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Red blood cell transfusions in preterm infants in 2021: a narrative review

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ABSTRACT

Anemia is frequent in preterm infants. Red blood cell transfusion practices vary between different centers. The objective of this study was to review red blood cell transfusion practices in preterm infants between 2020 and 2021. This was a narrative review that included studies published on PubMed (Medline) and Web of Science between October 2020 and October 2021. Ten studies were included finally. Red blood cell transfusion frequency was variable. Some neonatal units did not report transfusion protocols. Most studies reported volumes of 10-15 ml/kg per transfusion. The implementation of an anemia care bundle and adoption of restrictive transfusion resulted in a reduction in the number of transfusions, the volume transfused, and a reduction in the rate of multiple transfusions. We suggest that neonatal units that care for preterm infants should have a transfusion protocol based on the best evidence available and this issue may improve.

Keywords: anemia; infant, premature; neonate; blood transfusion; erythrocyte transfusion; review.

INTRODUCTION

Each year, 15 million preterm infants are born prematurely, defined as born before 37 completed gestational weeks. Despite advances in the reduction of child mortality worldwide, prematurity is the leading cause of death in children under the age of five years. Also, preterm birth complications are associated with disabilities and elevated health costs[1].

Anemia in the preterm infant is frequent, and multifactorial, and is named anemia of prematurity. It occurs secondary to the immature erythropoietin system, elevated volumes of blood withdrawn for laboratory analysis, scarce iron resources, accelerated postnatal growth, and, secondary to the various complications that preterm babies can experience[2].

After birth, there is a reduction in hemoglobin and reticulocytes that reaches its nadir near the second month of life. This reduction is more intense in preterm babies. Also, postnatal red blood cell transfusions with adult hemoglobin result in a lower proportion of fetal hemoglobin and thus, facilitate tissue oxygen transport. Consequently, erythropoietin levels remain low and stimulus to red cell production is worsened[3].

Blood transfusions may be associated with complications. Excessive blood transfusions may lead to body iron overload. Furthermore, it seems that red cell transfusions and retinopathy of prematurity (ROP) are associated, and it has been suggested that

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proinflammatory cytokines released after transfusion and oxidative stress may play a role in this mechanism[4,5]. Recently, a case report of TRALI (Transfusion Related Acute Lung Injury) following red cell transfusion in a preterm infant, was published. The preterm infant presented hypoxemia, hemodynamic alterations, and fever. The authors called attention to the need to periodically revise clinical transfusion protocols[6]. Transfusion-associated Associated Necrotizing Enterocolitis (TANEC) has also been described and corresponds to necrotizing enterocolitis that appears within 48 hours of transfusion[7].

The more immature the preterm is, the more red blood cell transfusions he receives, especially due to physiological characteristics, blood sampling, and a lack of a consensus protocol for blood transfusion in the preterm. Comparisons between higher and lower hemoglobin transfusion thresholds have been conflicting. In 2020, a study that investigated 1,824 preterm infants with birthweight below 1,000g concluded that there was no difference in mortality according to different thresholds and highlighted the possibility of a safe reduction in transfusion rates[8]. The absence of a consensus about the ideal hemoglobin threshold to transfuse red blood cells to the preterm infant contributes to different transfusion practices[9].

Therefore, the objective of this study was to review red blood cell transfusion practices in preterm infants between 2020 and 2021.

METHODS

A narrative review of the literature published in PubMed (Medline) and Web of Science between 2020 and 2021, using the terms "blood transfusion" AND ("neonate" OR "preterm infant") on October 15, 2021. The first Search yielded 51 results (30 from Medline and 21 from Web of Science). Titles and abstracts were scrutinized, and the studies were fully read independently by the two authors. Those who reported transfusion practices in preterm infants were included. We extracted information about the frequency of transfusion, volume transfused (ml/kg), and transfusion protocols. The data selection and extraction were conducted independently by the two authors, using an Excel form. There were no disagreements between the authors.

