

Multicenter Analysis of Platelet Transfusion Usage Among Neonates on Extracorporeal Membrane Oxygenation

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ABSTRACT. *Objective.* Multiple platelet transfusions are invariably given to neonates on extracorporeal membrane oxygenation (ECMO), and no alternative to repeated transfusions exists. Before any alternatives, such as administration of thrombopoietic stimulators, could be contemplated, data regarding the number of platelet transfusions received by neonatal ECMO patients is needed, and the mechanisms that cause the thrombocytopenia of these patients must be better defined. As a step toward determining this, we analyzed the use of platelet transfusions in this group of neonates. We conducted a historic cohort study of neonates who were treated with ECMO to determine the number of platelet units received as a function of 1) days on ECMO, 2) medical diagnosis for which ECMO was instituted, and 3) type of ECMO used (venovenous [VV] vs venoarterial [VA]).

Methods. We reviewed the hospital records of all neonates who were admitted to the neonatal intensive care units at Shands Children's Hospital, Arnold Palmer Hospital for Children and Women, and Tampa General Hospital and treated with ECMO between January 1, 1995, and June 30, 2000. Data were expressed as the number of platelet transfusions versus number of days on ECMO, diagnosis for which ECMO was instituted, and type of ECMO used.

Results. Of the 234 ECMO patients, 81 were placed on VV, 138 were placed on VA, and 15 were converted from VV to VA. The average number of platelet transfusions received per day was 1.3 and varied by diagnosis and by type of ECMO. Neonates with meconium aspiration and sepsis required more platelet transfusions per day than neonates with other conditions. Infants who were converted from VV to VA required more transfusions per day (mean: 1.57) than did patients on VA (1.47) or VV (1.06).

Conclusions. Platelet transfusions among neonates on ECMO are dependent of their medical diagnosis; they average 1.3 transfusions per day and are higher on VA than VV ECMO. *Pediatrics* 2002;109(6). URL: <http://www.pediatrics.org/cgi/content/full/109/6/e89>; neonates, extracorporeal membrane oxygenation, platelet transfusions.

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ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; PPHN, persistent pulmonary hypertension; CDH, congenital diaphragmatic hernia; MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; VV, venovenous; VA, venoarterial.

Extracorporeal membrane oxygenation (ECMO) is a mainstay therapy of modern neonatology. In fact, certain neonatal patients survive only because of ECMO.^{1,2} ECMO is used to treat a variety of conditions in neonatal patients, including respiratory and cardiac failure as a result of persistent pulmonary hypertension (PPHN), congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia, severe air-leak syndromes, and sepsis.

The platelet count falls immediately after a neonate is placed on ECMO. The rapidity of this fall suggests that the predominant mechanism that causes thrombocytopenia is accelerated platelet destruction.³ Presumably, this occurs by activation and adherence of platelets to the circuit tubing or the membrane oxygenator.⁴ When accelerated platelet destruction occurs among adult patients, platelet production rapidly increases in an attempt to compensate.⁵ The compensatory mechanisms include increasing the size, ploidy, and number of megakaryocytes. By deploying these mechanisms, platelet production can increase by 3- to 5-fold, and such compensation is successful unless the rate of platelet destruction exceeds the rate of maximum platelet production. It is not clear whether neonates on ECMO deploy these mechanisms as a compensation for their thrombocytopenia.

Multiple platelet transfusions are invariably given to neonates on ECMO, and no alternative to repeated transfusions exists. Before considering alternatives, however, more information is needed regarding the platelet transfusion requirements of neonates on ECMO and the mechanistic causes of this common variety of neonatal thrombocytopenia. As a step toward determining this, we analyzed the use of platelet transfusions among neonates on ECMO. We conducted a multicenter historic cohort study to determine the number of platelet transfusions received as a function of 1) days on ECMO, 2) medical diagnosis for which ECMO was instituted, and 3) type of ECMO used (venovenous [VV] vs venoarterial [VA]).

PATIENTS AND METHODS

Patients

We reviewed the hospital records of all neonates who were admitted to the neonatal intensive care units at the University of Florida Shands Children's Hospital (Gainesville, FL), Arnold Palmer Hospital for Children and Women (Orlando, FL), and Tampa General Hospital (Tampa, FL) and were treated with ECMO between January 1, 1995, and June 30, 2000. We obtained demographic and clinical data, including gestational age, birth weight, age at initiation of ECMO, indications for ECMO, type of ECMO, pre-ECMO platelet count, length of ECMO treatment, and the number of platelet transfusions and donor exposures from platelet transfusions per day of ECMO. Data were analyzed for the number of platelet transfusions versus the number of days on ECMO, diagnosis for which ECMO was instituted, and the type of ECMO used (VV vs VA). The study was approved by the Institutional Review Boards of the 3 participating institutions.

