Platelet Transfusion in the Neonatal Intensive Care Unit: Benefits, Risks, Alternatives

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Abstract
Platelet transfusions were introduced into clinical medicine about 60 years ago when they were shown to reduce the mortality rate of patients with leukemia who were bleeding secondary to hyporegenerative thrombocytopenia. In modern neonatology units, platelet transfusions are integral and indeed lifesaving for some neonates. However, the great majority of platelet transfusions currently administered in neonatal intensive care units (NICUs) are not given in the original paradigm to treat thrombocytopenic hemorrhage, but instead are administered prophylactically with the hope that they will reduce the risk of spontaneous bleeding. Weighing the risks and benefits of platelet transfusion, although imprecise, should be attempted each time a platelet transfusion is ordered. Adopting guidelines specific for platelet transfusion will improve consistency of care and will also generally reduce transfusion usage, thereby reducing costs and conserving valuable blood bank resources. Initiating specific programs to improve compliance with transfusion guidelines can further improve NICU transfusion practice.

The Reference Range Concept in Neonatal Hematology

The term ‘thrombocytopenia’ indicates a low concentration of platelets in the blood. For decades the definition of thrombocytopenia, among patients of all ages, has been a platelet count \(< 150,000/\mu l\) \([1, 2]\). However, a more accurate method to define any abnormal clinical laboratory test is to identify values that fall outside the appropriate ‘reference range’. Reference ranges are particularly applicable to neonatology because ‘normal ranges’ for laboratory tests are not available for neonates. This is because blood is not drawn on healthy neonates for the purpose of establishing normal ranges, as is generally done with adults. Instead, ‘reference ranges’ are used, which consist of the 5th to 95th percentile values assembled from very large numbers of neonates with minimal pathology or with pathology not thought to be relevant to the laboratory parameter under study. Using this approach, it is clear that, among preterm infants, the long-held definition of thrombocytopenia (platelet count \(< 150,000/\mu l\)) is overly simplistic, inaccurate, and sometimes quite misleading.
Defining the Reference Ranges for Platelet Count and Mean Platelet Volume in Preterm and Term Neonates Using Large Multihospital Databases

Reference ranges for blood concentrations of platelets in preterm and term infants on the day of birth are shown in figure 1a [3]. For neonates below 33 weeks’ gestation, the 5th percentile value is approximately 100,000/μl. Thus, platelet counts in the range of 100,000–150,000/μl, previously termed ‘mild thrombocytopenia’, should be recognized as within the reference range and therefore not abnormal. Although the reference ranges for platelet counts increase gradually from 23 to 40 weeks’ gestation, the mean platelet volume (MPV) stays the same during this period (fig. 1b) [3].

Platelet counts are expected to gradually rise during the first 2 weeks following birth. As shown in figure 2a, counts at 14–21 days of age are generally 50% higher than they were at birth. This increase is likely the result of a physiological surge of thrombopoietin (Tpo) at birth [4–6]. Tpo is the primary physiological regulator of platelet production. Similarly, MPV increases over the first 14 days following birth (fig. 2b), likely indicative of accelerated platelet production. When the reference range concept is applied to preterm and term neonates, the definitions of thrombocytosis and thrombocytopenia are both seen to be highly dependent on postnatal age [3].
Discovering thrombocytopenia in a pregnant woman can be concerning to families and physicians, including the pediatricians and/or neonatologists planning to provide care for the neonate. The reference range for platelet counts during pregnancy changes by trimester [7]. Largely the result of dilution of mother’s blood by her expanding plasma volume, her platelet counts gradually fall as pregnancy progresses; however, her MPV does not change (fig. 3b). The lower reference range for platelet count during the third trimester is about 115,000/µl; thus maternal platelet counts in the range of 115,000–150,000/µl, previously termed ‘mild thrombocytopenia’ are in fact within the reference range and, thus, should not be considered abnormal.

Pregnant women with a platelet count <50,000/µl most likely have hematopathology such as ITP or HELLP syndrome; however, a variety of causes have been identified and perhaps 20–25% of these women have no recognized etiology for their thrombocytopenia. If a woman’s platelet count is <50,000/µl at delivery, the relative risk of severe thrombocytopenia in her neonate is increased by about 8-fold. Based on this, we advise measuring the neonate’s platelet count when the mother’s count is found to be <50,000/µl [7].

Fig. 2. The effect of advancing postnatal age on platelet counts (a) and MPV (b) during the first 90 days following birth. Percentile curves in a were manually smoothed and curves in b were mathematically smoothed. a Platelet counts during the first 90 days after birth. b MPV measurements during the first 90 days after birth.
Cause of Severe Thrombocytopenia in Neonatal Intensive Care Unit Patients

Most cases of thrombocytopenia identified in the neonatal intensive care unit (NICU) are not severe. However, perhaps 25% of cases have a count that falls below 50,000/μl, a threshold where the condition is generally termed ‘severe neonatal thrombocytopenia’ [8–10]. The majority of cases of severe neonatal thrombocytopenia are recognized at birth or shortly thereafter [8–10]. This is the case among extremely low birth weight (ELBW) neonates (<1,000 g) [8], and is also the case when all NICU patients are studied, regardless of gestational age [9]. Clearly, thrombocytopenia at anytime during the NICU stay is more common in the smallest patients, with a prevalence exceeding 80% of those weighing less than 600 g at birth [8], compared with about 1% of those weighing over 2,000 g at birth [8–10]. Biological differences have been observed between fetal, neonatal, and adult megakaryocytes, and these are likely involved in the marked susceptibility of ELBW neonates to develop thrombocytopenia [11].