The research question of this review was "How were the contemporary practices of red blood cell transfusions in preterm infants between 2020 and 2021? Outcome measures of interest were transfusion rates, volume per transfusion, transfusion protocols, and number of transfusions per preterm infant. The search was made according to the acronym PICO, P-preterm infants, I-red cell transfusions, and C-other interventions.

Inclusion criteria were all clinical research published between October 15, 2020, and October 15, 2021. The exclusion criteria were duplicates, review articles, commentaries, experimental studies, or studies without any report of transfusion practices. The main results of the studies are described and discussed. Results are presented in three thematic sections: transfusion rates, transfusion protocols, and volume and number of transfusions per preterm infant. As this is a narrative review and is not related to either human or animal use, this study was not submitted to the Research Ethics Committee for approval.

RESULTS

Figure 1 illustrates the search results done on October 15, 2021. Fifty-one articles were recovered in the database and from those, ten studies were included finally.

The studies included neonatal intensive care units from levels 3 to 4, and some did not inform the level of complexity. Varying transfusion rates and number of transfusions per preterm infant were reported. Three studies reported 10-15 ml/kg per transfusion, one reported 10-20 ml/kg and one reported 20 ml/kg. Four studies reported that they followed transfusion protocols. The main results related to frequency and practices of red blood cell transfusions were summarized (Table 1).

Among preterm infants, red blood cell transfusion frequency was variable. The more immature the infant and the lower the birthweight, the higher the frequency of transfusion. Also, cumulative blood sampling volume and initial hematocrit were predictors of red blood cell transfusion. Some neonatal units did not report transfusion protocols. Most studies reported volumes of 10-15 ml/kg per transfusion. The use of pediatric bags was suggested, as they reduced red blood cell waste and exposure to multiple donors.

Considering transfusion practices in the past, and according to the practices described in the studies included in this review, there seems to be an increasing effort to reduce the number of transfusions and reduce exposure to multiple donors. Neonatal transfusion practices are still variable.

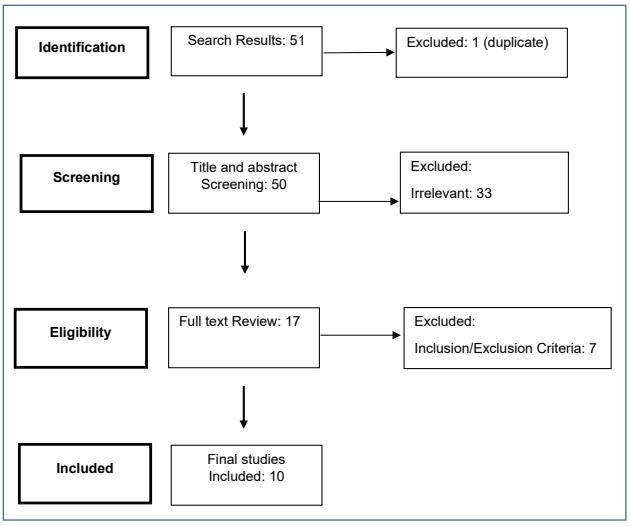

Figure 1: The PRISMA flowchart of study identification and study selection process.

Table 1: Summary of findings of included studies.

