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INTEGRATIVE REVIEW OF THE LITERATURE

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RED BLOOD CELL TRANSFUSIONS IN NEWBORN INFANTS THROUGH PERIPHERALLY INSERTED CENTRAL CATHETER: AN INTEGRATIVE REVIEW

*Transfusão de hemácias em neonatos pelo cateter central de inserção periférica: revisão integrativa**Transfusión de glóbulos rojos en neonatos a través de catéter central de inserción periférica: revisión integradora*

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ABSTRACT

Objective: this study aimed to identify in literature the implications related to red blood cell (RBC) transfusions, through Peripherally Inserted Central Catheter, in neonates. **Methods:** this is an integrative review conducted in the Web of Science, Scopus, Virtual Health Library, and PubMed databases. Publications in English, Spanish and Portuguese, available in full, without date limit, were included. **Results:** four (100.0%) studies that addressed hemolysis of RBCs were selected, of which two (50.0%) also addressed catheter obstruction during transfusion. Studies revealed the occurrence of hemolysis related to infusion rate and storage time of RBCs, however without clinical relevance. Regarding obstruction, it was verified in only one catheter out of 38 followed-up in a study; in the other, there was no obstruction and transfusions were considered technically feasible. **Conclusion:** there is urgent need for primary clinical studies to assess clinical consequences of red blood cell transfusions through this type of catheter in neonates.

DESCRIPTORS: Newborn; Red blood cell transfusion; Central venous catheterization; Neonatal nursing.

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RESUMO

Objetivo: identificar na literatura as implicações relacionadas à transfusão de hemácias, por meio do Cateter Central de Inserção Periférica, em neonatos. **Métodos:** revisão integrativa realizada nas bases de dados Web of Science, Scopus, Biblioteca Virtual em Saúde e PUBMED. Incluíram-se publicações em inglês, espanhol e português, disponíveis na íntegra, sem data limite. **Resultados:** selecionaram-se quatro (100,0%) pesquisas que abordaram hemólise das hemácias e dois deles (50,0%), também, versaram sobre obstrução do cateter durante a transfusão. Os estudos evidenciaram ocorrência de hemólise relacionada à velocidade de infusão e ao tempo de armazenamento das hemácias, porém sem relevância clínica. Referente à obstrução, observou-se ocorrência em apenas um cateter de 38 acompanhados em um estudo; no outro, não houve obstrução, sendo as transfusões consideradas tecnicamente viáveis. **Conclusão:** urgem estudos clínicos primários que avaliem as consequências clínicas das transfusões de hemácias por esse tipo de cateter, em neonatos.

DESCRITORES: Recém-nascido; Transfusão de eritrócitos; Cateterismo venoso central; Enfermagem neonatal.

RESUMEN

Objetivo: identificar en la literatura las implicaciones relacionadas con la transfusión de glóbulos rojos, por Catéter Central de Inserción Periférica, en neonatos. **Métodos:** revisión integrativa, en las bases de datos Web of Science, Scopus, Biblioteca Virtual en Salud y PUBMED. Se incluyeron publicaciones en inglés, español y portugués, disponibles en totalidad, sin fecha límite. **Resultados:** seleccionaron cuatro (100,0%) estudios que abordaban la hemólisis de glóbulos rojos y dos de ellos (50,0%) la obstrucción del catéter durante la transfusión. Los estudios señalaron ocurrencia de hemólisis relacionada con velocidad de infusión y tiempo de almacenamiento de los glóbulos rojos, pero sin relevancia clínica. Sobre la obstrucción, se observó en catéter de 38 seguidos en un estudio; en otro, no hubo obstrucción, y las transfusiones se consideraron técnicamente factibles. **Conclusión:** se necesitan estudios clínicos primarios para evaluar las consecuencias clínicas de las transfusiones de glóbulos rojos a través de este tipo de catéter en los recién nacidos.

DESCRIPTORES: Recién nacido; Transfusión de eritrocitos; Cateterismo venoso central; Enfermería neonatal.