While alloimmune neonatal thrombocytopenia is common among thrombocytopenic but otherwise healthy appearing term neonates [12–14], a wide variety of causes and associations are seen among ELBW neonates. Unfortunately, the largest etiologic category for thrombocytopenia among ELBW neonates is ‘unknown or idiopathic’ [8]. When an association or cause is known, the most common explanations are maternal hypertension, small for gestational age status, disseminated intravascular coagulation, bacterial or fungal infection, or necrotizing enterocolitis.
Severe congenital thrombocytopenia from any etiology can predispose a fetus or neonate to a significant intraventricular (brain) hemorrhage (IVH) [1, 2, 12–14]. Such hemorrhages can occur in utero or during or after birth. In contrast, most preterm neonates who develop a severe IVH do not have thrombocytopenia before their IVH, nor do they have a preexisting coagulopathy predating their IVH [15, 16]. However, they can develop thrombocytopenia and coagulopathy after the IVH has occurred, due to tissue thromboplastin release within the brain hemorrhage [17]. Moreover, most preterm neonates who develop a small grade 1 IVH that later extends to become a severe IVH do not have preexisting thrombocytopenia as part of the pathogenesis of their hemorrhage. Administering platelet transfusions to neonates because they have mild or moderate thrombocytopenia does not prevent IVH [18–20].

In general, the correlation is poor between the neonate’s platelet count and the odds of a clinical hemorrhage. As shown in Table 1, this is the case for various types of neonatal hemorrhage. When severe thrombocytopenia (platelets <50,000/µl) is recognized in a neonate, underlying causes or associations are shown in Table 2. Most cases of severe thrombocytopenia are associated with bacterial infection, small for gestational age or pregnancy-induced hypertension status, necrotizing enterocolitis, or disseminated intravascular coagulation [8–10].

### Table 1. Pathological bleeding recorded in the medical records among 273 NICU patients with 326 episodes of severe thrombocytopenia

<table>
<thead>
<tr>
<th>Lowest platelet count recorded</th>
<th>n</th>
<th>Percent with cutaneous hemorrhage</th>
<th>Percent with pulmonary hemorrhage</th>
<th>Percent with GI hemorrhage</th>
<th>Percent with all grades of IVH</th>
<th>Percent with grade 3 or 4 IVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20,000/µl</td>
<td>78</td>
<td>18(^1)</td>
<td>8</td>
<td>5</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>20,000–30,000/µl</td>
<td>78</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>31,000–50,000/µl</td>
<td>117</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>32</td>
<td>19</td>
</tr>
</tbody>
</table>

GI = Gastrointestinal.

\(^1\) Cutaneous hemorrhage was more common if the lowest platelet count was <20,000/µl than if it was 20,000 to 50,000/µl; p < 0.03.

### Table 2. Explanations given in the medical records for severe thrombocytopenia

<table>
<thead>
<tr>
<th>Factors identified to explain the thrombocytopenia</th>
<th>Number of episodes (% of total) whereby this explanation was given for the thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial infection</td>
<td>91 (25)</td>
</tr>
<tr>
<td>SGA or PIH</td>
<td>78 (22)</td>
</tr>
<tr>
<td>NEC</td>
<td>52 (14)</td>
</tr>
<tr>
<td>DIC</td>
<td>48 (13)</td>
</tr>
<tr>
<td>Unexplained or undiagnosed</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Alloimmune</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Genetic</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Thrombus</td>
<td>6 (2)</td>
</tr>
<tr>
<td>CMV</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

Values in parentheses represent percentages. 326 episodes of severe thrombocytopenia were detected among 273 NICU patients. 360 explanations were given for the 326 episodes because some episodes had two explanations given (e.g. bacterial sepsis plus DIC). SGA = Small for gestational age; PIH = pregnancy-induced hypertension; NEC = necrotizing enterocolitis; DIC = disseminated intravascular coagulation; CMV = cytomegalovirus.

### Guidelines for Administering Platelet Transfusions in the NICU

Guidelines for platelet transfusions have been published [21–23]. Almost all platelet transfusions administered to neonates are ‘prophylactic’, meaning the patient is not actively bleeding but the transfusion is given with the intent of preventing bleeding [24]. Guidelines for prophylactic platelet transfusions are generally based on two considerations: (1) the condition of the neonate and (2) the platelet count. The reason for considering the condition of the neonate relates to the observation that stable
neonates seem to have a much lower risk of serious hemorrhage. For simplicity, the condition of the neonate can be grouped into one of three categories: (1) on ECMO or pre- or postoperative; (2) neither on ECMO nor pre- or postoperative, but ‘unstable’, or (3) ‘stable’. Detailed definitions of these categories are generally lacking. For instance, the length of time pre- or postoperative has not been determined by data. Also precise definitions for ‘unstable’ and ‘stable’ are lacking, but these categories are intended to reflect a higher versus lower risk for spontaneous significant hemorrhage.

