



Risk Assessment of Red Cell Transfusion in Congenital Heart Disease

Christoph Zürn¹  René Höhn¹ David Hübner² Markus Umhau³ Johannes Kroll⁴ Fabian A. Kari⁴
Frank Humburger⁵ Sven Maier⁴ Brigitte Stiller¹

¹ Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Centre Freiburg – Bad Krozingen, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany

² Department of Machine Learning for Medical Applications, Averbis GmbH, Freiburg, Germany

³ Institute for Transfusion Medicine and Gene Therapy, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany

⁴ Department of Cardiovascular Surgery, University Heart Centre Freiburg – Bad Krozingen, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany

Address for correspondence Christoph Zürn, MD, Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Centre Freiburg – Bad Krozingen, Mathildenstr. 1, 79106 Freiburg, Germany (e-mail: christoph.zuern@uniklinik-freiburg.de).

⁵ Department of Anesthesiology and Critical Care, Medical Center – University of Freiburg, Faculty of Medicine, Freiburg, Germany

Thorac Cardiovasc Surg 2022;70:e15–e20.

Abstract

Background The storage time of packed red blood cells (pRBC) is an indicator of change in the product's pH, potassium, and lactate levels. Blood–gas analysis is a readily available bedside tool on every intensive care ward to measure these factors prior to application, thus facilitating a calculated decision on a transfusion's quantity and duration.

Our first goal is to assess the impact of storage time on pH, potassium, and lactate levels in pRBC. The influence of those parameters in the transfused children will then be evaluated.

Methods In this retrospective study, we conducted blood–gas analyses of pRBC units before they were administered over 4 hours to neonates, infants, and children in our pediatric cardiac intensive care ward. All patients underwent regular blood–gas analyses themselves, before and after transfusion.

Results We observed a highly significant correlation between the storage time of pRBC units and a drop in pH, as well as an increase in potassium and lactate of stored red cells ($p < 0.0001$). Median age of recipients with a complete blood–gas dataset was 0.1 (interquartile range [IQR] = 0.0–0.7) years; median pRBC storage duration was 6 (IQR = 5–8) days. Further analyses showed no statistically significant effect on children's blood gases within 4 hours after transfusion, even after stratifying for pRBC storage time ≤ 7 days and > 7 days.

Conclusion Stored red blood cells show a rapid decrease in pH and increase in potassium and lactate. Slow transfusion of these units had no adverse effects on the recipients' pH, potassium, and lactate levels.

Keywords

- ▶ blood transfusion
- ▶ congenital heart disease
- ▶ intensive care
- ▶ neonate
- ▶ pediatric

received
March 10, 2022
accepted after revision
June 21, 2022

DOI <https://doi.org/10.1055/s-0042-1756493>.
ISSN 0171-6425.

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Two critical incidents after rapid transfusion of packed red blood cells (pRBC) due to bleeding, followed by a severe drop in pH and acute increase in pulmonary resistance in the affected children with single ventricle anatomy led to the present study of how pRBC unit administration might cause metabolic irregularities in recipients.

Red blood cell transfusions are important therapeutic tools currently without a viable alternative.¹ Their use ranges from supportive to life-saving, which holds especially true for neonates and young children with acquired and congenital heart disease (CHD) undergoing cardiopulmonary bypass (CPB) surgery² and who are prone to anemia and blood loss.³

Risk-adjusted transfusion in general and in neonates and children with CHD in particular has long been a topic of discussion.⁴ One recurring argument is the storage time of blood cells as an independent risk factor. Packed red cells deteriorate over time, suffering from so-called storage lesion.^{5,6} These ex-vivo processes encompass cellular and molecular alterations to a blood product during blood bank storage. Some changes occur within hours, while others become apparent after days.