INTRODUCTION

Obstetric and neonatal care presents an important evolution due to the great advances in technology and scientific knowledge. This has allowed the survival and development of extreme premature newborns, previously considered unviable, in Neonatal Intensive Care Units (NICU).¹⁻²

During complex care at the NICU, different complications can affect the newborn. Among these, hematological alterations are common, with anemia of prematurity being the most frequent.³

The anemia of prematurity has several factors implicated in its development, one of them is the spoliation to perform laboratory tests. It is characterized by ineffective hematopoiesis, which results in inadequate delivery of oxygen to the tissues, leading to sucking difficulty, unsatisfactory weight gain, difficulty in tolerating stress associated with the increased need for oxygen, and poor growth. These situations cause hospitalized newborns to undergo constant transfusions of packed red blood cells, which is the only treatment for most cases of neonatal anemia.³⁻⁵

Researchers have shown that packed red blood cell transfusions are one of the most common procedures performed in NICUs, especially in very premature (< 32 weeks gestation) and extremely low birth weight (<1000g) infants; about 40% and 90% of these newborns, respectively, receive at least one packed red blood cell transfusion during hospitalization.²⁻⁴

As these patients usually remain hospitalized for long periods, providing safe vascular access to receive, in addition to

successive blood transfusions, total parenteral nutrition (TPN), intravenous hydration and drugs has become a key resource in the care of these patients.⁶

Among the growing technological and therapeutic advances in NICUs, there is the Peripherally Inserted Central Catheter (PICC), a long and flexible vascular device, composed of bio-compatible and hemocompatible material, which is inserted through a peripheral vein that, with the help of an introducer needle, progresses to the cavo atrial junction or proximal third of the inferior vena cava, characterizing a central venous access. To insert and handle it, it is necessary to have a protocol prepared by the health team and legally trained professionals, and the nurse is legally supported by the Federal Council of Nursing, through Resolution 258/2001.⁷⁻⁹

The PICC is widely used in NICU, due to high rates of success in insertion, lower rates of infection related to the catheter and for being less invasive, when compared to other catheters inserted by central venipuncture and for avoiding venous dissection, reducing the number of punctures and causing less stress and pain that are harmful to the newborn's development.^{5,10-11}

Even with the evident advantages of the PICC, there are still limitations in its use, such as in hemotransfusion, due to the potential for slow flow, related to the length of the catheter and the small caliber, which may increase obstruction rates, as well as the shear force in the narrow lumen of the catheter may damage red blood cells, causing hemolysis, which may result in hyperkalemia and hyperbilirubinemia.^{7,12}

Therefore, the importance of nurses' knowledge and expertise on the technologies used in practice is emphasized, adapting them to the characteristics of the patient and the therapy to be administered, ensuring the quality and safety of the care provided to the patient and minimizing the undesirable effects during and/or after this procedure.^{10,13-14}

Thus, we proposed to perform an integrative review, aiming to identify in the literature the implications related to RBC transfusion through the PICC in neonates. This analysis is relevant, considering that both RBCs transfusion and PICC maintenance are essential care to ensure the success of newborns' care in NICUs. Therefore, producing scientific knowledge on the subject can influence the quality of care for neonates, reducing exposure to risks of adverse events, collaborating with the proper management of these risks and the decision-making of nurses.

METHODS

This is an integrative literature review that followed the following steps: development of the guiding question; literature search; data collection and categorization of studies; critical analysis of the included studies; interpretation and discussion of results and presentation of the review/synthesis of knowledge.¹⁵ The development of the research question followed the PICO strategy (acronym for patient, intervention, comparison and outcome). In which P: neonates I: RBC transfusion by PICC; C: not applicable and O: implications that may occur by PICC transfusion. Thus, the guiding question was: what implications are related to RBCs transfusion via PICC in neonates?

The databases used were: Web of Science, Scopus via Portal de periódico CAPES, Biblioteca Virtual em Saúde (BVS) and U.S. National Library of Medicine (PUBMED). The search was conducted between January and March 2022.

The selection of studies involved the combination of Descriptors in Health Sciences – DeCS (newborn, central venous catheterization and red blood cell transfusion), Medical Subject Headings (MeSH) and synonyms (newborn, central venous catheterization, blood component transfusion, red blood cell) and keyword (PICC).

