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SPECIAL ARTICLE

Recommendations for transfusion of blood products in neonatology☆

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Abstract The scant evidence on the use of transfusions in neonatal care explains the limitations of current clinical guidelines. Despite this, in this document we explore the most recent evidence to make recommendations for the clinical practice. The prevention of anaemia of prematurity, the use of protocols and restrictive transfusion strategies constitute the best approach for clinicians in this field. In the case of platelet transfusions, the risk of bleeding must be assessed, combining clinical and laboratory features. Lastly, fresh frozen plasma is recommended in neonates with coagulopathy and active bleeding, with congenital factor deficiencies for which there is no specific treatment or with disseminated intravascular coagulation. All blood products have adverse effects that warrant a personalised and thorough assessment of the need for transfusion.

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PALABRAS CLAVE
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Recomendaciones para la transfusión de hemoderivados en neonatología

Resumen La escasa evidencia sobre el uso de las transfusiones en neonatología explica las limitaciones de las guías clínicas actuales. A pesar de ello, en este documento analizamos la evidencia más reciente para hacer unas recomendaciones para la práctica clínica. La prevención de la anemia de la prematuridad, el uso de protocolos y las indicaciones restrictivas de transfusión, componen la mejor estrategia para nuestros clínicos. En las transfusiones de plaquetas, es preciso valorar el riesgo de sangrado, integrando la situación clínica y analítica. Por último, el plasma fresco congelado está recomendado en neonatos con coagulopatía y sangrado activo, en déficits congénitos de factores sin tratamiento específico y en situaciones de coagulación intravascular diseminada. Todos los hemoderivados presentan efectos adversos que deben hacernos evaluar individual y minuciosamente la necesidad de una transfusión.

Transfusion of packed red blood cells

Introduction

Ninety percent of extremely low birth weight (ELBW) preterm (PT) newborns require transfusion of red blood cell (RBC) concentrates during their hospital stay. The evidence available on neonatal transfusion is limited, due to which current practices are widely heterogeneous.[1,2]

Isolated haemoglobin (Hb) measurements are an imperfect but necessary measure to assess the need of transfusion.[3,4] At present, decisions regarding transfusion are based on a combination of clinical manifestations, Hb/haematocrit (Htc) values and cardiorespiratory status. One non-invasive tool that may be of interest is near-infrared spectroscopy (NIRS). There is growing interest in intestinal and splanchnic oxygen saturation, and it is expected that they may play an important role in the identification of the optimal threshold for transfusion.[1,5] Both NIRS and the sonographic assessment of perfusion seem to perform well in identifying at-risk anaemic PT newborns.[6,7]

Pathophysiology. In the neonatal period and subsequent months, there are significant changes in the RBC mass: the production of RBCs decreases and the proportion of Hb A increases, which in turn increases the release of oxygen to tissues. Iron from degraded RBCs accumulates, which is useful for future haematopoiesis.

At 8–12 weeks post birth, Hb values reach the trough in term newborns at 11 g/dL, and production of erythropoietin is stimulated.

Anaemia of prematurity entails greater deficits compared with physiological anaemia, chiefly resulting from the immaturity of the haematopoietic system, iatrogenic blood losses, erythropoietin deficiency, a substantial growth rate and underlying disease. The trough of Hb is lower in PT newborns, as erythropoietin is stimulated at lower values (7—9 g/dL). In term newborns, 70%–80% of Hb is foetal haemoglobin (HbF); while in PT newborns, HbF amounts to up to 97% of the total. Foetal haemoglobin has a higher affinity for oxygen, so that under equal conditions, releasing oxygen to tissues will be more difficult in PT newborns.[8]

Prevention strategies

The prevention of anaemia of prematurity must be a key goal, given the lack of evidence on the use of transfusions in newborns.[9–11] The main preventive measures are (Table 1):

Delayed cord clamping in PT newborns: in term newborns, it is associated with a reduction in the need of RBC transfusion, improved haemodynamic stability and a decreased risk of intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC).[12] Studies of delayed cord clamping in PT newborns are scarce, although they suggest that the outcomes are similar to those in term newborns.[13,14] Based on the evidence available to date, umbilical cord milking does not seem to be a safe practice in PT newborns,[15] and one of the main limitations is technical, as these patients usually require respiratory support at the same time.

