Trojanowska Paulina, Trojanowska Alina, Tywanek Ewa, Wronecki Jakub, Zwolak Agnieszka, Łuczyk Robert Jan. Transfusions of packed red blood cells in the pathology of newborn. Journal of Education, Health and Sport. 2019;9(9):1091-1100. eISNN 2391-8306.
DOI http://dx.doi.org/10.5281/zenodo.3463165
http://ojs.ukw.edu.pl/index.php/johs/article/view/7526

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 25.08.2019. Revised: 31.08.2019. Accepted: 22.09.2019.

Transfusions of packed red blood cells in the pathology of newborn

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Abstract

Sick newborns are at present the largest group of patients receiving blood products. Therefore, packed red blood cells transfusion is one of the most common procedures performed in Intensive Care Units. However, in order to avoid unnecessary risk, and thus reduce the rate of adverse invents after transfusion, which are particularly common in this group of patients, there is a need to develop proper standards of administration.

The aim of this study is to review the current scientific literature on transfusion of packed blood cells in different medical situations in neonates.

Key words: packed red blood cells; newborns; transfusion

Introduction

Sick newborns are currently the most numerous group of patients receiving blood products [1]. Any decision to carry out a transfusion in the newborn must be based on answering a number of questions about such issues as: determining the cause of the newborn's anemia, possible alternatives to transfusion of blood components, risk assessment and the benefits of such treatment. This is particularly important in this group of patients, as it constitutes a significant percentage of reports on the occurrence of transfusion adverse reactions, and the frequency of these effects is estimated to be still actually low [2].

In general, blood components should only be transfused to a sick neonate if the potential clinical benefit outweighs the risk of procedure.

Often, however, clinical assessment of the need for transfusion in critically ill neonates is imprecise and may vary between different clinicians, while usefulness of more objective values, such as level of hemoglobin (Hb) and hematocrit (HTC) value, is in such cases rather controversial – during acute blood the level of Hb concentration and the HTC value may not change even for one hour and longer [3].

The basis of assumptions, which constitute the indications for treatment with blood preparations, are such issues as: physiological differences between the hematopoietic system of the newborn and the child in further periods of development, including different survival time of red blood cells, iron supply deficiencies, inhibition of erythropoiesis, adaptation processes (especially in premature newborns); exposure to adverse factors: hypoxia, infections, iatrogenic blood loss [1].

Transfusion of packed red blood cells remains the only treatment for most cases of neonatal anemia. As a result, PRBC transfusion is one of the most common procedures performed in Intensive Care Units. Current research shows that about 80% of newborns weighing <1.5 kg at birth require at least one of the PRBC transfusion [3].

The main indications for PRBC transfusion in newborns

The principal indication for the PRBC transfusion in newborns is a need to provide adequate oxygenation of their tissues and treatment of a clinically symptomatic anemia, when causal treatment is impossible to perform (such as supplementation of iron, vitamin B_{12}, folic acid or erythropoietin) or in the case of acute bleeding when there is no time for that. Neonatal anemia is defined as a 2SD decrease in hemoglobin and hematocrit values in relation to age norms. Detailed indications for neonatal blood transfusions are provided in Table 1.

Differential diagnosis of anemia should be based on a thorough history, including family and obstetric history (e.g. congenital anomalies, intrauterine infection) and initial evaluation should include red blood cells parameters in morphology, including reticulocyte count and direct antiglobulin test (DAT).

The decision on blood transfusion should be based on the assessment of the severity and duration of anemia, taking into account the child's biological and gestational age, and the onset of clinical symptoms of anemia, such as tachycardia, shortness of breath, poor weight gain or reduced activity. Additional factors should also be considered, which include the presence of respiratory diseases, breathing disorders, respiratory distress syndrome, which reduce anemia tolerance [5].

