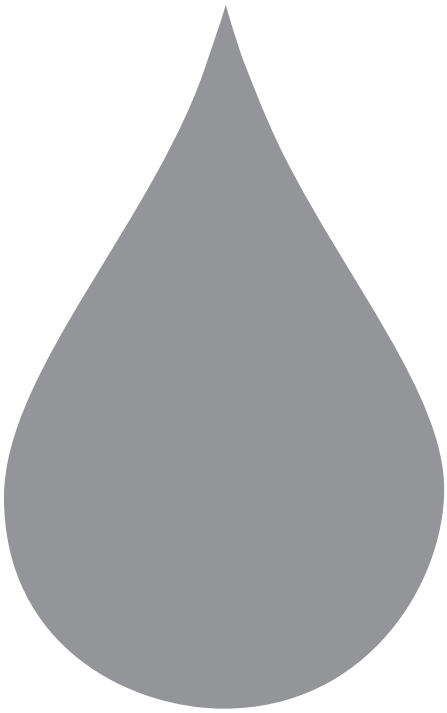
Neonatal transfusion practices

Lindern, J.S. von

Chapter 11

Discussion and future perspectives



Anemia and thrombocytopenia are common hematologic disorders in (preterm) infants admitted to neonatal intensive care units (NICUs). In the first months of life all newborn infants experience a decrease in hemoglobin (Hb) level due to normal physiologic processes such as body growth, shorter life span of neonatal red blood cells (RBCs) compared to adult RBCs, and relative insufficient erythropoiesis. Very preterm infants, however, also experience iatrogenic blood loss due to routine laboratory investigations increasing the decline in RBCs. For healthy term infants a decrease in Hb to10 g/dL at 10–12 weeks of age is considered normal. In preterm infants the nadir is reached at a younger age (4–6 weeks after birth) and can be as low as 7 g/dL in infants with a birth weight <1 kg.[1] Nearly all of very preterm infants (<32 weeks gestation) develop anemia and 25–35% may encounter thrombocytopenia (a platelet count <150 x 10^9/L). Severe thrombocytopenia (a platelet count <50 x 10^9/L) is seen in approximately 5% of extremely preterm infants.[2] Blood products, especially RBCs, are therefore frequently used in neonatal medicine. RBC transfusion might well be the single most prescribed 'drug' for extremely preterm infants (born before 28 completed weeks' gestation) as up to 95% of these infants receive at least one RBC transfusion during their postnatal hospital stay. In newborn infants with severe thrombocytopenia (platelet count <50 x 10^9/L) up to 86% receive one or more platelet transfusions.[3]
Despite the frequent use of RBC and/or platelet-transfusions, there is no international consensus on the transfusion threshold, the correct dose, the optimal product and no adequate information available on the long-term effects of transfusions.

Red blood cells

Due to lack of large randomized controlled trials (RCT), guidelines for RBC transfusions differ all over the world. The uncertainty of the effects of RBC transfusions, both positive and detrimental, is probably the cause of the wide variety in transfusion guidelines. Iron deficiency and relative hypoxia due to a lower Hb level may damage the developing brain.[4] Prolonged anemia has a negative effect on growth, although a threshold is not known.[5] On the other hand, a low Hb level stimulates the production of erythropoietin, a growth factor with neuroprotective properties.[6,7] RBC transfusion can increase oxidative stress and injure the immature lung, resulting in prolonged oxygen dependency and chronic lung disease.[8] The increase in free iron in preterm infants after RBC transfusion increases the presence of oxygen radicals which may induce the development of retinopathy of prematurity.[9] Several recent studies have reported an increase in the incidence of necrotizing enterocolitis (NEC) within 24–48 hours after a RBC transfusion.[10,11] Krimmel et al. showed that the usual postprandial increase in blood flow to the gut is not present immediately after a RBC transfusion, which may explain the increased

risk for NEC.[12] A low level of nitric-oxide in stored RBCs may reduce their vasodilatory effects and ability to enhance oxygen delivery and increase the risk of relative hypoxia in the gut.[13] El-Dib showed that withholding feeds during RBC transfusion decreased the previously found higher incidence of NEC significantly from 5.3% to 1.4% (p=0.047).[14] Due to the increased risk of NEC after RBC transfusions, especially in preterm infants and in infants receiving larger volumes of (cow's milk based formula) feeds, Christensen also advises to stop enteral feeding prior to and during RBC transfusions.[13]
Another aspect that may be related to blood flow reduction affected by RBC transfusions is the observation of Baer et al., who even showed that RBC transfusions given before the development of an intraventricular hemorrhage (IVH) are an independent risk factor for the development of a severe IVH.[15]
The pro's and con's for giving a RBC transfusion and at which moment should therefore be taken into consideration before actually giving the transfusion.