Use of umbilical cord/placental blood for laboratory tests in ELBW PT newborns: it significantly reduces the number of transfusions given in the first week of life.

Adherence to guidelines: it reduces the number of transfusions.

Reduction of iatrogenic blood losses through optimization of the schedule of blood draws and the use of point-of-care (POC) devices.[5]

Erythropoietin (EPO): systematic reviews and meta-analyses have failed to demonstrate a clear benefit. The time when the need of transfusion is greatest in PT infants is usually the first weeks of life, when administration of EPO offers no benefits. It could be beneficial in reducing late transfusions. The British Committee for Standards in Haematology does not recommend routine administration of EPO or darbepoetin alfa in PT newborns to reduce the number of transfusions (grade 1B recommendation).[9] However, current studies focused on the use of high-dose EPO[16] and recombinant human (rhEPO) have found promising results.[17]

Iron supplementation: it appears to improve iron stores after 2–3 months if initiated early. Most guidelines recommend supplementation with 2–3 mg/kg of iron in PT newborns, initiated early (delivered with an enteral feed volume of 100 mL/kg).

Table 1 Evidence level for preventive measures against anaemia of prematurity.

Strategy	Quality of evidence	Strength of recommendation	Recommendation of the Standards Committee of the SENeo
Delayed cord clamping	1A	High/substantial A	Recommended for routine clinical practice
Initial cord/placental blood tests	2B	Moderate/ moderate B	Recommended for routine clinical practice
Reducing phlebotomy losses	1B	Moderate/substantial B	Recommended for routine clinical practice
Erythropoietin	1A	Moderate/ moderate B	Further research is required to recommend its clinical use.
Darbepoetin	1B	Moderate/small C	Further research is required to recommend its clinical use

Source: adapted from Christensen et al.[11]
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Drawbacks and complications of RBC transfusion

Red blood cell transfusions have unquestionably been one of the key factors in increasing the survival of extremely PT newborns. Anaemia in PT newborns can affect the oxygen supply of the brain, which, combined with intermittent hypoxia and apnoea or circulatory failure at a time of rapid cerebral growth, can contribute to development of brain damage. Red blood cell transfusions are beneficial due to the increase in circulating Hb, which results in improved tissue oxygenation and a decrease in cardiac output.[5] On the other hand, there is evidence that they may have a negative impact on neurodevelopment.[18]

In current clinical practice, the need for transfusion must be weighed against its risks. In addition to the already established risks associated with transfusion (transmission of infection, alloimmunization, febrile reactions, haemolytic reactions, allergies, additional donor exposure), in PT newborns RBC transfusions are associated with the development of bronchopulmonary dysplasia (DBP), retinopathy of prematurity (ROP), NEC or IVH, although a causal relationship has not been established.[19] Other events, such as transfusion-related acute lung injury and transfusion-associated circulatory overload may go unnoticed, mainly in ill extremely PT newborns with respiratory symptoms. Some observational studies have found an association between NEC and transfusions, but these findings are not supported by data from randomised clinical trials.[20] One prospective study found that the probability of NEC increased if the Hb trough was below 8 g/dL before the transfusion, which suggests an association with anaemia rather than with transfusion.[21]