Cross-referencing of the descriptors was performed, using the Boolean operators AND and OR, in each database. VHL: ((Newborn) OR Neonate OR Neonates OR (Newborn (RN)) OR (Infant, Newborn)) AND ((Blood Component Transfusion) OR (Blood Component Transfusion) OR (Erythrocyte Transfusion) OR (RBC Transfusion) OR (Erythrocyte Transfusion)) AND ((Central Venous Catheterization) OR (Catheterization, Central

Venous) OR (Central Venous Catheters) OR (Central Venous Catheters) OR PICC), Web of Science: (((((TS=(Newborn)) AND TS=(blood component transfusion)) OR TS=(erythrocyte transfusion)) OR TS=(red blood cell transfusion)) AND TS=(central venous catheterization)) OR TS=(PICC)) Scopus: (infant, AND newborn) AND (blood AND component AND transfusion) OR (erythrocyte AND transfusion) OR (red AND blood AND cell AND transfusion) AND (catheterization AND central AND venous) OR (central AND venous AND catheters) OR (picc), and PubMed: (((((Infant, Newborn) AND (“red blood cells transfusion”[All Fields])) OR (erythrocyte transfusion)) OR (“blood component transfusion”[All Fields])) AND (Catheterization, Central Venous)) OR (“picc”[All Fields])).

Inclusion criteria were: productions published in English, Spanish, and Portuguese that portrayed RBC transfusion using the neonatal PICC, available in full, and any study design. No publication date was defined. One of the articles was not available in full and was obtained by contacting the authors through their e-mail addresses.

The pre-selection of the studies was carried out by two reviewers, by reading the titles and abstracts independently, with no disagreement between the reviewers about the inclusion of the studies. After this step, the articles repeated in the databases were counted only once, and those that met the criteria were selected for reading in full, which provided the application of the following exclusion criteria: addressing hemotransfusion of other blood components such as plasma, platelets, cryoprecipitate etc., peripheral catheter and PICC larger than 2Fr.

In total, four scientific productions were included in the review. For data extraction, a data collection form was prepared with the items: article identification, methodological aspects, interventions and main results found. The synthesis of the extracted data was presented descriptively in a table with data regarding authorship, year, study objective, sample, and results. Figure 1 shows how the selection of articles in each base occurred.

RESULTS

The four articles selected (100.0%) were written in English. As for the place of study, one was produced in the USA, one in Switzerland, and the other two in Austria. Regarding the year of publication, the oldest dates back to 2004, and the most recent was published in 2021.

Regarding the design of the selected studies, three were laboratory experiments and one was a retrospective cohort study. The articles are shown in Table 1.