Early signs of storage lesion are falling pH and rising potassium and lactate levels,⁷ the latter being a well-accepted marker for poor outcome in neonates and infants undergoing early bypass surgery, being prone to suffer from low cardiac output syndrome (LCOS).^{8,9} The ongoing glycolysis in the red cells produces adenosine 5'-triphosphate, leading to an increase in lactate and protons which in turn lowers the pH in pRBC.¹⁰ Meanwhile, a gradually diminishing cation gradient caused by membrane loss due to erythrocytic vesiculation and dehydration accelerates a rise in extracellular potassium.^{5,6,11}

Structural changes in red cells begin to appear after days, and steadily become irreversible as their surface and shape turn from echinocytes to spherocytes. These alterations reduce the erythrocytes' ability to withstand hydrodynamic and osmotic stress; they start to reveal a fragility and tendency to hemolysis, as in patients with hereditary spherocytosis.^{10,12,13} The in vivo recovery rate of pRBC falls as its storage time lengthens,¹¹ and according to most of the literature, pRBC stored for under 14 days can be considered fresh.^{10,14} As damaged blood cells are promptly cleared from the recipient's circulation, the transfusion of older products is regarded as less beneficial for the patient.¹³

The objective of this study was to carry out point-of-care blood-gas analysis (BGA) on pRBC units to evaluate the effect of storage time on pH, potassium, and lactate levels, precursors to the irreversible cellular alterations in the products' erythrocytes,¹⁵ and investigate any impact on children's BGAs after transfusion.

Material and Methods

Approval for this single-center study was obtained from the Institutional Research Board of the University (local IRB number 20-1220), along with a waiver of written consent. The trial

was registered at <https://www.drks.de> with the identification number DRKS-ID 00023980 on January 8, 2021.

Study Population and Design

From August 2019 to December 2020, baseline in vitro BGAs of pRBC were obtained before their administration to patients on the pediatric cardiac intensive care unit (PCICU). A total of 85 pRBC units were analyzed immediately before transfusion to correlate the resulting pH, lactate, and potassium levels with storage time, which was calculated according to the packaging date on the blood product.

In the second step, all BGAs obtained from infants and children undergoing intensive care treatment were retrospectively studied for significant changes in pH, potassium, and lactate levels after the transfusion event. In case a child received multiple transfusions within 1 hour, BGA results for the first transfusion were retained. Subsequent transfusions between 1 to 4 hours were discarded and hence not considered for analysis. Transfusions administered 4 hours apart were considered as independent events. Administrations occurring less than an hour apart accounted for five events, and four transfusions occurred between 1 and 4 hours from each other, all of which were discarded. After levelling the data by the aforementioned method, 76 pRBC applications remained for analysis. Sifting through 6,782 blood-gas measurements of intensive care unit (ICU) patients, we identified the timeframe corresponding to the blood transfusion. The last BGA values before pRBC administration and the mean measurements 4 hours after the transfusion were computed for the key features and saved together with the corresponding blood products' BGA. The dataset was complete for a total of 45 blood transfusions in 26 children. Measurements from 31 pRBC units were excluded due to missing patient BGAs.

To analyze any impact from "fresh" (storage time ≤ 7 days, $n = 29$) and "older" (storage time > 7 days, $n = 16$) pRBC on the recipients BGA, the measurements were stratified accordingly. The 7-day limit was chosen in an effort to keep the storage time as short as possible while ensuring a reasonable time frame for pRBC unit provision. Electronic medical records were obtained for all patients.

► **Fig. 1** illustrates the distributive process.

Data Aggregation and Analysis

A linear regression analysis was used to investigate the influence of storage time on pH, lactate, and potassium in pRBC as well as the impact from a blood transfusion on children's pH, lactate, and potassium levels. After stratifying the data according to pRBC storage time (≤ 7 and > 7 days) a Wilcoxon signed-rank test was conducted to reveal any significant changes in mean measurements of recipients' pH, lactate, and potassium after the transfusion event.

A Radiometer ABL800 FLEX (Krefeld, Germany) was used as a point of care blood-gas analyzer for the pRBC and patients on PCICU. The level of instrument detection accounted for a minimal pH of 6.3, maximum potassium and lactate of 25 and 30 mmol/L, respectively. In a supplementary figure (► **Supplementary Fig. S1**) we show that our