Transfusion thresholds

Leaving aside that the Hb concentration or the Htc are probably not the best parameters to consider when determining the need of transfusion, there are no defined optimal cut-off points for transfusion that are based on evidence. In 2005, Bell published a randomized trial comparing liberal versus restrictive guidelines for RBC transfusion in preterm infants based on haematocrit thresholds that included 100 PT newborns with weights ranging from 500 to 1300 g. The number of transfusions decreased with the application of restrictive guidelines. In the restrictive group, there was a higher probability of major neurologic adverse events and a higher frequency of apnoea. The outcomes suggested that the increasing use of restrictive criteria should be carefully reevaluated.[22] However, a study conducted in 56 patients from the same cohort at 8–15 years found significant differences between groups, with patients in the restrictive group performing better on measures of associative verbal fluency, visual memory, and reading.[23]

The PINT study, conducted in 451 PT newborns and published in 2006, analysed whether the mortality or morbidity at discharge (primary outcome) in ELBW PT newborns differed between those who received transfusions based on a higher Hb level (liberal group) or a lower Hb level (restrictive group). The authors found no differences between groups in the primary outcome, and therefore concluded that in ELBW PT newborns, the application of a higher Hb threshold increased the frequency of transfusion in the absence of strong evidence of any benefits.[24]

At a later date, long-term functional outcomes in the PINT study were analysed. The outcome of death or neurodevelopmental impairment at 18 months of corrected age (CA) was observed in 45.2% of the children assigned to the low Hb threshold group compared to 38.5% in the high threshold group, with a *P*-value of 0.091 in favour of the liberal threshold group. The difference in cognitive delay (<2 standard deviations below the mean) approximated statistical significance (24.4% in the restrictive group vs 17.6% in the liberal group; odds ratio [OR], 1.7; $P = .06$). This study provides weak evidence of a potential benefit of a higher Hb threshold after a secondary analysis of cognitive delay. The results for this outcome in the statistical analysis neared significance with the post hoc analysis, although the result is thus inconclusive.[19]

A 2011 Cochrane review concluded that the restrictive approach does not seem to have a significant impact on morbidity of mortality either at hospital discharge or during the follow-up.[4]

A meta-analysis published in 2014 that included 3 randomised controlled trials (Bell, Cheng and Kirpalani) showed that restrictive thresholds achieved a significant decrease

in the number of transfusions and did not have a significant impact on short-term morbidity or mortality. However, the strength of the evidence is questionable due to the heterogeneity of the studies included in the analysis.[25]

The evidence on long-term results on this aspect has been, therefore, limited and contradictory. Overall, there has been no evidence of restrictive transfusion approaches having a significant impact on morbidity or mortality. We ought to mention that the safety of Hb thresholds below those used in published studies is unknown.

The scarcity of the data that suggested that higher Hb thresholds could reduce the risk of cognitive delay[26] motivated the development of 2 multicentre randomised trials: the Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) trial[21] and the Transfusion of Prematures (TOP) trial.[20]

In the ETTNO trial (n = 928 ELBW PT newborns) the liberal transfusion strategy, compared to the restrictive strategy, did not reduce the probability of the primary outcome (death or disability at 24 months of CA). The incidence of NEC, DBP, ROP, intestinal perforation, brain injury, patent ductus arteriosus (PDA) and nosocomial infection, in addition to growth outcomes, did not differ significantly between the 2 groups.[27]

In the TOP trial (n = 1824 ELBW PT newborns) the higher Hb threshold for transfusion was associated with a greater number of transfusions. The frequencies of the primary outcome (death or neurodevelopmental impairment at 22–26 months of CA) and the secondary outcome (survival without severe complications at discharge) were similar in both groups (high vs low threshold). Although the post hoc analysis of a previous study by Whyte suggested a positive impact on cognitive outcomes at 18–21 months in infants allocated to a higher Hb threshold, this study of larger scope did not find evidence supporting an improvement in this or any other clinically relevant outcome measured during the initial hospital stay or at 22–26 months.[20]

Transfusion volume and type of product

Red blood cell transfusion volumes for newborns range from 5 to 20 mL/kg, but the evidence on the optimal volume is also limited. The United Kingdom guideline considers volumes of 15 mL/kg prudent for newborns without bleeding (grade 2C recommendation).[9] Several studies suggest that transfusion volumes of 20 mL/kg, could be beneficial without negative respiratory effects, reducing the need for frequent transfusions.[10] Volumes of more than 20 mL/kg could increase the risk of volume overload in patients without bleeding.

