Neonatal Intensive Care Unit Patients Receiving More Than 25 Platelet Transfusions

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Abstract

Objective A few patients in neonatal intensive care units (NICU) receive numerous platelet transfusions. These patients can become refractory, defined as transfusions of ≥10 mL/kg failing to increase the platelet count by at least 5,000/μL. Causes of, and best treatments for, platelet transfusion refractoriness in neonates have not been defined.

Study Design Multi-NICU multiyear retrospective analysis of neonates receiving >25 platelet transfusions.

Results Eight neonates received 29 to 52 platelet transfusions. All eight were blood group O. Five had sepsis, four were very small for gestational age, four had bowel resections, two Noonan syndrome, two had cytomegalovirus infection. All eight had some (19–73%) refractory transfusions. Many (2–69%) of the transfusions were ordered when the platelet count was >50,000/μL. Higher posttransfusion counts occurred after ABO-identical transfusions ($p = 0.026$). Three of the eight had late NICU deaths related to respiratory failure; all five survivors had severe bronchopulmonary dysplasia requiring tracheostomy for prolonged ventilator management.

Conclusion Neonates who are high users of platelet transfusions appear to be at high risk for poor outcomes, especially respiratory failure. Future studies will examine whether group O neonates are more likely to develop refractoriness and whether certain neonates would have a higher magnitude of posttransfusion rise if they received ABO-identical donor platelets.

Keywords

- neonate
- NICU
- platelet transfusion
- refractoriness
- bronchopulmonary dysplasia
- ABO

Key Points

- Many of the platelet transfusions given in the NICU are given to a small subset of patients.
- Refractoriness to platelet transfusions is common among these very high recipients.
- Neonates who are high users of platelet transfusions appear to be at high risk for poor outcomes.

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Many of the platelet transfusions administered in neonatal intensive care units (NICU) are given to a small subset of patients.[1–4] Refractoriness to platelet transfusions, meaning the transfusion fails to increase the platelet count or does so minimally, is common among these very high recipients.[4,5] When refractoriness is encountered in a NICU patient, its cause is seldom obvious, and the best treatment approach is usually unclear.

The Trial to Reduce Alloimmunization to Platelets study, performed on thrombocytopenic adult patients, defined platelet transfusion "refractoriness" as a posttransfusion platelet rise <5,000/μL after two sequential transfusions of the freshest available platelets.[6] One approach to managing adult patients with platelet transfusion refractoriness involves meeting future platelet transfusion needs using ABO-identical platelets.[5,7–9] To our knowledge this approach has not been studied for NICU patients, and it has been suggested as ineffective for older children.[10]

We conducted this study in our multi-NICU health care system, identifying all neonates during the past few years who received >25 platelet transfusions, and analyzing each transfusion to determine whether it met a definition of refractoriness. We also identified the platelet counts that "triggered" each transfusion, and whether the ABO group of each donor/recipient was related to the posttransfusion magnitude of rise.

Materials and Methods

The Intermountain Healthcare Institutional Review Board (IRB) approved this study (IRB number 1051883) as a data-only retrospective analysis. We identified NICU patients who received >25 platelet transfusions from March 1, 2020 through June 30, 2022, using the SafeTrace TX System (Haemonetics, Corp., Boston, MA). Transfusion records were linked with data in the Intermountain Healthcare Enterprise Data Warehouse. This time-period was selected because, starting March 1, 2020, all Intermountain Healthcare NICUs received donor platelets exclusively from the American National Red Cross. All NICUs utilized the same platelet transfusion guidelines, updated April 2019 (►Fig. 1). Neonates with a diagnosis of cancer were excluded from the database to reduce heterogeneity.

The donor platelets were apheresis platelets obtained from plateletpheresis instruments (Fenwal, Baxter Healthcare, Deerfield, IL) utilizing double venous access kits according to the manufacturer's recommendations and the American National Red Cross standard operating procedures. Platelets were stored in autologous plasma or a mixture of platelet additive solution and autologous plasma at 20 to 24°C with agitation. TRALI mitigation strategies had been implemented in all of our transfusion services by April 2014. Bacterial contamination mitigation strategies including pathogen reduction were fully implemented by June 1, 2021. Pathogen-reduced platelets have been prioritized for our NICU population.

Our specific aims were: (1) describe our highest users of platelet transfusions, (2) record the platelet count that preceded each transfusion to these high users, (3) calculate the magnitude of rise in posttransfusion platelet count for every transfusion, and (4) classify each transfusion according to the ABO type of the donor and recipient. We calculated magnitude of rise as the increment in recipient's platelet count (assessed by counts before and after the transfusion). The preferred posttransfusion count was within 60 minutes of completing the transfusion, but we included counts up to 8 hours.