Transfusion Protocol

Platelets <5 days old were transfused whenever the circulating platelet concentrations fell to <110 000/ μL (center A) or 100 000/ μL (centers B and C). The platelet product transfused varied in the different centers; center A routinely administered 3 random-donor platelet units per transfusion (packed and pooled), and the other 2 routinely transfused a single random-donor platelet unit.

Statistical Analysis

Initial descriptive statistics were calculated, and plots were generated. For the primary analysis, the outcome variables were the number of platelet transfusions and the number of donor exposures (on the basis of platelet transfusions) while on ECMO. Given that the outcome variables consisted of count data, a Poisson regression model was fit. This model regressed both the number of platelet transfusions and the number of donor exposures on days on ECMO. The covariates consisted of ECMO type (VV, VA, VV-VA) and disease status (PPHN, CDH, sepsis, MAS, and RDS). The final model used to assess the relative importance of each variable was determined through a forward stepwise regression. As a secondary analysis, we evaluated the length of ECMO run as a function of the center, initial platelet count, and indication for ECMO (PPHN, CDH, confirmed sepsis, MAS, sepsis + MAS, and RDS) adjusting for time-dependent covariates using a Cox proportional hazards model accounting for ties. We treated the ECMO run as right censored for those subjects who died while on ECMO. Alpha was set at 0.05 for all analyses. All continuous values are reported as mean \pm standard deviation. All analyses were conducted using SAS 8.0 (SAS Institute, Cary, NC).

RESULTS

A total of 234 neonates underwent ECMO during the study period: 83 at center A, 73 at center B, and 78 at center C. The neonates had a gestational age of 38.8 ± 1.9 weeks and a birth weight of 3254 ± 579 g (mean \pm standard deviation). No differences in these features were observed among the 3 centers. The

mean pre-ECMO platelet count was $180.3 \pm 75.8 \times 10^3/\mu\text{L}$ (range: 21–421). The median platelet count was $177.0 \times 10^3/\mu\text{L}$. The mean pH and lactic acid values before ECMO cannulation were 7.28 ± 0.2 and 4.3 ± 3.7 , respectively. Neither the initial pH nor the lactic acid values differed by ECMO type.

Patients were started on ECMO on day of life 2.2 ± 3.6 (range: 0–22). The mean length of ECMO therapy was 7.9 ± 6.3 days. Two neonates were treated with a second ECMO run, as their condition deteriorated after the initial run had concluded. As expected, a significant correlation was found between the length of the ECMO run and the total number of platelet transfusions received ($r = 0.81, P = .0001$). However, the number of platelet transfusions administered per day remained constant throughout the ECMO run, at 1.3 per day (Fig 1). No differences in these variables were apparent among the 3 centers. Thirty-two of the 234 neonates required platelet transfusions after completion of the ECMO run, up to a maximum of 10 days.

The most frequent diagnoses were MAS (33.8%), PPHN (32.5%), CDH (15.8%), and confirmed sepsis (5.1%; Table 1). The relative proportions of these indications were similar at all centers. Neonates with a combination of sepsis and MAS required more daily platelet transfusions than did neonates with other conditions, although the number of patients in this group was small ($P = .004$; Table 2). Neonates with CDH or culture-proven sepsis had significantly longer ECMO runs than patients with other indications ($P = .0002$), which resulted in a higher number of total platelet transfusions administered to these neonates.

There were 32 deaths (13.7%) among the 234 neonates. Of these, the majority had a diagnosis of PPHN (18) or CDH (7). Seventy-five percent of the neonates who died were on VA ECMO, whereas the VV and the VV-VA groups each accounted for 12.5% of the 32 deaths. The mean length of ECMO was 6.7 ± 3.6 days for neonates who lived and 9.5 ± 7.4 days for those who died ($P < .0007$).

Of the 234 patients, 81 (34.6%) were placed on VV, 138 (58.9%) were placed on VA, and 15 (6.4%) were converted from VV to VA at some point during the run. The type of ECMO used varied significantly depending on the center, as shown in Table 3. In fact, VA ECMO was the only type of ECMO used at

Fig 1. Average number of daily platelet transfusions per center. The number of platelet transfusions administered per day remained constant throughout the ECMO run, at approximately 1.3 transfusions per day.