Author/year/ country	Design, participants, and unit characterization	Transfusion rates	Transfusion protocols and blood processing	Volume and number of transfusions per preterm infant	Other results
Fontana et al. 2020[10] Italy	Retrospective cohort 644 preterm infants ≤ 32 weeks and birthweight <1,500g; 360 completed longitudinal follow-up to 5 years of age. Mean CRIB II score for transfused: 10.1. Mean CRIB II score for non-transfused: 5.4. Neonatal Intensive Care Unit of Granda Ospedale Maggiore Policlinico of Milan (level 3 unit)	Overall: 54.3% A frequency of 92.7% in the neonatal period in infants that completed the longitudinal follow-up	10-15 ml/kg for four hours without feeding interruption.	The median of two transfusions (range 1-9)	The median age in the first study was 9 days
D'Amato et al. 2021[11] Italy	Retrospective cohort study of 181 infants ≤ 32 weeks gestational age. Neonatal Intensive Care Unit of Di Venere Hospital	44% received at least one transfusion	≤12 g/dL with cardiorespiratory disorders and/ or major surgery; ≤10.4 g/dL between days 1-7, ≤9.0 g/dL between days 7-14 and ≤7.7 g/dL after 15 days of life, with a stable clinical condition receiving respiratory support; ≤9.0 g/dL between days 1-7, ≤7.7 g/dL between days 7-14 and ≤6.8 g/dL after 15 days of life, with a stable clinical condition receiving no respiratory support. RBC was irradiated, leukoreduced, and aliquoted into a pump-compatible syringe 10-20 ml/kg (3 to 4 hours)	Mean 2.3 ± 1.6 per infant.	After the implementation of a transfusion-reduction strategy, it was observed a reduction of 31%
Rocha et al. 2021[12] Portugal	Retrospective study of 106 preterm infants <1,000g birthweight Neonatal Intensive Care Unit of São João University Hospital (level 3 unit)	90 preterm infants were transfused with packed red cells (84.9%)	15 ml/kg each transfusion of cytomegalovirus-negative donors, over 2-4 hours. Irradiation was performed when immunodeficiency was suspected, organ transplantation was anticipated, or intrauterine transfusions have been given	The number of transfusions per patient varied from 0 to 18.	The age when the first transfusion occuried varied from 10 to 18 days. The total volume transfused varied from 0 to 270 ml/kg
Balasubramanian et al. 2021[13] India	Retrospective before-and-after study 163 neonates <1,000g birthweight before and 182 after the bundle implementation. Median SNAPPE-II before 30 Median SNAPPE-II after 28Neonatal Intensive Care unit of Suria Hospital in Western India (level 3 unit)	24.7% of infants received multiple transfusions after the bundle implementation and 53.3%, before Overall rates: 62% (after) and 78% (before)	Restrictive transfusion thresholds and anemia care bundle with satellite RBC packs of 50 ml each, prepared from a single bag of packed RBC with a shelf life of 30–32 days, were allocated for transfusing each infant. Typical transfusion aliquot 20 ml/kg (administered over 4 hours) of washed and packed red blood cells (homologous or directed donation)	After: 25.7 ml/kg Before: 46.4 ml/kg Number of transfusions per neonate: before was 2.1 and after was 1.1.	The implementation of an anemia care bundle was analyzed: subcutaneous erythropoietin twice each week (600 IU/kg/week) from day 7 through 8 weeks of age and blood sampling stewardship in the first five postnatal weeks. 50% reduction in the rate of multiple RBC transfusions (adjusted RR 0.45, 95% CI: 0.34–0.59)
Alboalqez et al. 2021[14] Germany	Retrospective cohort 132 preterm infants <1,500g birthweight. Neonatal Intensive Care Unit of University Hamburg-Eppendorf Medical Center (level 3 unit)	At least one packed red blood cell transfusion: 31.8%	Transfusion triggers were restrictive; they followed the restrictive arm of the ETTNO trial study	20 ml/kg	Cumulative blood sampling volume was higher in transfused neonates (12.7 vs 39.4 ml/kg). Cumulative blood sampling volume and initial hematocrit were predictors of red cell transfusion. The cumulative blood transfused volume was 33.5 ml on average

Continue...

Table 1: Continuation.