Tab. 1. Recommendations for packed red blood cells transfusions in premature babies, newborns and infants up to 4 months of age [5]

Age (in days)	**Mid HCT (%)**	**HCT threshold value and / or risk factors**
1	56	<40%
<15	50	<35%
15-28	45	<30%
> 28	40	<25%
		• use of mechanical ventilation, *Fi*O2> 0.4 • life-threatening symptoms due to anemia or hypovolemia • planned surgery

The main causes of neonatal anemia, which are also the main indications for PRBC transfusion, are different medical situations involving blood loss.

Most indications are primarily associated with perinatal blood loss and taking blood samples for testing, while in subsequent developmental periods cases like injuries, acute and chronic bleeding in the course of gastrointestinal and urinary tract diseases or blood loss related to coagulation disorders are dominant. It should be remembered that the clinical manifestations of anemia due to blood loss result directly from the quantity of blood lost, the loss rate and the degree of hypovolemia. In addition, as soon as bleeding occurs, hemoglobin and hematocrit levels may still be correct due to the launch of the body's defense mechanisms in the form of arterioles contraction. These parameters generally change a few or several hours after bleeding occurs, and the reticulates index increases after 2-3 days. In anemia due to blood

loss, the size of red blood cells is normal and the decrease in serum iron concentration is not rapid.

Hemolysis (e.g. alloimmunological hemolytic anemia or hemolytic disease of the newborn) is another clinical situation that could be an indication for transfusion of blood components. In these patients dominates weakness and jaundice and clinical laboratory findings show elevated bilirubin level with a predominance of unconjugated bilirubin fraction, increased reticulocytes index, serum iron concentration and urobilinogen levels in the urine. Hemolytic anemia can be congenital and acquired. The acquired cases are found much more often.

The necessity of PRBC transfusion often occurs in cases of reduced erythrocyte production. The most common bone marrow disorders associated with deficiency of factors necessary for normal erythropoiesis (deficiency anemia, e.g. iron, vitamins, trace elements deficiency) are rarely indications for treatment with blood preparations, due to readily available causal adjuvant therapy.

A less common, but more often requiring transfusions, are cases with hypo- and aplastic anemia, which may be congenital (e.g. Diamond-Blackfan anemia) or acquired (e.g. conditioned by physical and chemical factors, caused by infectious agents, including Parvovirus B19 or CMV, conditions associated with hypersplenism or red blood cell production failure, which may occur due to erythropoietin output disorders or bone marrow insufficiency). Congenital anemia is revealed at different times after child's birth and acquired one - usually in children over 6 years of age. They are relatively rarely observed in children under 3 years of age. Also in these forms of anemia, the properly gained history is of decisive importance in diagnosing the disease and should include information on treatment with cytostatics, antibiotics, anti-epileptic drugs, as well as contact with toxins (benzene, toluene), ionizing radiation or recent infections (hepatitis A, B, C, HIV, EBV, rubella, mumps, measles, flu). Often in these cases, the correct diagnosis is made only on the basis of a bone marrow examination. In addition, the number of reticulocytes, neutrophiles and platelets should be assessed [4].

Types of preparations and PRBC transfusion methods

For newborns, it is recommended to supply blood products that come only from donors who have been donors at least once in the last two years and there have not been found any microbial markers in their blood. Preparations older than 5 days cannot be used in transfusion in order to reduce the risk of hyperkalemia. The most commonly used PRBC types in the treatment of newborns are: leukocyte poor PRBC, containing $<1x1x10^6$ white blood cells in 1

ml, the use of which reduces the risk of alloimmunisation with HLA antigens and cytomegalovirus infection; irradiated PRBC - irradiation takes place not earlier than 24 hours prior to transfusion and such formulation is especially recommended for newborns with low birth weight and in exchange transfusions; washed RBC - removal of plasma components, especially proteins, reduces the number of antibodies in the preparation and prevent hyperkalemia. The PRBC solution is transfused at a dose of 10-15 ml / kg at a rate of 5 ml / kg / hr., maximum of 4 hours. Larger blood volumes may be necessary in the case of hemorrhagic shock, major surgery and cardiopulmonary bypass [5].