Besides the clinical condition, the other usual consideration for platelet transfusion is the platelet count. Some guidelines advocate keeping the platelet count >100,000/μl for neonates in the highest risk category (on ECMO or pre- or postoperative), >50,000/μl for those in the intermediate category (unstable) and >20,000/μl for those in the lowest risk category (stable) [21–23].

The above approach is flawed in many ways; one of which is the lack of consideration for variation in platelet function. The capacity of platelets to form a hemostatically effective platelet plug [25] can be impaired in neonates receiving indomethacin [26], ibuprofen (to a lesser extent) [27], ampicillin [28, 29], inhaled nitric oxide [30], or therapeutic hypothermia [31]. Moreover, large platelets function better than small platelets to form an effective platelet plug [24]. This latter consideration can be incorporated into the platelet transfusion guidelines using the principle of ‘platelet mass’. The platelet mass is a simple calculation, accomplished by multiplying the platelet count by the MPV. This calculation may reflect overall platelet function better than the platelet count alone. In a NICU collaborative before versus after practice change study, we discovered that the use of platelet mass (rather than platelet count) in the transfusion decision reduced the number of prophylactic platelet transfusions given by about one third, with no increase in bleeding complications [24]. The reduction in transfusions came about because some neonates who qualified for a platelet transfusion on the basis of platelet count did not qualify on the basis of platelet mass since they had large platelets. Guidelines for prophylactic platelet transfusions based on platelet mass are provided in Table 3.

### Compliance with Platelet Transfusion Guidelines

Agreeing to abide by a set of practice guidelines for transfusion is a positive step toward better transfusion practice, but agreeing does not guarantee compliance in actual practice. Petäjä et al. [32] reported that only about 35% of platelet transfusions given were compliant with previously agreed upon guidelines. In the Intermountain Healthcare System, we audited all NICU transfusions during the year 2006 and determined that about 65% of platelet transfusions were compliant with our guidelines, thus 35% were not [33]. In January 2009, we initiated a system-wide program aimed at increasing compliance with transfusion guidelines. This program included electronic order entry of transfusions, monthly reports to each NICU regarding compliance, and monthly reminders of the system-wide goal of improving to 90% compliance. The year began with transfusion compliance of about 60%, but after a few months this increased to the goal level where it has remained ever since. Accompanying better compliance was a significant reduction in platelet transfusion usage, lower transfusion-related costs, and conservation of blood bank resources [34].

### Risks and Benefits of Platelet Transfusion in the NICU

Platelet transfusions can be life-saving, but they also carry risks. Some such risks are at least partly defined, such as a risk of bacterial contamination of the donor platelets [35]. Other risks are poorly defined but still quantifiable. Figure 4 is typical of several reports showing a positive association between the number of platelet transfusions received and mortality rate [36–38]. This re-
The relationship is multifactorial and complex, but analyses indicate a very high likelihood that the multiple transfusions themselves are involved in the elevated mortality rate [36].

It is not possible to precisely evaluate and contrast the risks versus benefits each time a platelet transfusion is considered in the NICU. Although imprecise, this process of attempting to weigh the risks and benefits is important before any platelet transfusion is ordered. Benefits are more likely in cases of thrombocytopenic hemorrhage than in cases where the platelets are given prophylactically. Unfortunately, some platelet transfusions are given in situations where the potential benefits are nil. Surveys indicate some clinicians give prophylactic platelet transfusions to stable neonates with platelet counts in the range of 100,000–150,000/μl [39]. Since the bleeding time is not prolonged in this platelet count range [40] and since these platelet counts are within the reference range, it is very unlikely that any benefit is provided by a platelet transfusion. Thus when well-appearing neonates receive prophylactic platelet transfusions because of a platelet count in the 100,000–150,000/μl range, they are being subjected to risk unbalanced by any known benefit.

**Fig. 4.** Mortality rate of NICU patients with severe thrombocytopenia is displayed according to the number of platelet transfusions received.

### Thrombopoietin Mimetics

In 1994, Tpo was identified and the recombinant molecule became available for study [41]. Trials with Tpo and a pegylated form of Tpo were promising until some patients developed anti-Tpo antibodies, leading to aplastic anemia, which led to the cessation of development of this potential approach to treat thrombocytopenia. Subsequent studies focused on means of stimulating the Tpo receptor using molecules that have no homology with Tpo. Two such products have been approved by the US FDA: eltrombopag (GlaxoSmithKlein) and romiplostim (Amgen). Few neonates have been treated with either agent. No consistent approach or consensus for treatment has been developed for thrombocytopenic neonates, but caution has been issued [41, 42]. Tpo receptors have been identified on nonhematopoietic cells, including brain, and nonthrombopoietic actions during the neonatal period have not been defined.

### Disclosure Statement

The author has no conflicts of interest regarding this work.

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