Product and volume

Transfusion products worldwide differ greatly. In the United States most RBC products have a high hematocrit (Hct) up to 0.80 L/L compared to, for example, a Hct of 0.55–0.65 L/L in the Netherlands. Even though the transfusion volume may be equal when comparing studies, the number of erythrocytes given may differ greatly making comparisons difficult, if not impossible. Studies comparing transfusions of similar volumes need therefore take the Hct into account. The volume per transfusion given varies (inter)nationally between 5 and 20 mL/kg with possible effects on the hemodynamics of the infant and as a result a change in cerebral blood flow or pressure which may influence neuromotor and cognitive development.
We performed a two-center study in very preterm infants (<32 weeks gestation) comparing two different transfusion volumes of an identical transfusion product using the same transfusion protocol except for a different volume per transfusion (15mL/kg vs. 20 mL/kg). We found no difference in the number of transfusions given, short-term and long-term outcome in the infants born before 28 weeks' gestation as is shown in chapter 5 and 6.[16,17] One explanation could be that the difference in transfusion volume per transfusion event is too small to detect a difference in outcome or that the volume per transfusion does not influence outcome. The total transfusion volume, however, was significantly lower in the unit transfusing the lower volume per transfusion event and reduced the number of donors to which the infants were exposed. In preterm infants born between 28 and 31 6/7 weeks' gestation, the lower transfusion volume per event led to an increase in the number of RBC transfusions needed and thus a higher donor exposure if a single-donor program was not used. A study by Paul et al., comparing RBC transfusions of 10 to 20 mL/kg, showed a significantly higher post-transfusion

Hct, but no negative effects on pulmonary function when giving the higher volume.[18] A study by Wong et al. comparing 15 to 20 mL/kg also showed higher post transfusion Hcts, but no impact on the number of RBC transfusions given.[19]

The only study focusing on the relation between long-term outcome and transfused RBC volume is our observational follow-up study comparing transfusion volumes of 15 and 20 ml/kg. This study did not show a significant difference in post-discharge mortality, deafness, blindness and neuromotor developmental delay.[17]

More research is clearly needed, preferably RCT, focusing on long-term outcome comparing identical transfusion products with different transfusion volumes per transfusion given as well as long-term outcome taking total transfusion volume into account. Our results suggest, in particular with respect to donor exposure, that it may be important to have a different policy in extremely preterm infants (born <28 weeks' gestation) and less preterm infants.

Triggers

In analogy with optimal volume, guidelines on optimal thresholds for RBC transfusion also differ greatly between (and within) countries. Some studies suggest that restrictive transfusion guidelines lead to similar results compared to liberal guidelines and reduce donor exposure and total transfusions. However, which of the two strategies (restrictive versus liberal) is superior remains controversial.

In the Premature Infants in Need of Transfusion (PINT) trial, comparing restrictive to liberal RBC transfusion thresholds, there was no difference in short-term mortality or major disability (retinopathy of prematurity, chronic lung disease or ultrasound findings of white matter injury).[20] A study by Chen et al. also did not show a difference in short-term neurological outcome when comparing liberal to restrictive guidelines.[8] However, they did find a significantly higher rate of chronic lung disease among infants with a total transfused red blood cell volume >30 mL in 30 days. In another recent RCT (Iowa trial), a group of very low birth weight infants (500–1300 gram) was treated with either a restrictive or liberal transfusion guideline; the infants in the restrictive transfusion group more frequently had an IVH grade 4 and cystic periventricular leukomalacia, while other clinical parameters were equal.[21]

Long-term follow-up of the PINT study at a corrected age (CA) of 18–21 months showed no difference in the primary composite outcome defined as severe cognitive delay (Mental Developmental Index (MDI) <70 (<−2 SD), death, blindness or deafness.[22] However, in a post-hoc analysis with developmental delay redefined as a MDI < 85 (<−1 SD), the authors found a significant difference in favor of the liberal RBC transfusion threshold. Long-term developmental follow-up in the Iowa trial has not been published yet. However, the authors recently published a study on cerebral imaging performed in infants at 12 years included in the initial

Iowa trial and reported that intracranial volume was significantly smaller in the liberal group compared with term controls.[23] These finding may seem to contradict the conclusions from their short-term follow up. However, the imaging study was hampered by several important methodological limitations: A) a high loss to follow-up rate (only 44% of the initial cohort was available for analysis), and B) intracranial volume (which includes cerebrospinal fluid) is not the best predictor of neurodevelopmental outcome.
The relatively small number of infants in these studies (the PINT study is the only larger study on this topic) makes it difficult to use them as principal guidance for a transfusion guideline and is reflected in the prevailing variety of guidelines shown in a recent international practice survey.[24]