It is estimated that the supply of one unit of PRBC or a transfusion of 3 ml red blood cells per 1 kg of body weight, increases Hb concentration by 1g / dl, HTC by 3-4%, and the expected survival of red blood cells after transfusion is ~ 60 days - shorter in case of acute bleeding, hypersplenism and in the presence of allo- / autoimmune antibodies. The volume of transfused red blood cells in children can be calculated according to the following formula:

$$\text{Transfused volume (ml)} = \frac{\text{expected HTC} - \text{current HTC}}{\text{HTC of PRBC (55-65\%)}} \times \text{current circulating blood volume}$$

- circulating blood volume in neonates: approx. 90 ml / kg body weight
- the volume of blood in older children: approx. 80 ml / kg body weight

Before each transfusion, a crossmatching of the transfused blood with the blood of the mother and child should be performed - this test remains valid for 48 hours. In newborns with Rh incompatibility, the use of PRBC with Rh negative factor is required. In newborns with AB0 incompatibility there is a need to use a PRBC formula including components of group AB0 and Rh factor compatible with the child's blood. PRBC should be mixed with suitable plasma (e.g. PRBC received from group 0 donor with plasma received from group AB donor) [6].

PRBC transfusions in premature neonates

In addition to rapid blood loss situation, the assessment of the need of PRBC transfusion requires careful consideration of each case. Infant anemia is widespread. All children in the first quarter of life experience a decrease in Hb concentration during physiological adaptation to the relatively oxygen-rich external environment. In full-term newborns a decrease in Hb concentration occurs around 2-3 months of age. In premature newborns this decrease is faster and more rapid due to additional physiological and iatrogenic factors, making them a group more often requiring treatment with blood components. Premature babies have a relatively reduced erythropoietin response to anemia and its lower plasma concentration. Higher levels

of fetal hemoglobin (HbF) and reduced levels of 2-3 bisphosphoglycerate (2, 3 DPG) increase the affinity of Hb for oxygen. In addition, these babies are found to have a lower rate of erythrocytes precursor cells in the bone marrow, compared to full-term newborns. Other physiological parameters, such as increased growth rate and shorter red blood cell survival, along with external factors such as frequent sampling from lower total circulating blood volume, concomitant disease processes (e.g. sepsis), and inadequate nutrition, also significantly contribute to development and deepening anemia in this particular group of patients. Therefore, preterm infants are mainly transfused preparations with complementary HTC value of 60-80% in order to obtain Ht> 40%. Indications for the administration of PRBC depend on the need for mechanical ventilation or by CPAP method, the concentration of oxygen in the breathing mixture, efficiency of child's breathing and on the day of the child's life (Table 3) [1].

Table 3. Indications for PRBC transfusion in preterm infants [1]

premature infants mechanically ventilated			
	***Fi*O2**	**Hb**	**HTC**
<28 days of age	≥0.3	≤12g / dl	<40%
	<0.3	≤11g / dl	<35%
>28 days of age	-	≤10g / dl	<30%
ventilated preterm infants by CPAP method			
<28 days of age	-	<10 g / dl	<30%
>28 days of age	-	<8 g / dl	<25%
spontaneously breathing preterm infants			
<28 days of age	> 21%	<8 g / dl	<25%
>28 days of age	=21%	<7g / dl	<20%

Exchange transfusion (ET)

Indications for exchange transfusion are: severe and moderate hemolytic disease of the newborn as a result of immunization by Rh factor; severe hyperbilirubinemia without severe anemia - elevated hyperbilirubinemia with total serum bilirubin level (TSB) so toxic that it threatens to damage nervous system; gradually increasing hyperbilirubinemia when TSB due to hemolysis increases by> 0.5 mg / dL / hr, in spite of intensive phototherapy; clinically apparent neonatal polycythemia (HTC> 65% and Hb> 22g / dl). Recommendations for exchange transfusion can also be used for transfusions in infants with anemia of various origins (e.g. hemorrhage, sepsis, body weight <1200g, in case of cardiac surgery) [5].