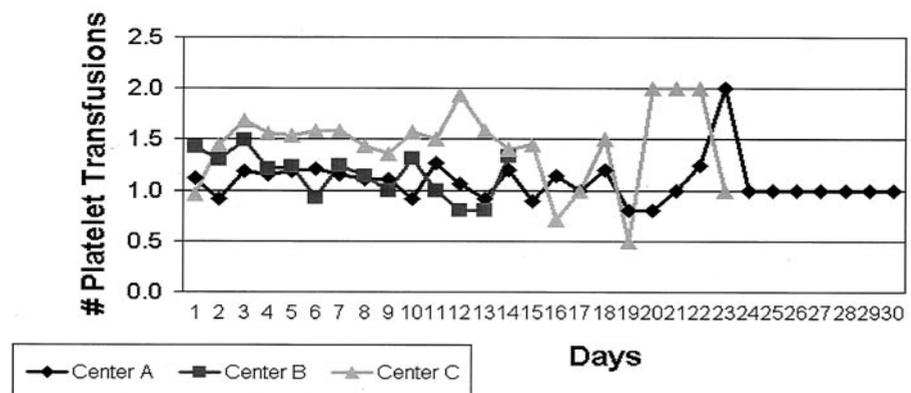


TABLE 1. Indications for ECMO by Center

Indication	Center		
	A	B	C
PPHN	31%	38%	29%
CDH	19%	16%	12%
Sepsis	2%	6%	8%
MAS	33%	36%	33%
Sepsis + MAS	4%	0%	6%
RDS	5%	4%	5%

Values refer to the percentage of total patients at each center on ECMO.

center C, and there was a significant difference in the proportion of patients who were placed on VA ECMO between centers A and B ($P < .001$). In addition, there were significant differences in the number of daily platelet transfusions given, depending on the type of ECMO used. Patients who were on VA ECMO required more platelet transfusions per day (1.47 ± 0.82) than patients who were on VV ECMO (1.06 ± 0.36 ; $P < .0001$). Neonates who were converted from VV to VA ECMO received the highest number of platelet transfusions per day (1.57 ± 0.66). The mean number of platelet transfusions per day correlated directly with the ECMO type used at each center. Fewer platelet transfusions were administered per day at center A (1.14 ± 0.45), which primarily uses VV ECMO, than at center B (1.25 ± 0.51), which uses mostly VA ECMO. Center C, where VA was used exclusively, administered 1.61 ± 0.97 transfusions per day.

The number of daily donor exposures, exclusively on the basis of platelet transfusions, varied significantly depending on the platelet transfusion policy of each center. In centers B and C, the number of platelet transfusions closely matched the number of "platelet donor exposures," because a single random-donor platelet unit was used for most transfusions. Occasionally, a platelet pheresis was used for more than 1 transfusion, so the number of donor exposures was slightly lower than the number of transfusions. In center A, however, most transfusions consisted of 3 random-donor platelet units, packed and pooled, thereby exposing the infant to 3 different donors. As a consequence, the number of "platelet donor exposures" per day was higher at center A (mean: 3.14) than at centers B (1.25) or C (1.61).

TABLE 2. Platelet Usage and ECMO Duration, Listed by Indication for ECMO

Indication	Patients	Platelet Transfusions per Day	Days on ECMO
PPHN	76	1.4 ± 0.6	6.9 ± 4.2
CDH	49	1.3 ± 0.6	10.7 ± 8.0
Sepsis	31	1.5 ± 0.5	9.2 ± 4.0
MAS	88	1.2 ± 0.4	6.1 ± 2.9
Sepsis + MAS	8	1.9 ± 1.1	7.1 ± 3.8
RDS	8	1.5 ± 0.6	8.1 ± 3.6

Patients with sepsis + MAS required the greatest number of platelet transfusions per day ($P = .004$). Neonates with either CDH or sepsis required significantly longer runs than the other groups ($P = .0002$).

TABLE 3. Type of ECMO Used by Center

ECMO type	Center		
	A	B	C
VV	65%	37%	0%
VA	23%	56%	100%
VV-VA	12%	7%	0%

Values refer to the percentage of total number of patients placed on ECMO at each center.

DISCUSSION

Thrombocytopenia during ECMO might occur as a result of several mechanisms, including decreased production, increased destruction, sequestration in extravascular sites, hemodilution, blood-surface interaction, and platelet activation and aggregation in the circuit tubing.^{3,6} Regardless of the mechanism, repeated platelet transfusions are needed to prevent bleeding complications, but those transfusions place the infant at risk for transfusion-acquired infections, graft-versus-host disease, and white cell-mediated febrile reactions. To define better the platelet usage among neonates on ECMO, we studied the number of platelet units administered as a function of the number of days on ECMO, the medical indication for which ECMO was instituted, and the type of ECMO used.

We found a significant correlation between the length of the ECMO run and the total number of platelet transfusions administered. However, the number of platelet transfusions administered per day remained constant throughout the ECMO run, at approximately 1.3 transfusions per day. We initially suspected that as the ECMO circuit aged, more platelets would be consumed in the tubing and in the membrane oxygenator. Our finding of a constant number of platelet transfusions throughout the ECMO run does not support this hypothesis.