Data were managed using the Redcap (Research Electronic Data Capture) electronic data capture tool. Summary statistics (means, counts, and proportions) were the primary quantitative tools used for analysis. To estimate the difference in mean increase in platelet count in ABO-identical versus nonidentical transfusions, while accounting for clustering by hospital, a linear mixed-effects model was used. Statistical analysis was done in the R language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria).

Results

During this period, 458 NICU patients received 1,948 platelet transfusions. A total of 309 (16%) were administered to only eight neonates, each of whom received >25. ►Table 1 shows features of these eight. The group was heterogeneous in birth weight, diagnosis related to thrombocytopenia, and gestational age at birth, but all were blood group O.

Product	Condition	Indication	Treatment
Platelets	ECMO, surgery, or bleeding	Pl count <100,000/μL	15 - 20 mL/kg over 1 - 2 h
	At risk for IVH and in the first 5 days of life	Pl count <50,000/μL	
	All others	Pl count <25,000/μL	

Fig. 1 Platelet transfusion guidelines used in Intermountain Healthcare during the study period (March 1, 2020, through June 30, 2022). ECMO, extracorporeal membrane oxygenation; IVH, intraventricular hemorrhage; Pl, platelet. Data adapted from Curley et al 2019.[16]

Table 1 Features of the eight neonatal intensive care unit patients[a] who received the highest number of platelet transfusions in the Intermountain Healthcare Neonatal Intensive Care units March 2020 to June 2022[b]

Plt tx received (*n*)	Primary diagnosis related to thrombocytopenia	Birth weight (g)	Birth weight percentile	Gestational age at birth (wk)	Sex	Race/ethnicity	ABO blood group	Outcome
52	Trisomy 21, TMD, DIC, Pul Hem, sepsis	3,700	40th	$39^{0/7}$	F	White Hispanic	O	Died, DOL 38, BPD
44[c]	SGA, acquired CMV	310	<1st	$24^{3/7}$	F	White Hispanic	O	Lived, BPD, trach, NICU 12 mo
42	SGA, SIP, bowel resection (×2)	500	9th	$26^{5/7}$	F	White non-Hispanic	O	Lived, BPD, trach, NICU 12 mo
41	TEF/EA, Noonan PTPN11, sepsis	1,250	40th	$29^{4/7}$	M	White Hispanic	O	Lived, still in NICU at >310 d, BPD, trach.
40	SGA, ECMO, Noonan PTPN11, sepsis	3,105	10th	$40^{5/7}$	M	White non-Hispanic	O	Lived, BPD, trach., chronic kidney failure, NICU stay 7 mo
32	SGA, recurrent NEC × 5; lap. ×3	575	<1st	$27^{5/7}$	M	White non-Hispanic	O	Died, BPD, DOL 294, trach.
29	NEC, lap. ×3, sepsis, acquired CMV	600	60th	$24^{0/7}$	F	White Hispanic	O	Lived, BPD, ROP, NICU stay 240 d, trach.
29	Lap. ×2, meconium ileus, sepsis	690	40th	$25^{5/7}$	F	White Hispanic	O	Died, DOL 138, BPD, trach.

Abbreviations: BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus; DIC, disseminated intravascular coagulopathy; DOL, day of life; ECMO, extracorporeal membrane oxygenation; F, female; lap., laparotomy; M, male; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NR, not recorded; plt tx, platelet transfusion; Pul Hem, pulmonary hemorrhage; ROP, retinopathy of prematurity; SGA, small for gestational age birth weight (≤10th percentile for Intermountain normative data); SIP, spontaneous intestinal perforation; TDM, transient myeloproliferative disorder; TEF/EA, trachea–esophageal fistula with esophageal atresia; trach., tracheostomy.

[a]Neonates on the Oncology Service were not included, in an attempt to limit heterogeneity.

[b]In March 2020, the Primary Children's Hospital Transfusion Service changed from Arup to American Red Cross, Lewis and Clark Division; thus, all platelet transfusions in this analysis are from one supplier.

[c]This patient is one of the 236 neonates in the report, "Platelet Transfusions in a Multi-NICU Healthcare Organization Before versus After Publication of the PlaNeT-2 Study," Bahr TM et al, submitted for publication September 2022.

Table 2 Platelet transfusions administered to the eight neonatal intensive care unit patients receiving the highest number of transfusions in the Intermountain Healthcare Neonatal Intensive Care Units March 2020 to June 2022

Plt tx received (*n*)	Age at first plt tx (d)	Plt count at first plt tx ($\times 10^3$/μL)	Change in plt count after first plt tx ($\times 10^3$/μL)	Lowest plt count ($\times 10^3$/μL)	Plt tx that were refractory[a] (% and fraction)	Plt tx ordered when plt count was ≥50,000/μL (% and fraction)
52	22	65	−8	9	31% (16/52)	27% (14/52)
44	0	65	21	7	73% (32/44)	2% (1/44)
42	37	20	32	9	33% (14/42)	5% (2/42)
41	23	29	23	26	22% (9/41)	66% (27/41)
40	10	41	89	10	23% (9/40)	30% (12/40)
32	0	32	100	25	19% (6/32)	65% (21/32)
29	28	63	19	28	24% (7/29)	69% (20/29)
29	30	40	−7	27	31% (9/29)	48% (14/29)

Abbreviation: Plt tx, platelet transfusion.
[a]Refractory defined as a posttransfusion platelet count that is not at least 5,000/μL higher than the pretransfusion platelet count.