Leukodepleted RBC transfusion is universally recommended, in addition to irradiation of RBCs in PT newborns with weights of less than 1500 g.[1]

The findings of the Age of Red Blood Cells in Premature Infants Trial suggest that the use of fresh RBCs compared to different storage ages does not improve outcomes in PT newborns. Hospitals should develop policies aimed at minimising exposure to multiple donors. Thus, the use of multiple aliquots for paediatric transfusion made from one adult blood donation (paedipacks) can decrease donor exposure.[9,19]

Recommendations. Comparison of international guidelines

There is a broad range of guidelines on the management of neonatal anaemia, mostly based on expert opinion,[10,12,19] which need to be applied on the basis of clinical experience and information acquired from reliable sources.

Each unit should approve the specific guideline that best matches local clinical practices. It is also important to adhere strictly to the guideline to reduce heterogeneity in clinical practice.[19]

There is evidence that the application of blood transfusion guidelines and adherence to them is associated with a decrease in the number of transfusions[9] and with an improving trend in the incidence of IVH and NEC.[28] Safe thresholds are needed to avoid an unwanted increase in adverse events associated with a decreased oxygen supply to the brain, lungs and intestine.[29]

The British guideline on transfusion in newborns was published in 2016, and developed based on studies in PT newborns with ELBW (<1.5 kg) and born before 31 weeks of gestation. Transfusions in newborns of other gestational ages would be conducted following the same recommendations, although there is little evidence on term babies delivered after 32 weeks.[9] Table 2 presents the transfusion thresholds proposed in current guidelines,[9,30,31] developed based on restrictive thresholds obtained in randomised controlled trials in VLBW PT newborns, and consistent with the data of the National Comparative Audit of Blood Transfusion, 2010.

Platelet transfusion

Introduction

Thrombocytopenia (<150,000 platelets/μL) is frequent in newborns, with an incidence of 1%–2% in healthy newborns that rises to 20%–35% in ill ones. The incidence increases with decreasing gestational age, and may reach 70% in extremely PT newborns. Thrombocytopenia may be caused by intrauterine infection, placental insufficiency, neonatal sepsis, adverse drug effects or immune thrombocytopenia. The more premature the baby, the lower the normal range, with platelet counts between 100,000 and 150,000/μL.[32]

The incidence of bleeding in newborns also increases with decreasing gestational age. The most frequent type of bleeding, which also has the most devastating consequences, is IVH, which chiefly develops in the first 3 days post birth and is currently attributed to cardiorespiratory changes rather than haematological abnormalities.

When thrombocytopenia and active bleeding co-occur, platelet transfusion is unquestionably part of the indicated treatment. Thus, in current clinical practice, in the case of isolated thrombocytopenia, prophylactic platelet transfusions are given to prevent bleeding despite limited evidence of their usefulness. Multiple studies in adults, children and newborns have not found a clear correlation between the platelet count and the risk of bleeding, making it difficult to establish thresholds for prophylactic platelet transfusion.[33] Furthermore, there is no evidence that prophylactic platelet transfusion decreases the risk of bleeding, but there is evi-

Table 2 Haemoglobin thresholds (g/dL) for red blood cell transfusion in preterm newborns proposed by different international guidelines.