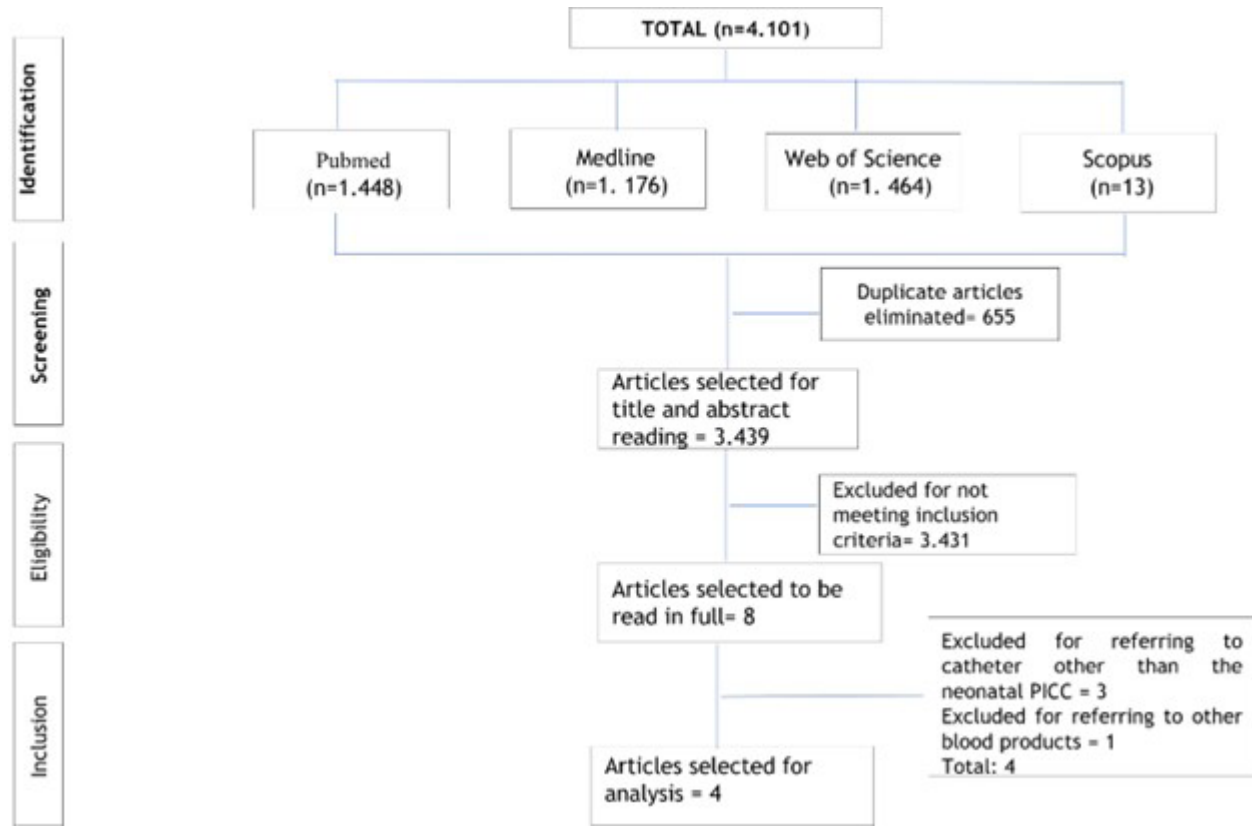


Figure 1 – Flowchart of article selection by database according to PRISMA. Curitiba, PR, Brazil, 2022

Table 1 – Presentation of the synthesis of articles from the integrative review. Curitiba, PR, Brazil, 2022

Authors, Place and Year	Purpose	Study design	Sample and results
Wong EC, et al. USA, 2004 ¹⁶	To determine whether RBC concentrate transfusions through small-caliber central venous catheters used in critically ill neonates result in significant hemolysis.	Experimental study in vitro	RBC aliquots in 60 ml syringes, storage period 5 to 8 days and 29 to 30 days. Infusion rates were 2 and 20 mL/h. Evidence of hemolysis was found at the 20 mL/h rate when comparing fresher and older RBCs. However with unlikely clinically significant hemolysis.
Repa A, et al Austria, 2013 ¹²	Investigating the safety of 27 Gauge PICC for RBC transfusion with gamma irradiation	Controlled experimental study in vitro	Aliquots of 50 ml of packed red blood cells, storage period of 5 to 9 days, irradiated at 30 gray. It was identified a small increase of Free Hb and LDH using PICC of 20 and 30cm only in the lower speed (2.5ml/h), but not significant. RBC transfusion through the PICC does not cause clinically relevant hemolysis.
Repa A, et al. Austria, 2014 ¹⁷	To analyze incidence, safety, and feasibility of RBC transfusions through 27Gauge PICC	Retrospective cohort	38 transfusions in premature infants through the PICC. There was an incidence of 14.5% of transfusions through the PICC and 2.6% of obstruction. The neonates' biomarkers and clinical signs were unchanged. Thus, the RBCs transfusions through the PICC were viable and without hemolysis signs.
Rosa-Mangeret F, et al. Switzerland, 2021 ¹⁸	To evaluate the safety of packed red blood cells transfusion through a 1Fr and 2Fr PICC compared to a 24G short peripheral catheter	Experimental non-inferiority study in vitro	20ml aliquots of packed red blood cells in 50ml syringe, storage period of 14 days or less, irradiated at 25Gray. Hemolysis values at the end of transfusions were not statistically significant between catheter groups. There was no statistical difference in mean hemolysis before and after transfusion. Potassium and LDH had a non-significant variation among the three catheter types. Potassium remained stable and LDH increased in all 3 catheter types. And there was no obstruction of the catheters during the experiments.

Key: Hb: Hemoglobin; HDL: Lactate Dehydrogenase; PICC: Peripherally Inserted Central Catheter.

Of the four articles analyzed, all (100.0%) approached RBC hemolysis and two (50.0%) also talked about PICC obstruction. Thus, these results were listed for analysis and presented below.

As mentioned, the selected studies evaluated the relationship between RBC hemolysis and the administration of concentrated RBCs through the PICC 1.0 Fr and 1.9 Fr. For this, they used volumetric infusion pumps and/or syringe to perform the procedure, but none of the publications focused on the theme of propensity to hemolytic damage related to infusion pumps.

Of the four selected publications, three (75.0%) were experimental and, regarding infusion rates, in one of these studies the authors used a constant rate of 4 mL/h, while in the other two, the rate ranged from 2.0 mL/h to 20 mL/h. While in the retrospective study, the infusion rate was a constant 5mL/h. However, two of these experimental studies differed on the infusion rate that pointed to hemolysis. One showed evidence of hemolysis at a speed of 2.5mL/h in the longer, 30 cm 1 Fr catheter, and the other at a speed of 20mL/h in the 1.9 Fr catheter, but both with insignificant levels of hemolysis.