Author/year/ country	Design, participants, and unit characterization	Transfusion rates	Transfusion protocols and blood processing	Volume and number of transfusions per preterm infant	Other results
Patel et al. 2021[15] United States	Retrospective cohort study 60,243 infants; 10.5% preterm infants and 1.6% birthweight < 1,500g included all neonatal transfusions (red blood cells, plasma, and platelets). Seven academic Neonatal Intensive Care units in the United States (level 3 and level 4), included infants with congenital heart disease submitted to extracorporeal membrane oxygenation	Any transfusion of red cells was: <27 weeks: 70% 27-28 weeks: 44% 29-32 weeks: 13% 33-36 weeks: 3.1%	A wide variability in pretransfusion hemoglobin levels was observed	4.7 transfusions per patient	The red cell was the most common component transfused.
Vu et al. 2021[16] United States	Randomized clinical trial: Preterm Erythropoietin Neuroprotection (PENUT) Trial 628 preterm infants (24-27 $^{6/7}$ weeks). Nineteen Neonatal Intensive Care units in the United States	Overall: 81.5% Control group: 91%. Erythropoietin group: 72%	No consensus recommendations for transfusions. For critically ill infants requiring mechanical ventilation, hematocrit triggers for transfusion ranged from 28 to 45%. For stable infants, hematocrit triggers ranged from 21 to 25%.	In the control group, mean transfusion was 5.4- and 83.7-ml cumulative volume. The erythropoietin group received a mean of 3.2 transfusions and 46.6 ml cumulative volume.	
Sahin et al. 2020[18] Turkey	Randomized controlled study, one group withholder feeding during transfusion. Median CRIB score: 4 for both groups. Neonatal Intensive Care Unit of Zekai Tahir Burak Maternity Teaching Hospital, in Ankara (level 3 unit)	154 transfusion episodes were analyzed in 112 preterm infants.	Unit transfusion thresholds: Hct 35 %: Mechanically ventilated, seriously ill, or critical congenital heart disease, Hct 25%: Signs of anemia, unexplained lethargy, weight gain <10 g/kg despite adequate calories, heart rate >165/ bpm for >48 hours, unexplained apnea, Hct 20%: even if no signs of anemia are detected. Volume: 15 ml/kg (during a 3-hour infusion)	1.37 transfusions per neonate	There were no observed differences in necrotizing enterocolitis in withholding feedings (8-12 hours) during blood transfusion
Schecter et al. 2021[19] United States	Retrospective medical record review of 456 eligible preterm infants ≤1,500g birthweight. Neonatal Intensive Care unit of the University of Maryland (level 4 unit)		Transfusion is decided by the clinical care provider (not protocol dependent). 10-15 ml/kg (over two to three hours)	Male infants received 1.6-fold more transfusions than females.	If ≤ 28 weeks, it was observed a 4.35-fold higher number of transfusions, compared to those 29-40 weeks
Haghpanah et al. 2021[20] Iran	Cross-sectional study that included 70 transfused neonates; mean gestational age 33.2 weeks. Neonatal Intensive Care Unit of Nemazee Hospital (level 3)		Current practice: adult 250 ml pack of fresh red cells stored within < 7 days, plasma reduced, CMV antibody negative. Pediatric pack set fewer than 7 days old, leucocyte depleted (mean leucocyte count 2 × 106 /unit after filtration), filtered (Sepacell R-500 filter) in conjunction with a Sterile Connecting Device to preserve a 35-day shelf life for dedicating to one neonate.	Mean transfusion number per neonate: 3.5. Mean volume transfused per neonate: 71.4 ml	Total number of transfusions: 250 Mean exposure to donor per neonate: 3.1 The use of a pediatric pack set led to a reduction in red blood cell waste per transfusion and reduced exposure to donors

ETTNO trial: Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants trial; PENUT Trial: Preterm Erythropoietin Neuroprotection trial; SNAPPE-II: Score for Neonatal Acute Physiology Perinatal Extension-II; CRIB II: Clinical Risk Index for Babies II; CRIB: Clinical Risk Index for babies.