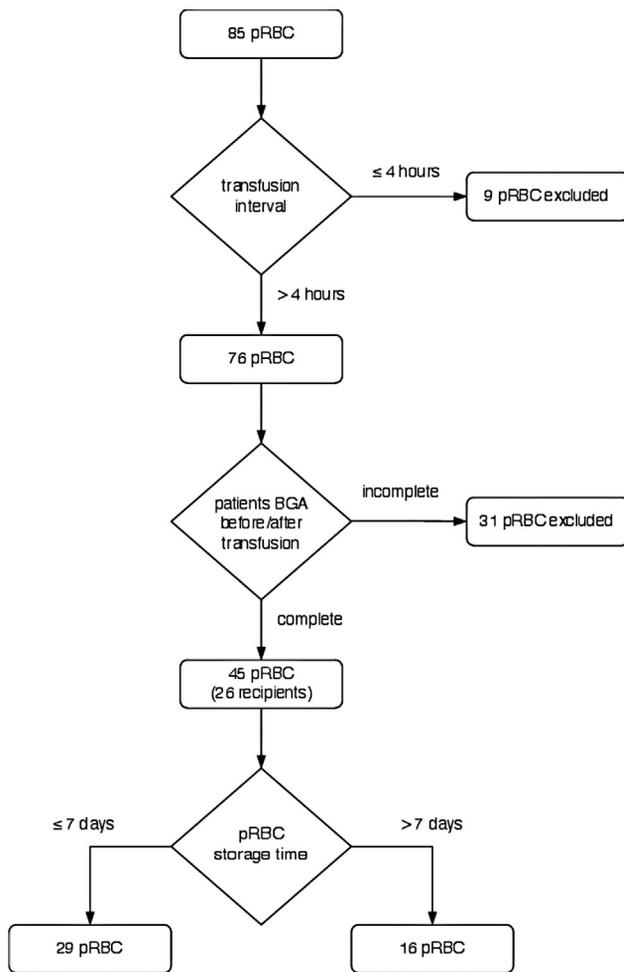


Fig. 1 Flowchart illustrating the pRBC distributive process according to study protocol.

point-of-care measurement of potassium and lactate in pRBC in the ICU (Radiometer ABL800 FLEX) yields nearly identical results, whereas pH levels are a mean 0.3 lower in the ICU than the quality assessment measurement taken by the Institute for Transfusion Medicine and Gene Therapy (blood bank), Medical Centre - University of Freiburg.

Each pRBC unit is obtained from 500 mL citrate anticoagulated allogeneic blood donation. After centrifugation and separation, the leucocyte-depleted erythrocyte concentrate is suspended in 110 mL PAGGS-M (phosphate, adenine, guanine, glucose, and sorbitol–mannitol) solution; the final product has a mean volume of 290 mL with a hematocrit of 50 to 70% and a maximum shelf life of 49 days.

The standard transfusion in children consists of 15 to 20 mL/kg body weight of pRBC over 4 hours. The transfusion threshold is variable and set depending on many factors such as age, cyanotic or acyanotic CHD, cardiac index, and tissue oxygenation. The individual clinical situation of each patient has to be considered. Red cells are administered to severely ill PICU patients at a hemoglobin (Hb) level <10 g/dL in acyanotic children and at a Hb level <13 g/dL in neonates and infants with cyanotic CHD. However, these threshold values can fall short in clinically stable infants and children.

Results

Our analysis of how the storage duration affects pH, potassium, and lactate levels relied on 85 pRBC units, whereas the rest of this investigation considered 45 pRBC with a complete dataset on children’s BGAs before and after the transfusion event.

Packed red cells exhibited a linear drop in pH level and corresponding rise in potassium and lactate over time. Linear regression analysis showed a highly significant correlation between pRBC storage time and pH ($p = 2.41 \times 10^{-24}$, $R^2 = 0.71$), potassium ($p = 1.66 \times 10^{-13}$, $R^2 = 0.55$) as well as lactate ($p = 1.21 \times 10^{-21}$, $R^2 = 0.67$) levels (► Fig. 2).

Of the 85 analyzed pRBC units, 45 had a complete set of patient BGAs data around the transfusion. Some patients received multiple pRBC units as well as more than one operation during their PICU stay, hence 26 infants and children aged a median 0.1 (IQR = 0.0–0.7) years (3 days to 15.2 years) and with a median body weight of 3.8 (IQR = 3.0–5.8) kg (2.3–47.5) accounted for all transfusions as well as a total of 41 procedures with a median STAT (Society of Thoracic Surgeons–European Association for Cardio-