Alternatives

Micro-blood sampling, transcutaneous measurements and increased awareness on anemia of prematurity (AOP) have diminished the amount of blood drawn for laboratory sampling, one of the most important causes for AOP. Baer et al. showed that implementation of a transfusion ordering and monitoring instrument improved compliance to the local transfusion guideline and diminished the number of transfusions given.[25]
A Cochrane review in 2004 showed that delaying cord clamping (DCC) for 30 seconds to 3 minutes in preterm infants reduces the number of RBC transfusions needed and the number of IVH without detrimental effects.[26] In term infants, however, DCC leads to an increased need for phototherapy to treat hyperbilirubinemia, but not to an increase in the indication for partial exchange transfusion because of polycythemia. The Hb level in these infants is better than in infants subjected to immediate cord clamping and their ferritine levels are significantly higher at six months of age.[27]
Umbilical cord blood (UCB) harvesting is a possibility to obtain red blood cells for autologous transfusion. It is a costly procedure and harvesting for extremely preterm infants (<28 weeks gestation), who would benefit most from these products, is often difficult due to their small placenta and thus a small volume retrieved. Our study described in chapter 4 showed that it is not feasible to routinely harvest UCB in all preterm infants for autologous RBC transfusion due to small volumes harvested or processing difficulties.[28] Strauss et al. show similar results in their overview article on autologous RBC transfusion for anemia of prematurity.[29] Several studies have shown that UCB, harvested at term deliveries, can be used for (full term) neonatal surgical patients to avoid allogenic RBC transfusions,[30,31] but this is a very limited group of patients. UCB has been safely used for allogenic red blood cell or whole blood transfusions in pediatric patients and adults in source-restricted areas where availability of blood products is scarce.[32]

Cochrane reviews have shown that erythropoietin (EPO) administration (early: started in the first week of life or late: started after day 7) in preterm infants has no clinical meaningful benefit in diminishing the number of RBC transfusions, total transfusion volume and, thus donor exposition, when given the first weeks of life, in particular not in sick children. Together with the increased risk for severe retinopathy of prematurity as a side effect of early EPO administration, indications for EPO are very limited.[33,34] Selected groups of patients such as infants of Jehovah's Witness might benefit from avoidance of late RBC transfusions.
Enteral iron therapy started when enteral feeds have reached 100 mL/kg/day may reduce late RBC transfusions (>2 weeks) in infants <1301 grams without negative side effects.[35] It does not affect the number of RBC transfusions given in the first few weeks of life when the majority of these very preterm infants are transfused.
Measures to diminish donor exposure are possible, but mainly used in the Western countries. Single donor programs, dividing an adult unit of RBCs into four or five pediatric units and assigning these to one or two infants can limit donor exposure.[16,36,37]
Restrictive use of RBC, either in volume per transfusion event or by a restrictive transfusion threshold, can lead to a lower total transfusion volume, and if single donor programs are not used, less donor exposure in particular for infants born before a gestational age of 28 weeks.[38-40]

Platelets

Thrombocytopenia can be divided into fetal onset, early onset (<72 hours after birth) and late onset thrombocytopenia (>72 hours after birth), each with their own causes, albeit partly overlapping. Early thrombocytopenia is often caused by maternal causes (auto- and allo-antibodies against platelets) and due to asphyxia during delivery and can affect both term and preterm born infants, whereas late thrombocytopenia often affects mainly preterms in relation to infection and thrombosis and impaired bone marrow response to compensate low platelet counts.
Platelet transfusions may be administered to prevail over an extremely low platelet count (<30–50 x 10^9/L) or to help stabilize an acute severe hemorrhage before a sustained rise in platelets is induced by treating the underlying cause. Most feared is IVH.
In a study by Bear et al. in neonatal intensive care patients with a platelet count <50 x 10^9/L the rate and grade of IVH was independent of the severity of the thrombocytopenia below this level.[3] In severe thrombocytopenia (<20 x 10^9/L) the rate of cutaneous bleeding (defined as extensive bruising or oozing from puncture sites) is also reported to be significantly higher than in infants with higher platelet counts. Our study presented in chapter 8 shows that