The purpose of exchange transfusions is to reduce hyperbilirubinemia, remove erythrocytes coated with antibodies, that are a potential source of bilirubin, correct possible anemia and to remove maternal antibodies. Detailed indications for performing an exchange transfusion are the following:

a) TSB is ≥5 mg / dl (85 mmol / l) above a threshold value for ET;
b) TSB is greater than a threshold value TW after 4 h intensive phototherapy;
c) TSB still increases for> 1 mg / dL / h despite intensive phototherapy;
d) clinical symptoms of acute bilirubin encephalopathy are present.

For ET used in the treatment of hyperbilirubinemia, PRBC should be mixed with freshly frozen plasma (FFP) in a ratio of 3: 1, with a hematocrit value of 50-60% and a blood volume equal to two times the blood volume of the newborn. When calculating the volume of blood to ET, it should be remembered that in premature babies the blood volume can be up to 95 ml / kg. In the case of severe anemia (Hb 6-7 g / dl, HTC 15-20%) associated with the risk of heart failure in newborns, partial ET should be performed. In this case, PRBC (HTC 75-80%) should be udes and 100 ml of blood should be exchanged.

Management of polycythaemia depends both on the appearance of hyperviscosity symptoms and the HTC value; when HTC is 65-70% and there are no symptoms, it is recommended to irrigate the newborn and check complete blood count (CBC) every 6-8 hours; whereas at HTC> 70% and without symptoms and at HTC> 65% and clinical manifestation of polycythaemia, partial exchange transfusion is indicated to reduce HTC and blood viscosity [1].

Adverse effects of ET, like any PRBC transfusion, include, among others, cardiovascular disorders (e.g. thrombosis or air embolism), hematological (haemolysis with rebound increased bilirubin level, coagulation disorders due to thrombocytopenia or decreased concentration of coagulation factors), adverse gastrointestinal reactions (necrotizing

enterocolitis), biochemical (hypoglycemia, hypocalcemia, hyperkalemia and hypomagnesemia), infections, hypothermia and death [6].

Transfusion complications

Numerous epidemiological studies have shown that children, especially newborns and infants, constitute a disproportionately large percentage among patients with transfusion-related complications, compared to adults. Adverse events occur relatively frequently in this group of patients as a result of faulty transfusion, including transfusion of an improper blood component.

Possible side effects after transfusion of PRBC preparations in newborns, although rare, are:

- graft versus host disease (GVHD)
- transfusion-related acute lung injury (TRALI)
- circulatory overload (TACO) - PRBC transfusions can cause a hemodynamic load that impairs heart function, as the routine volumes of transfused blood per kilogram of body weight used in adults may be relatively higher in newborns; therefore, echocardiographic abnormalities in newborns may persist longer after transfusion;
- necrotizing enterocolitis (NEC) - clinical trials have shown that some patients developed NEC within 48 hours after blood transfusion;
- intravenous and periventricular bleeding (IVH-PVH) - most often it concerns transfusions in premature babies (30% of cases), and in full-term newborns to the first 48 hours of their life.

Transfusion-related infections (e.g. bacteremia or infection with blood-borne viruses such as CMV, HIV, HCV and HBV) are becoming less common, due to the rigorous selection of blood donors and high standards for the collection, processing and testing of blood components. Other possible transfusion complications are fever, metabolic disorders (decrease in blood pH), hyperkalemia, glucose level fluctuations (hyperglycemia followed by hypoglycemia), hypocalcemia, hypomagnesemia, and immune responses.

It should be noted that there is probably an underestimated and / or reduced reporting of post-transfusion adverse events in newborns, which is caused by pre-existing severe neonatal disease and thus possible diagnostic difficulties in diagnosing complications after treatment with blood components in this group of patients [3].

Summary

In spite of numerous indications for PRBC transfusions, established during clinical observation, still in many cases blood products are often used as the only treatment available. Therefore, clinically controlled, randomized study on the use of these preparations in newborns should be conducted in order to develop standards for their administration, by taking into account the type and maturity of the fetal pathology. Such actions could contribute to reducing the usage of this product in unjustified situations, avoiding unnecessary risk and thus reduce the percentage of transfusion complications, which are particularly common in this group of patients.

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