	British Committee for Standards in Haematology, 2016[9]			Australian National Blood Authority, 2016[30]		Canadian Blood Services, 2017[31]	
Postnatal age	MV	O_2, NIPPV	WITHOUT O_2	Respiratory support (MV, CPAP, high-flow, O_2)	No respiratory support	Respiratory support (FiO_2 > 25% o VM)	No respiratory support
24 h	<12	<12	<10				
1 week	<12	<10	<10	11–13	10–12	11.5	10
2 weeks	<10	<9.5	<7.5*	10–12.5	8.5–11	10	8.5
3 weeks	<10	<8.5	<7.5*	8.5–11	7–10	8.5	7.5

CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MV, mechanical ventilation; NIPPV, non-invasive positive-pressure ventilation; VM, mechanical ventilation.
* 8.5 g/dL may be appropriate depending on the clinical context.

dence of the significant complications and adverse effects that they can cause.

Pathophysiology. Platelet production, function, haemostasis and even bleeding are managed differently in PT newborns, term newborns and adults.[34] Megakaryopoiesis is the process by which platelets are produced. In the past 20 years, important biological differences have been found in megakaryopoiesis in newborns versus adults. First of all, the concentration of thrombopoietin is significantly higher in newborns than in adults. Megakaryocyte (MK) precursors have a greater proliferative potential in newborns compared to adults, giving rise to significantly larger megakaryocyte colonies with counts up to 10-fold compared to those generated by adult progenitors. Neonatal MKs are smaller and with a lower ploidy, that is, each MK in newborns divides into fewer platelets that are also smaller compared to the platelets formed in adults. The greater proliferation is how this gets compensated, so that platelet counts are similar in newborns than adults. When thrombocytopenia develops in adults, both the size and ploidy of MKs can increase. However, in newborns, only the number can increase. In vitro assessments of platelet aggregation in term newborns found hyporreactivity to different platelet agonists that was not clinically correlated to abnormal haemostasis. In fact, studies of primary haemostasis and platelet function (PFA-100) have demonstrated that bleeding times in healthy newborns are significantly shorter compared to adults.

In short, the haemostatic system differs significantly in newborns (including those born preterm) compared to adults, but is delicately balanced to prevent bleeding. The platelet transfusions given to newborns, independently of gestational age, are from adult donors, and it is not known how these platelets may affect the haemostatic system of the newborn.

Prophylactic platelet transfusion

The definition of the threshold of clinically significant thrombocytopaenia based solely on the platelet count does not take into account factors such as platelet function or the capacity to respond to a state of thrombocytopenia. The clinical evidence to help define these thresholds is very scarce.

In 2019, the researchers of the Platelet Transfusion Thresholds in Premature Neonates (PlaNeT-2) compared 2 transfusion thresholds, 25,000/μL vs. 50,000/μL, in PT newborns delivered before 34 weeks' gestation. The incidence of the primary outcome of death or severe bleeding was significantly higher in the group with a threshold set at 50,000/μL compared to the threshold of 25,000/μL. There was also a higher incidence of DBP in the higher threshold group, which reinforces the recommendation of applying the 25,000/μL threshold in PT newborns.[35]

A substudy of the PlaNeT-2 study analysed the risk of death or severe bleeding in patients with high or low risk of bleeding. Independently of the risk of bleeding, patient outcomes were better in the 25,000/μL threshold group, with the greatest benefits observed in patients at high risk.[36]

Other properties of platelets

The role of platelets in inflammation and the immune response is a field of research that has been very active in the past few years. Platelets produce several cytokines and proinflammatory molecules (interleukin 1β or CD40L, among others) that facilitate the interaction of platelets and white blood cells. They also act as sentinels, recognising invading microorganisms and thereby linking their haemostatic activity with innate immunity.[37]

On account of this and several other immune functions of platelets, thrombocytopenia not only has an impact on haemostasis, but may also affect the immune system. The potential impact of transfusion of adult-donor RBCs on the immune system and inflammatory response of PT newborns has yet to be established.

Recommendations

Correct assessment of bleeding risk including both clinical and laboratory parameters as opposed to sole consideration of the platelet count seems the most appropriate path to

Table 3 Definition of coagulopathy in preterm and term infants, at birth (A) and in the first 3 months of life (B) based on the prothrombin time, activated partial thromboplastin time and fibrinogen levels.