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DISCUSSION

Transfusion rates

Fontana et al. studied preterm infants ≤ 32 weeks in a retrospective cohort study. The neonates received late administration of recombinant erythropoietin (250 UI/kg, three times a week, for one month) and iron supplementation of 2 mg/kg/day. Three hundred and sixty infants completed the follow-up, the authors reported an overall transfusion rate of 54.3%, and most of them occurred during the neonatal period[10]. D'Amato et al.[11] also studied infants ≤ 32 weeks. They observed an overall transfusion rate of 44% and a reduction of transfusion rate after the implementation of a transfusion-reduction strategy, which is promising. Rocha et al.[12] included infants with birthweight <1,000g and observed a transfusion frequency of 84.9%, revealing that this frequency can be extremely high. In infants <1,000g birthweight, submitted to restrictive transfusion thresholds, the addition of an anemia care bundle that included administration of subcutaneous erythropoietin and blood sampling stewardship, resulted in an overall transfusion rate of 62% and a reduction of multiple transfusions from 53.3% to 24.7%[13]. Considering that anemia in the preterm infant is multifactorial, a bundle approach is appropriate. The lower transfusion rates were observed by Alboalqez et al.[14], in Germany, using a restrictive transfusion protocol. They observed a 31.8% transfusion frequency in exceptionally low birthweight neonates and, they found that cumulative blood sampling and initial hematocrit were predictors of red cell transfusion.

Patel et al.[15] reported a transfusional rate that was inversely proportional to gestational age, being 70% for those < 27 weeks, 44% for those between 27-28 weeks, 13% for those between 29-33 weeks, and 3.1% for those between 33-36 weeks. Even in preterm infants <28 weeks gestational age, who presented an overall transfusion rate of 81.5%, it was possible to reduce 19% of this rate, with the administration of erythropoietin[16]. These results suggest that, although rates were variable, with different cut-offs for gestational age and birth weight, when a transfusion-reduction strategy was applied, even to the more immature infants, a reduction in transfusion rate was observed and we suggest that this should be encouraged. Also, we suggest that cumulative blood losses should be reduced, and initial hematocrit could be increased as they were predictors of red blood cell transfusion.

Transfusion Protocols

Balasubramanian et al.[13], applied restrictive transfusion thresholds and an anemia care bundle, resulting in a reduction of transfusions. In the study of Alboaquez et al.[14], the authors reported restrictive triggers for transfusions, by the Effects of Transfusion Thresholds on Neurocognitive Outcomes of Extremely Low-Birth-Weight Infants (ETTNO) trial. The ETTNO trial, published before the period of this review, included 1,013 infants from 36 centers in Europe, and recommended in the restrictive arm, transfusion thresholds according to clinical condition (critical or non-critical), postnatal age and hemoglobin levels (range from 4.3 mmol/L to 7.0 mmol/L). The authors observed no differences in death or disability at 24 months of corrected age, suggesting that the restrictive protocol was safe[17]. Sahin et al.[18], reported their transfusion thresholds according to hematocrit and clinical parameters. Schecter et al.[19], in the United States, reported that transfusions were decided by the clinical care provider and were not guided by a protocol. Patel et al., in the United States, included seven hospitals that participated in the REDS-III study.

Their study aimed to evaluate transfusion practices. They observed a wide variability in pretransfusion hemoglobin levels and concluded that practices varied too much and needed to be supported by the best available evidence[15]. Vu et al.[16], reported no consensus recommendations for transfusions. According to volume for each transfusion, most of the studies reported volumes varying from 10 to 15 ml/kg per blood transfusion for 2 to 4 hours[10,18,19]. Balasubramanian et al., reported a 20 ml/kg volume per transfusion[13].

Three studies reported that there was no protocol for transfusion decisions. In one study, transfusion was decided by the clinical care provider, another study revealed this varied too much and another revealed there was not a consensus[15,16,19]. We suggest that all neonatal units that care for preterm infants should have a transfusion protocol based on the best evidence available.

Four studies detailed the processing of blood transfused. D'Amato et al.[11] described the use of irradiated, leuco-reduced red blood cells. Rocha et al.[12] reported the use of cytomegalovirus-negative donors and irradiation when immunodeficiency was suspected. Balasubramanian et al.[13] described the typical transfusion as a washed and packed red blood cell. Haghpanah et al.[20] described current practices as plasma-reduced and cytomegalovirus (CMV) antibody-negative. These authors introduced a new practice with a leucocyte-depleted and filtered pack set. These studies reported strategies to reduce cytomegalovirus risk of transmission, which is an issue of concern in preterm infants, as their immune system is immature, and this infection could be serious. Literature has shown that the use of a prestorage leuco-reduced and CMV-seronegative donor blood reduces but does not eliminate CMV transmission[21].