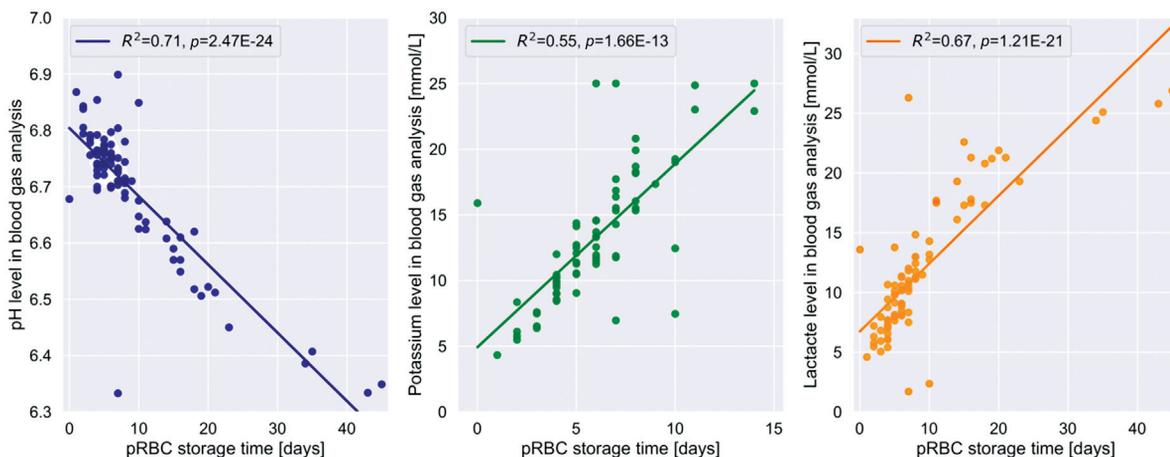


Fig. 2 Graphs showing pH, potassium and lactate levels of pRBC over storage time.

Table 1 Somatic data and STAT mortality categories of all procedures

Procedures	n = 41
Age (years), median (IQR)	0.1 (0.0–0.7)
Body weight (kg), median (IQR)	3.8 (3.0–5.8)
STAT (1–5), median (IQR)	4 (4–5)
Procedure overview of transfused children	
Heart transplant	8
Norwood 1	7
SCPC	6
Aortic arch repair	5
TOF repair	4
ASD/Cor triatriatum repair	4
VSD/DORV repair	2
Pulmonic valve replacement	2
Others	3

Abbreviations: ASD, atrial septal defect; DORV, double outlet right ventricle; IQR, interquartile range; SCPC, superior cavopulmonary connection; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Thoracic Surgery) Mortality Category distribution of 4 (IQR = 4–5) (►Table 1). Out of the remaining four pRBC administrations, one child was transfused after interventional cardiac catheterization, another while awaiting Norwood 1 surgery, and two children while on the waiting list for heart transplantation. ►Table 1 shows an overview of all the procedures the pRBC recipients underwent.

The 45 pRBC median storage duration was 6.0 (IQR = 5.0–8.0) days; median pH level is 6.7 (IQR = 6.7–6.8), with minimal values reaching the detection limit of 6.3; median potassium is 13.4 (IQR = 11.4–20.0) mmol/L, reaching the maximum detection limit of 25 mmol/L; median lactate accounts for 10.6 (IQR = 8.1–13.6) mmol/L, without ever attaining the maximum detection limit. ►Table 2 provides the above pRBC unit information as well as data stratification for ≤7 and >7 days of storage duration.

We found no significant relationship when analyzing for a pRBC transfusion impact on the children's BGAs during their ICU stay (►Fig. 3).

After stratifying for storage time, 29 pRBC were identified as fresh and 16 as older. The effect between pRBC storage

time and recipients' BGA was not statistically significant (►Fig. 4).

Discussion

The present findings demonstrate how decreasing pH as well as increasing lactate and potassium levels in pRBC deviate rapidly in a linear fashion from the physiological norm, showing a highly significant correlation ($p < 0.001$) between storage time and measured values. However, further analysis failed to demonstrate any significant pRBC influence on recipients' median pH, potassium and lactate levels 4 hours after the transfusion event, which remained true after stratifying for "fresh" (storage ≤7 days) and "older" (storage time >7 days) pRBC. This could indicate that deviations from the physiological norm in the blood products are tolerable to some degree, as they seem to be accommodated by the children's metabolism under intensive care surveillance and treatment. Note that administered pRBC were relatively fresh with an overall median storage time of only 6 days.