As for the storage period of the analyzed RBCs, it varied from five to 30 days. One study (25.0%) showed evidence of hemolysis when comparing the use of fresher RBCs (five to eight days) versus older ones (29 to 30 days), inferring that the use of fresher RBCs is preferable in cases of PICC transfusion.

Regarding the preservative solution, two (50.0%) studies used the sodium chloride-adenine-glucose-mannitol (SAG-mannitol) solution and one (25.0%), the citrate-phosphate-dextrose-adenine (CPDA-1) solution; the other study did not point out which preservative solution was used. However, none of the publications addressed the relationship of cell injury to the preservative solution.

In two (50.0%) studies the RBCs used were irradiated with gamma irradiation at 30Gray and one (25.0%) at 25Gray, the other study did not mention the degree of radiation. However, the studies did not point out clinically relevant hemolysis.

In the selected publications, cell integrity was analyzed using outcome variables such as free hemoglobin, LDH, potassium, percent hemolysis grade, and hematocrit. Free hemoglobin and potassium were the biomarkers present in all studies. Regarding the presence of hemolysis, the studies pointed out changes in free hemoglobin and increased potassium only in one study (25.0%), but analyzed as clinically insignificant changes, and all studies recommend further research to confirm the findings.

Regarding PICC obstruction during packed red blood cells infusion, of the four selected studies, two (50.0%) assessed the feasibility of using the neonatal PICC as a RBC transfusion route (one of the experimental studies and the retrospective study). This retrospective study pointed out that from the sample analyzed, four catheters were removed in the period analyzed, but only one for obstruction, and in this case there was coinfusion of NPT during transfusion. In the other study, before the packed red blood cells infusion, the catheters received NPT infusion for one hour, and showed that there was no obstruction in any of the catheter types monitored. Although the studies consider

transfusion through the PICC technically feasible, they recommend prospective studies to ensure the recommendation of this practice.

DISCUSSION

The studies selected in this research identified that, when using the neonatal PICC for RBC transfusion, hemolysis occurs, and that it depends on the infusion rate and RBC storage time; however, the studies differed on the flow rates that cause RBC lysis. However, in all studies, hemolysis was considered clinically insignificant, which reveals the feasibility in the evaluated procedure.^{12,16-18}

The use of the PICC may compromise the transfusion process, affecting the infusion speed, due to its smaller caliber and longer length, which allow higher rates of obstruction, in addition to the shear stress exerted on RBCs that may compromise their integrity, causing hemolysis. Moreover, in premature newborns, gamma irradiation of RBC concentrates causes a decrease in the mechanical strength of RBCs. This may also increase the risk of hemolysis using a narrow catheter.^{12,19}

The possible hemolysis caused by the passage of blood through different devices may cause deleterious effects to the body, as a result of the increase of several substances in the blood plasma, such as hemoglobin, bilirubin, and potassium. In neonates, due to the low blood volume, hyperkalemia represents a particularly significant risk, since it is associated with arrhythmias and cardiac arrest. Furthermore, free hemoglobin in plasma can cause endothelial injury, interfering with platelet aggregation, and renal injury, which presents itself through hemoglobinuria.^{16,20-23}

To identify RBC lysis, one looks for the presence of free hemoglobin in the plasma, increased potassium, LDH, among other biomarkers.²⁴ Thus, hemolysis was evidenced in the publications by the release of these substances after the experiments and transfusions in newborns, in addition to clinical changes in them. The most evaluated biomarkers were free hemoglobin and potassium. In two studies, the authors analyzed the release of biomarkers along with the degree of hemolysis to determine if there was hemolysis of clinical relevance.^{12,18}

The degree of hemolysis is a mandatory analysis for quality control in blood banks. In Brazil, the maximum degree of hemolysis on the last day of storage is 0.8% in red cells stored in CPDA-1 for quality control.²⁴⁻²⁵