We searched in all included studies for information about differences in indication and volume for those infants with congenital cardiopathy. Patel et al. included level 3 and level 4 neonatal intensive care units. They reinforced that 100% of infants who needed surgery with cardiopulmonary bypass were transfused, as expected, and so were those submitted to therapeutic extracorporeal membrane oxygenation[15]. Sahin et al.[18] reported as an indication for red blood cell transfusion a higher hematocrit level cutoff (35%) for those with critical congenital heart disease.

Volume and number of transfusions per preterm infant

A mean transfusion number per preterm infant of 3.5 was observed by Haghpanah et al.[20], in preterm infants with a median gestational age of 33.2 weeks. Fontana et al.[10] observed a median of two transfusions in infants ≤32 weeks and Sahin et al.[18] observed in ≤32 weeks infants 1.37 transfusions per preterm infant. D'Amato et al.[11] also studied infants ≤ 32 weeks and observed a mean of 2.3 transfusions per infant. Patel et al. observed a frequency of 4.7 transfusions per infant and the authors highlighted that there was an opportunity to improve patient blood management[15]. Rocha et al.[12] observed in infants <1,000g birthweight a volume transfused that varied from 0 to 270 ml/kg and several transfusions per infant up to 18. It must be emphasized that these preterm infants were frequently transfused with a total amount of blood superior to their volume. Infants ≤ 32 weeks received several transfusions that varied from 1.37 to 4.7 and this can be explained by different protocols or even the lack of protocols. This range suggests that there is an opportunity to reduce the number of transfusions in these preterm infants.

The implementation of an anemia care bundle and adoption of restrictive transfusion thresholds for infants <1,000g birthweight resulted in a reduction of number of transfusions (2.1 to 1.1), the volume transfused (46.4 ml to 25.7 ml) and a 50% reduction in the rate of multiple transfusions[13]. In the PENUT trial, which included infants <28 weeks gestational age, differences in mean transfusion and cumulative volume transfused between the control and erythropoietin groups were observed[16]. Again, the adoption of strategies even isolated or in bundles, resulted in a reduction of volume and number of transfusions and this should be encouraged.

Considering that these infants are exposed to multiple transfusions, the use of satellite bags for transfusion in the neonatal period has been suggested as a good practice that reduces the neonate exposure to multiple donors and reduces blood waste, as the volume transfused is sometimes too small[22]. Haghpanah et al.[20], compared the use of adult bags and pediatric bags. The authors showed that by using pediatric bags, the blood waste was reduced by 24% per transfusion. This result reinforces that it is possible to reduce exposure to multiple donors and reduce blood waste, by using pediatric bags.

The results of this narrative review should be interpreted considering some limitations. This review searched the databases for the period between 2020 and 2021, as we had the objective to describe contemporary practices reported in clinical studies that investigated red blood cell transfusion in preterm infants. The results observed may not reflect worldwide transfusion practices in these preterm infants. Although these results cannot be generalized to all preterm infants, they are helpful in the understanding of how these babies have been transfused.

Conclusion

In conclusion, there was a great variability in transfusion rates, and there is still an opportunity to reduce the number of transfusions in these infants. Cumulative blood losses and initial hematocrit were predictors of red blood cell transfusion. Most studies reported volumes varying from 10 to 15 ml/kg per blood transfusion during 2 to 4 hours. Some neonatal units did not report transfusion protocols. The use of pediatric bags may reduce exposure to multiple donors and blood waste. The implementation of an anemia care bundle and adoption of restrictive transfusion resulted in a reduction in the number of transfusions, the volume transfused, and a reduction in the rate of multiple transfusions. We suggest that neonatal units that care for preterm infants should have a transfusion protocol based on the best evidence available and this issue may improve.

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