We found that patients who had culture-proven sepsis and MAS received the highest number of daily platelet transfusions, although the number of patients in this group was small. Patients with sepsis or with MAS alone did not receive more platelet transfusions during their ECMO run than did the other groups. Because neonatal sepsis is usually associated with increased platelet consumption,⁷ independent of ECMO, and MAS is often associated with fetal and perinatal hypoxia,⁸ we hypothesized that the combination of increased platelet consumption and decreased megakaryocytopoiesis associated with perinatal hypoxia could account for our observation.

Patients with a diagnosis of CDH or sepsis had significantly longer runs of ECMO than did the other groups. Because the total number of platelet transfusions correlated directly with the length of the ECMO run, these were the patients that required the highest total number of platelet transfusions. McCoy-Pardington et al⁹ also reported that neonates with CDH had longer ECMO runs and used significantly more platelets than other groups. In their series of 11 patients, the duration of ECMO was 6.3 days with 2 platelet transfusions per day. Although our neonates with CDH spent, on average, more

days on ECMO, only 1.3 daily platelet transfusions were given to each patient.

The type of ECMO used varied significantly between the centers. The majority of neonates who were placed on VA ECMO were from center C, where VA ECMO was used exclusively. Historically, VA ECMO has been the most widely used strategy, accounting for approximately 66% of all neonatal ECMO cases since 1995.¹⁰ However, the use of VV ECMO is increasing, with certain institutions (such as center A) using VV ECMO as the first option. In fact, among the 5367 neonates who were reported to the Extracorporeal Life Support Organization between January 1, 1995 and June 30, 2000, the percentages of neonates who received VV, VA, or VV-VA ECMO were similar to those in our study.

Significant differences in the daily number of platelet transfusions administered were observed when comparing the types of ECMO. Neonates who were on VA ECMO received more transfusions than patients who were on VV and less than those who were converted from VV to VA. It is not known whether the VA ECMO circuit consumes more platelets than VV ECMO or whether the differences are related to the severity of the disease processes. However, because the use of one type of ECMO versus another is partly based on the physician's preference, it seems less likely that the observed differences in platelet usage were attributable to disease severity. Furthermore, our indices of severity of disease (pH and lactic acid measurements before ECMO) did not correlate with the type of ECMO used. The circuit tubing and membrane oxygenator are the same for VV and VA ECMO. However, the interaction of the pressure wave delivered from the pump to the right atrium and that delivered to the aortic arch are different, and this may explain the different effects on platelets to some degree. It is also possible that the higher "afterload" pressure in the aorta as compared with the right atrium may affect platelet survival, but more studies are necessary to elucidate clearly the effects of these mechanical factors on platelets.

Our findings indicate that the use of more than 1 platelet unit per transfusion does not significantly prolong the interval between platelet transfusions but rather increases the number of donor exposures without any evident benefit. In the treatment of thrombocytopenic neonates (not on ECMO), the practice of using more than 1 unit of platelets per transfusion is discouraged.¹¹ Usually, this practice requires the use of volume reduction, a process associated with platelet activation, clumping, and dysfunction. The administration of dysfunctional platelets to neonates who already have evidence of platelet dysfunction (eg, patients on ECMO) is counterintuitive, although Moroff et al¹² showed the number and function of platelets to be acceptable when volume-reduced platelet components were used.

Several investigators have shown a significant impact among changes in ECMO transfusion procedures on blood donor exposure. In 1990, Minifee et al¹³ showed a significant reduction in donor exposure through elimination of packed red blood cell

exchange transfusions, discontinuation of fresh-frozen plasma and cryoprecipitate infusions, and use of a higher volume (15 mL/kg body wt) of packed red blood cell transfusions. Because platelets composed the largest source of donor exposures in their population, platelets were transfused to maintain the total platelet count $>80\,000/\mu\text{L}$. By lowering their threshold to transfuse platelets, the overall number of units and therefore the number of donor exposures were reduced. They also obtained platelets by pheresis from either a single or a limited number of donors to minimize their number of exposures. In 1994, Rosenberg et al¹⁴ demonstrated a significant reduction in platelet donor exposures, primarily as a result of using aliquoted platelet pheresis.

Several investigators have documented that platelet transfusions account for the majority of donor exposures among neonates on ECMO.^{6,9,14,15} These studies, as well as our observations, clearly demonstrate that donor exposures can be significantly decreased by transfusion practices in the different institutions. Until safer alternatives to platelet transfusions are available for neonates on ECMO, every effort should be made to minimize donor exposures. In this regard, our results suggest that the use of VV ECMO, shorter ECMO runs, and single platelet units for transfusions (or aliquoted platelet pheresis, if available) would contribute to this goal. Additional studies are needed to understand better the mechanisms underlying the thrombocytopenia in this group of neonates and to determine whether treatment with recombinant thrombopoietic growth factors could significantly reduce the number of platelet transfusions administered to neonates on ECMO.

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