An integrative review pointed out that hemolysis occurs during the red blood cell manipulation processes and in the passage of blood through infusion pumps and catheters.²⁶ Differently from the results of this research, it evidenced that hemolysis does not depend on the infusion speed, but corroborated the issue that RBC lysis always occurs as storage time increases. Another integrative review showed that there may be changes in the RBC integrity when transfused by infusion pump, showing that the volumetric pumps with cassette mechanism are the safest for this practice. This review corroborated this by showing divergence in the results when the variable was the infusion speed that would

cause damage to the red blood cells, and that the storage time of the RBCs can influence their fragility.²⁴

Several authors indicate that hemolysis can occur due to different factors, such as the physical properties of the blood bag, such as viscosity and storage time, or due to mechanical trauma in the transfusion process, such as catheter size and width, infusion rate, preservative solutions, irradiation, type of equipment used in intravenous infusion (type of infusion pumps, macrodrop and microdrop administration sets). However, in the studies analyzed in this review, the changes found do not cause adversities that clinically affect the patient.^{12,16–17,22,27}

Thus, the infusion of red blood cells through the neonatal PICC seems to be safe in terms of blood quality; however, one should be aware of the risk of obstruction, due to blood viscosity and the catheter's inherent characteristics that promote a reduction in infusion speed.¹⁹

It is emphasized that the packed red blood cells should not come in contact with solutions of unknown compatibility, since hypotonic or hypertonic solutions can increase the final osmolarity of the solution, and the calcium in the NPT solutions antagonizes the RBC concentrate anticoagulant preservatives, favoring catheter obstruction.^{17,27}

The two studies that assessed PICC obstruction after transfusion considered the procedure feasible and safe^{17–18}, and only the retrospective study identified, in the sample analyzed, a catheter removed due to obstruction. It is assumed that the occurrence of obstruction in this study may be related to the infusion of NPT concomitant to the transfusion of RBCs through the same PICC. However, it is not possible to state precisely, since the study does not bring the other solutions and/or medications used during the period in which the PICC was observed.

Obstruction is among the most common complications associated with catheter maintenance, with rates ranging from 11% to 50% and may be partial, when the flow is maintained and there is no reflux, or total, when both are impaired. It may be caused by different factors, such as mechanical dysfunctions, like poor positioning of the catheter tip or of the patient, thrombus formation, or drug precipitation. It is noteworthy that the reduced diameter of the PICC used in neonates favors the occurrence of obstruction.^{19,28}

This complication may bring many losses to newborns, by causing delay or interruption of drug treatment or NPT, need for multiple punctures, which causes pain and stress, greater manipulation of the catheter, predisposing to infection and, consequently, delays in hospital discharge or additional procedures,

such as catheter replacement, resulting in more distress to the newborn and the team, also raising hospital costs.¹⁹

A cross-sectional study on factors associated with adverse events with PICC, in a NICU of a university hospital in the northeast of Brazil, found that 53.70% of the catheters presented adverse events, obstruction being the most frequent event, with a rate of 31.81%.²⁹ And an integrative review on the use of PICC in neonates highlighted obstruction as the second most common complication.³⁰

In the retrospective study included in this review¹⁷, the strategy used to maintain catheter patency was not mentioned, thus it was not possible to perform a more detailed analysis about which factors facilitated the occurrence of PICC obstruction in that study. In the other study that also assessed obstruction, the researchers used catheter flushing with 1mL of saline solution before and after transfusion.¹⁸ In view of this, it may be inferred that adequate catheter maintenance may reduce and/or avoid this complication, as corroborated by an integrative review which points out that catheter flushing/flushing should be performed periodically and that the use of pulsatile flushing is more effective in the removal of solid deposits than continuous flushing.³⁰

The publications presented in this review are of international origin, which demonstrates the need for the development of research regarding the transfusion of packed red blood cells through the PICC, on a national level.

CONCLUSION

This integrative review identified four publications that analyzed the transfusion of packed red blood cells in neonatal PICC. The implications refer to changes in RBC integrity when transfused through the neonatal PICC, but did not show high clinical risk of this practice. Also, the two publications that evaluated catheter obstruction indicate that RBC transfusion through the PICC is technically feasible. However, it is emphasized the need to develop further research on the subject.

One of the limitations of this study is the small number of publications on the subject, which hindered a more robust assessment. Thus, it is reiterated that the study of the investigated practice in the daily NICU care is fundamental.

The analysis of the use of PICC for RBC transfusion contributes to the advancement of neonatal nursing knowledge and shows that there are still many questions to be clarified when it comes to RBC transfusion through the PICC, both about the clinical consequences for the neonate in relation to RBC lysis, and about complications related to the catheter, such as obstruction.

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