Associations with thrombocytopenia included sepsis in five, small for gestational age in four, bowel resection in four, Noonan syndrome with *PTPN11* mutations in two, acquired cytomegalovirus infection in two (each of the eight had more than one such association). Four were White non-Hispanic and four were White Hispanic. All eight had adverse outcomes; three died and the five that lived all had severe bronchopulmonary dysplasia requiring tracheostomies due to ventilator dependence.

Aspects of the transfusions pertinent to our study are shown in ►**Table 2**. Two neonates, both with a birth weight below first percentile for gestational age, were thrombocytopenic on the day of birth and received their first platelet transfusion that day. The other six developed thrombocytopenia 10 to 37 days later. The two who received the most platelet transfusions received their first when their count was 65,000/μL. Neither had active bleeding charted at the time. All eight had some platelet transfusions followed by an increment <5,000/μL.

Also shown in ►**Table 2**, many of the platelet transfusions were ordered when the count was ≥50,000/μL. The rationale for most of these was not apparent in the medical record. However, a few were ordered prior to a procedure such as a lumbar puncture, placement of a percutaneous deep-line, or placement of a peritoneal drain. One patient had only 2% (1 of 44) of platelet transfusions ordered with a count ≥50,000/μL, but one had 69% (20 of 49) of transfusions with a count ≥50,000/μL.

Of the 309 platelet transfusions given, 68 (22%) were from donors who were ABO-identical with the recipient. The change in platelet count following each transfusion is shown ►**Supplementary Table S1** (available in the online version). The first patient (52 transfusions) averaged an increase of 27,000/μL after ABO-identical versus 13,000/μL after nonidentical transfusions. The second patient (44 transfusions) received no ABO-identical transfusions. Of the other six, five had a higher average increase after ABO-identical transfusions. After accounting for clustering by patient, the mean increase in count was 7,068/μL higher after an ABO-identical than after nonidentical transfusion ($p = 0.026$).

Two of the eight received romiplostim (Amgen Inc., Thousand Oaks, CA) in an attempt to raise the platelet count and thereby reduce the need for further platelet transfusions. The patient who received 44 transfusions had romiplostim begun at a dose of 1 μg/kg/wk subcutaneously on day of life (DOL) 51 when the count was 14,000/μL and transfusions were being given once or twice daily. Dosing was increased weekly over the next 3 weeks to 4, 8, and 10 μg/kg weekly. Thereafter, no further transfusions were given and the dosing was stopped. The other was the infant who received 42 transfusions. Dosing was begun at 4 μg/kg/wk subcutaneously on DOL 70 when the platelet count was 26,000/μL and 15 transfusions had been given over the prior 30 days. Dosing was increased weekly over the next 2 weeks to 8 and then 10 μg/kg weekly. During that period, six transfusions were given over 34 days. The dosing was discontinued, and platelet transfusions increased to 15 during the next 7 days. Romiplostim was restarted at 10 μg/kg once per week for the

Table 3 Speculations regarding the pathogenesis, prevention, and management of platelet transfusion refractoriness of neonatal intensive care unit patients

Topic	Speculations
Pathogenesis of NICU platelet transfusion refractoriness	• Rapid clearance of transfused platelets by antibody-mediated mechanisms; HLA, HPA, ABO, drug-dependent platelet-reactive antibodies • Rapid clearance of transfused platelets by nonantibody-mediated mechanisms; hypersplenism • Impaired ability to compensate for rapid platelet clearance by increasing platelet production (hepatic synthetic disfunction limiting thrombopoietin production)
Prevention of NICU platelet transfusion refractoriness	• Limit platelet transfusions, for most thrombocytopenic neonates, only to those with platelet counts <25,000/μL
Management of NICU patients who develop platelet transfusion refractoriness	• Do not give "prophylactic" platelet transfusions unless the platelet count is <10,000/μL. When the platelet count is 10,000–25,000/μL, order a platelet transfusion only if there is oozing, bruising, or bleeding • Discuss with the transfusion service ABO-identical platelets • Discuss with the transfusion service freshest-possible platelets • Review patient medications and consider changing potentially offending drugs[a] • If >10 platelet transfusions have been given, and the above measures fail, consider romiplostim at 10 μg/kg subcutaneously once/week for 3 wk

Abbreviations: HLA, human leukocyte antigen; HPA, human platelet antigen; NICU, neonatal intensive care unit.
[a]Drugs confirmed to elicit drug-dependent platelet-reactive antibodies include: ceftazidime, ceftizoxime, ceftriaxone, ciprofloxacin, fentanyl, heparin, ibuprofen, phenytoin, ranitidine, sulfamethoxazole, and vancomycin.[21,22]

next 3 weeks. Over the following 55 days, six transfusions were given, and thereafter, no further transfusions were given. In both cases the dosing was well-tolerated and no adverse effects were ascribed.