thrombocytopenia <150 x 10^9/L in (preterm) neonates is associated with a higher risk of (intraventricular) hemorrhage than a normal platelet count, but that the severity of thrombocytopenia has no correlation with the severity of IVH. Setzer et al. found a higher prevalence of IVH in infants with a lower platelet count, next to an increased number of hemostatic abnormalities in infants with IVH.[41] In 1987 Andrew et al. published a prospective study and found an abnormal bleeding time in thrombocytopenic infants that was corrected after platelet transfusion.[42] Thrombocytopenia correlated with more severe IVH and other hemorrhages. There was a significantly higher percentage of infants with severe neurologic sequelae (cerebral palsy, deafness or hydrocephalus) at twelve months follow-up in the infants <1500 grams at birth with thrombocytopenia (<100 x 10^9/L) compared to the infants with a normal platelet count. However, the group of thrombocytopenic infants had also a significantly lower Apgar score at 5 minutes after birth. Whether the neurologic sequelae were caused by thrombocytopenia or other factors remains unclear.
Incidentally, platelet transfusions have been associated with detrimental effects such as the transmission of infectious agents and transfusion reactions.[43,44] Several studies have shown a significantly higher mortality rate after platelet transfusions in neonates.[45-47] Whether this higher mortality rate is causally related to the platelet transfusion or the underlying disease severity indicating platelet transfusions is unknown. The question therefore remains whether and when to transfuse thrombocytes.

Product and volume

As far as the properties of the transfusion products are mentioned most clinicians transfuse between 10 and 20 x 10^9/kg thrombocytes. The volumes of these transfusions differ greatly depending on the type of preservation fluid and technique of processing. Products can be random single donor, acquired through apheresis, in compatible plasma or preservation fluid. Alternatively, products can be part of an adult unit derived from 5 random donors, either whole-blood derived or by buffy-coat technique. In our medical center a single donor plasma reduced platelet product, acquired through apheresis, is used limiting the volume transfused to approximately 5 mL/kg (containing 20 x 10^9 platelets/kg). Platelets can be suspended in plasma or a PAS (platelet additive) solution (PAS-1: D-mannitol, phosphate and citrate; PAS-2: supplemented with acetate, but low citrate concentration). Each suspension fluid has its advantages and disadvantages. Plasma is known to cause adverse transfusion reactions. PAS-1 and -2 have the advantage of being able to remove the majority of plasma, but during storage in PAS-1 and -2, platelets tend to deteriorate faster because maintenance of the pH above 6.5 is decreased and in adult recipients post-transfusion platelet increment is lower than after storage in plasma.[48]

Infants with thrombocytopenia due to fetal/neonatal allo-immune thrombocytopenia (FNAITP) may need HPA-1a or HPA-5b negative matched platelet products to provide a longer lasting rise in platelet count. In acute situations random platelets can be given awaiting the matched platelets.[49]

Triggers

Various guidelines for platelet transfusions can be found in the literature, but none are evidence based. In the previously mentioned international practice survey by New et al. several transfusion guidelines are mentioned.[24] Most guidelines take the platelet count and clinical condition, combined with gestational age, into account when deciding whether to transfuse or not. Most consensus based guidelines have a lower platelet transfusion threshold of 20–30 x 10^9/L.[50-52] For clinically unstable infants or those in need of surgery higher platelet counts are preferred (from 50 to 100 x 10^9/L).

In the only prospective RCT on prophylactic platelet transfusions in non-bleeding preterms by Andrew et al. no reduction in IVH was detected when prophylactic platelet transfusions for platelet counts between 50 and 150 x 10^9/L were compared with no transfusion.[53] Murray et al. performed a retrospective review in a group of 53 preterm infants with severe thrombocytopenia. All infants with a platelet count <30 x 10^9/L and all unstable infants or infants with an IVH and a platelet count 30–50 x 10^9/L received a platelet transfusion. They found no difference in major hemorrhages whether the infants had received a platelet transfusion or not.[54]

In our study described in chapter 9, we compared the outcome in two neonatal intensive care centers in the Netherlands using different transfusion guidelines (restrictive versus liberal) and found no significant difference in the incidence of any hemorrhage or severe hemorrhages between both units. Bonifacio et al. also reported that the development of IVH was strongly associated with a lower gestational age and not with the severity of thrombocytopenia.[46]

Alternatives

No studies have evaluated the use of thrombopoietin (TPO) mimicking proteins to treat thrombocytopenia in human newborns. Human and animal studies show that these TPO analogues produce a rise in platelet count after 6–7 days of therapy.[55,56] Because thrombocytopenia in human infants usually resolves within a week, the usefulness of TPO mimicking proteins in neonates is questionable.

