelet transfusion is indicated without question. However, in the context of prophylactic transfusions, the risk may outweigh the benefit because they are not harmless, and an increase in inflammatory diseases has been observed in the long term.⁴

In the studied population, the only prophylactic platelet transfusions—that is, in patients without active bleeding and without platelet counts below 25,000—were those administered prior to surgical procedures. It should be noted that during surgery, several patients with normal platelet counts received transfusions due to active bleeding during or after the procedure.

Adult platelets, when used in neonatal hemostasis, generate a prothrombotic phenotype by promoting microvascular thrombosis in critically ill neonates, worsening diseases characterized by tissue ischemia such as enterocolitis.¹⁴⁻¹⁶ In the present study, a statistically significant increase in cases of enterocolitis was found after platelet transfusions; however, it should be noted that transfusions are not the only direct cause, as necrotizing enterocolitis is a multifactorial neonatal pathology.

In the present study, a slight increase in the requirement for platelet transfusions was observed in critically ill patients with late neonatal sepsis, and in patients who required a greater number of platelet transfusions.

Among patients who received platelets, the increased incidence of reported cases of bronchopulmonary dysplasia without respiratory distress syndrome is noteworthy. Although dysplasia is a disease of prematurity associated with multiple causes, the fact that they received adult (hyperreactive) platelets is likely a contributing factor to the pulmonary inflammation.

Conclusion

It is vitally important to know the maternal history, and to identify if there is a hypoxic intrauterine environment as one of the risk factors for thrombocytopenia secondary to maternal preeclampsia, or any of the maternal morbidities already described in order to identify and monitor at-risk newborns.

Currently, the use of platelet transfusions in neonates is poorly studied and analyzed; however, the literature already contains substantial evidence of their pro-inflammatory potential associated with an increased risk of diseases such as bronchopulmonary dysplasia, neonatal sepsis, and necrotizing enterocolitis, which increase morbidity and mortality in newborns, especially premature and critically ill infants, making it necessary to standardize practices.

The use of protocols with restrictive indications in platelet transfusions to neonates is probably the best preventive strategy, and it is necessary to assess the platelet count, the patient's clinical picture, the risk of bleeding, and the long-term benefits and risks.

Acknowledgments

None.

Funding

This work did not receive external funding.

Conflict of interest

The author declares no conflict of interest.

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