Discussion

From our case series we can draw only tentative conclusions, due to the small number and inhomogeneity of the subjects. It is curious that all eight were blood group O, because in the population we serve the prevalence of group O is 47%.[11] We had eight cases during a 28-month period from a population of approximately 80,000 live births and 6,400 NICU admission. This suggests an incidence of approximately one case per 10,000 births or one case per 800 NICU admissions. Despite the rarity, the condition is important because these neonates appear to be at very high risk for poor outcomes.

Because the incidence of thrombocytopenia is much higher in preterm neonates than term neonates, it is not surprising that six out of eight cases occurred in preterm neonates (all born at <30 wk gestation). The remaining two cases were in term neonates. Despite this, lung disease, need for tracheostomy, and death were occurred in both preterm and term neonates. In addition, refractoriness rates and other parameters reported in these two groups were roughly similar.

Regarding causation, thrombocytopenic adults who become refractory to platelet transfusions are sometimes classified as having either immunological or nonimmunological mechanisms.[5] Naturally occurring anti-A and B antibodies are predominantly of the IgM type, but can be IgG, which could cross the placenta from mother to fetus.[12] In fact the anti-A,B antibody that reacts with both A and B antigens is present in the sera of many group O people and is often partly or mostly IgG.[13] Consequently, mothers who are group O can pass to their fetus IgG antibodies that could attach to A or B antigens on donor platelets and could lead to donor platelet removal.

Strategies to prevent platelet transfusion refractoriness in NICU patients are untested. One such might involve restricting platelet transfusions to a greater extent than was done with our eight patients. Ordering a transfusion when the platelet count is >50,000/μL is common in the United States,[14,15] but this may not be the best practice. Withholding transfusions until the count falls below 25,000/μL appears to be better for patient outcomes.[16–20] The explanation might involve damaging effects of donor platelets in the lung and other organs,[17,18,20] which might have contributed to the severe lung damage seen in all eight of our high transfusion recipients. Whether preventing refractoriness could occur by transfusing only ABO-identical platelets is highly speculative and awaits further study.

Once a thrombocytopenic NICU patient has developed transfusion refractoriness, there are a few approaches that could be tried. However, we caution that none we mention are proven to be effective, and additional investigation should be performed before any could be considered standard. First, for neonates who develop refractoriness, we deem it reasonable to restrict further transfusions to active bleeding, suspending prophylactic transfusion unless the platelet count falls below 10,000/μL. Second, when further platelet transfusions are needed for a refractory patient, we suggest communicating with the blood bank about providing ABO type-specific donor platelets, and the freshest possible, even though these requests may adversely affect inventory management procedures. Third, we suggest reviewing the patient medications for the possibility of drug-dependent platelet-reactive antibodies and consider changing potentially offending drugs.[21,22] Finally, if a refractory neonate has already received a large number of platelet transfusions and

the above steps have not reduced the need for further transfusions, consider a short course of romiplostim. This medication is Food and Drug Administration approved for children 1 year old and above who have refractory immune thrombocytopenic purpura, but its use for neonates with platelet transfusion refractoriness is "off label."[23] We are aware of only two previously published cases of thrombocytopenic NICU patients where this approach appeared to stop the need for further transfusions.[24,25] Romiplostim does not result in an immediate rise in platelet count, typically taking at least 2 weeks before the count rises. If used it should be for the fewest doses needed.

Limitations

We recognize limitations of our report, related principally to the small number of neonates we found with this condition and to their heterogeneity. Hence, in ►Table 3, we state our summaries not as conclusions but as speculations awaiting further studies, and not as recommendations but as possibilities to try in a desperate situation.

Conclusion

Newborn infants who receive multiple platelet transfusions during their NICU stay are at very high risk for poor outcomes, including severe bronchopulmonary dysplasia, long-term requirements for ventilation, and late death from respiratory failure. Strategies that prevent platelet transfusion refractoriness in neonates are needed to avoid multiple platelet transfusions and to reduce adverse outcomes. Note added in production: A fourth patient (received 44 platelet transfusions) had late death (at 20 months) from ventilatory failure.

Conflict of Interest

None declared.

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