(A) Gestational age at birth (weeks)	PT, upper limit (s)	aPTT, upper limit (s)	Fibrinogen, lower limit (mg/dL)
<28	>21	>64	<71
28–34	>21	>57	<87
30–36	>16	>79	<150
≥37	>16	>55	<167
(B) Gestational age (WG) and postnatal age (days)	**PT, upper limit (s)**	**aPTT, upper limit (s)**	**Fibrinogen, lower limit (mg/dL)**
30–36 WG and postnatal age			
5	>15	>74	<160
30	>14	>62	<150
90	>15	>51	<150
≥37 WG and postnatal age			
5	>15	>60	<162
30	>14	>55	<162
90	>14	>50	<150

Source: Table adapted from Andrew et al.[40]
aPTT, activated partial thromboplastin time; PT, prothrombin time; WG, weeks of gestation.

Table 4 Recommendations for clinical practice.

Packed red blood cells

- Prevention is the best approach to the management of anaemia of prematurity (Table 1):
- Delayed cord clamping
- Fewer blood draws
- Use of restrictive guidelines adapted to the specific NICU
- Decisions on transfusion must be individualised and take into account the clinical context in addition to test results (Table 2).
- A possible recommendation on transfusion thresholds in preterm newborns, based on the aforementioned guidelines, could be:

	FiO_2 > 0.25 or invasive or non-invasive ventilation	No respiratory support
Week 1 of life	12	10
Week 2 of life	10	8.5
Week 3 of life	9	7.5

Platelets

- In the case of thrombocytopenia concurrent with active bleeding, transfusion is a must.
- Prophylactic transfusion should be preceded by an individualised clinical assessment and laboratory workup to determine the risk of bleeding.
- In very low birth weight newborns without active bleeding or other risk factors, it is appropriate to use a threshold of 25 000/μL.
- In the case of alloimmune thrombocytopenia or thrombocytopenia preceding a surgery, many authors recommend a higher threshold of up to 50 000/μL.

Fresh frozen plasma

- Values of PT, aPTT or fibrinogen must be assessed based on gestational age and chronological age in days (Table 3).
- The use of FFP is recommended in patients with coagulopathy and active bleeding, in patients with disseminated intravascular coagulation and in the case of congenital factor deficiency if treatment with the specific factor is not available.

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; NICU, neonatal intensive care unit; PT, prothrombin time.

assess risk in each patient and thus make decisions regarding the use of transfusion.

Taking into account the current medical evidence and after an individualised risk assessment, it seems reasonable to apply a threshold of 25,000 platelets/μL to determine the need of transfusion in very low birth weight PT newborns without active bleeding. In the case of alloimmune thrombocytopenia or thrombocytopenia prior to surgery, many authors recommend higher thresholds. Typically, a volume of 10–15 mL/kg is administered to achieve increases in the platelet count of 50,000–100,000 platelets/μL.

Fresh frozen plasma transfusion

Fresh frozen plasma (FFP) is widely used in neonatal intensive care units (NICUs), especially in severely ill newborns. The pronounced variability of normal ranges of clotting factors in relation to gestational and chronological age make the diagnosis of coagulopathy particularly challenging.[38] If we also consider that standard coagulation tests have exhibited a very poor correlation with the risk of bleeding, it is no surprise that the recommendations in current guidelines are based on low-quality clinical evidence, contributing to the frequent inappropriate use of FFP in neonatal care.[39]

The scarce literature currently available recommends the use of FFP in patients with coagulopathy (assessed based on gestational age and days of postnatal age) (Table 3)[40] and active bleeding, in patients with disseminated intravascular coagulation and in the case of congenital factor defects for which the specific factor is not available. We do not recommend routine performance of coagulation tests in PT newborns. The usual transfusion volume is 10–15 mL/kg of FFP.

Conclusion

The conclusions are presented in Table 4.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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