To date no studies with substitutes for platelets have been performed in newborn infants. Several (adult) animal studies have shown a possible positive effect of the administration of alternative products such as polymerized albumin particles or activated Factor VII improving hemostasis in patients with bleeding and thrombocytopenia.[57,58]

High dose intravenous immunoglobulin (IVIG) has a role in immune-mediated (early) thrombocytopenia, such as FNAITP and immune thrombocytopenia (ITP) causing (early) thrombocytopenia irrespective of gestational age. Infusions of high dosages of IVIG given weekly to women pregnant with a fetus with FNAITP decrease the risk of intracranial hemorrhage in all infants and induce an increase in the fetal platelet count in 30–85% of these infants.[59] How IVIG exactly exerts this effect is unknown but the treatment can replace hazardous intra-uterine platelet transfusions.[60-62] Postnatal IVIG administration to newborns with NAITP has a delayed effect on their platelet count and HPA-matched transfusions are first line treatment.[49,63,64] In contrast, in case of neonatal thrombocytopenia due to maternal auto-antibodies in ITP, maternal administration of IVIG is ineffective, but neonatal administration of IVIG can raise the platelet count within 2–3 days and is recommended in a non-bleeding infant.[65]

Due to the pathogenesis of hemorrhage in newborns and especially in preterm infants, focusing on a normal platelet count to diminish bleeding in these infants is not enough. Furthermore, the timing of the hemorrhage does not seem to be related with the onset of a low platelet count.[66]

Concluding remarks and future perspectives

Transfusion guidelines for the treatment of anemia or thrombocytopenia in newborns are not well established nor evidence based. Although various studies have been performed to address this problem, absolute thresholds based on evidence based research have not yet been established. Combining the findings of several studies is not possible due to difference in patient categories, cause of anemia/ thrombocytopenia, transfusion products and outcome measurements. The ten Dutch neonatal intensive care units each use their own guidelines for RBC and platelet transfusions despite the availability of national consensus recommendations. As long as alternatives to donor blood products do not seriously diminish the need for transfusions in neonatal medicine, more sufficiently powered prospective RCTs are needed to establish well founded guidelines. This asks for multicenter cooperation because in a fast evolving field like neonatology, many confounding factors may be introduced due to changes in treatment of this group of patients.

Studies should not only focus on different transfusion regimens but should also take the different products into account. Using RBC products with a different Hct will have impact on the blood viscosity and this in itself may have effect on the blood circulation and oxygen delivery in the body. The effect of transfusion volume per event, total transfused volume and red cell or platelet content of the transfusion product should be studied. The various fluids used for

platelet preservation may also have their effect on the recovery of platelets and their lifespan. Platelet studies should be stratified for the cause of thrombocytopenia, gestational age and have relevant (bleeding) endpoints.
Short-term and especially long-term effects of blood product transfusions need to be investigated as possible later detrimental effects of RBC transfusions have been shown in the few studies that have been conducted.
Ways to improve harvesting and processing of umbilical cord blood should be found to make this a more feasible way to produce autologous RBCs for very preterm infants. Alternatives to donor products should be further studied.

In summary, RBCs are probably the most frequently used drug given to very preterm infants without its long-term effects being well studied and known. Except for reduction of the amount of blood drawn for laboratory tests and use of a single donor program, no measures have been shown to be an irrefutable safe way to reduce donor exposure.
Thrombocytopenia is also a frequently encountered problem in neonatal medicine with an increased risk for hemorrhages. But why, when and what to transfuse remains a topic of clinical research.
To acquire broad support from the clinicians taking care of these vulnerable (preterm) infants, large studies showing safety of the guidelines is of utmost importance. Future research should be directed at identifying a safe lower transfusion trigger for transfusion products without short-term or long-term detrimental effects.
Until that time, the data in this thesis suggest the use of 15 mL/kg body weight of RBCs with a Hct of 60 (± 5)%, in particular for extremely preterm infants (gestational age at birth <28 weeks), using a single donor program to reduce donor exposure. RBC transfusion triggers should be based on clinical condition and postnatal age. In stable infants older than 4 weeks Hb should be maintained above 4.5 mmol/L. In younger infants or with signs of anemia or oxygen dependency (O_2<30%) a Hb of 6.0 mmol/L is recommended. In case of mechanical ventilation, higher oxygen need or cardiopulmonary disease the transfusion threshold has to be adjusted upwards.
Platelet transfusions should contain 10–20 x 10^9/kg of platelets, derived from a single donor in platelet additive solution or volume-reduced. Platelets should only be given when the platelet count drops below 50 x 10^9/L in the presence of an active major hemorrhage or the need for invasive procedures. In the absence of a significant bleeding a lower threshold (20 x 10^9/L) is recommended, unless further decrease of the platelet count is foreseen such as in immune mediated thrombocytopenia's.

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