Considering the literature, it remains unclear to what extent pRBC units beyond a certain age influence transfusions' safety and efficacy. Some studies imply that there is no detrimental clinical effect to be expected from the pRBC age in children. One trial comparing transfusions of red cells stored for less than 11 versus more than 20 days showed no difference in children of 12 years or older undergoing heart surgery.¹⁶ Another analysis on premature, very low-birth-weight infants yielded no beneficial outcome for treatment with pRBC stored for less than 8 days and standard blood bank products.¹⁷

Blood transfusions in general, however, are reported to have a negative impact on outcome in critically ill acyanotic neonates.¹⁸ Some speculate that damaged erythrocytes that are rapidly cleared from the circulatory system after transfusion are among the main culprits for unwanted transfusion-related side effects.¹² These include changes in iron metabolism, inflammation, hemolytic as well as febrile non-hemolytic transfusion reactions and transfusion-related lung injury.^{14,19,20}

A recent study detected a significant increase in ST segment variability with evidence of myocardial ischemia temporally associated with pRBC transfusions in neonates following the Norwood procedure.²¹

In clinical practice, the relative transfused quantity of pRBC often differs between adults and children, whose ratio of total blood to transfusion volume is much higher, as the

Table 2 Storage time and blood gas analysis of packed red blood cell units

Administrated pRBC	n = 45	n = 29 (fresh ^a)	n = 16 (older ^b)
Storage time (days), median (IQR)	6.0 (5.0–8.0)	5.0 (4.0–6.0)	10.5 (8.0–16.0)
pH level, median (IQR)	6.7 (6.7–6.8)	6.7 (6.7–6.8)	6.6 (6.6–6.7)
Potassium (mmol/L), median (IQR)	13.4 (11.4–20.0)	11.9 (10.3–13.7)	21.9 (17.7–25.0)
Lactate (mmol/L), median (IQR)	10.6 (8.1–13.6)	9.0 (7.6–10.6)	16.1 (12.7–18.1)

Abbreviations: IQR, interquartile range; pRBC, packed red blood cell.

^aStorage time ≤7 d.

^bStorage time >7 d.

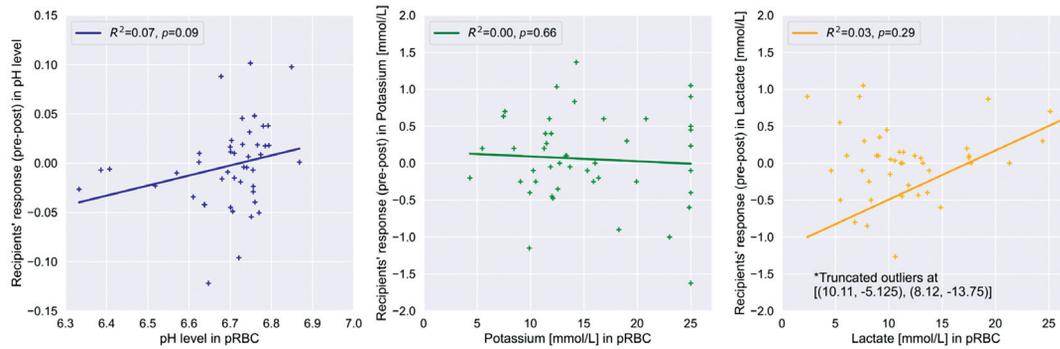


Fig. 3 Graphs showing patients' BGA response after pRBC transfusion.

following example shows: according to the age-based modified total blood volume (TBV) calculation (TBV = ideal body weight \times 70 mL/kg in patients under 65 years of age),²² the estimated TBV of an adult with 80 kg body weight would be 5.6 L. In this scenario, for instance, the transfusion of a whole bag of pRBC (250–300 mL) would correspond to 4.5 to 5.4% of the TBV. By contrast, in a child with 5 kg body weight and an estimated TBV of 400 mL receiving the usual quantity of 20 mL/kg, the transfusion would account for 25% of their TBV. Thus it is all the more astonishing and fortunate that we found that the effect of red cell transfusion seems to have no significant impact on children's BGAs in this study, no matter how old the blood unit is. However, our cohort is very heterogeneous concerning the patients' age, weights, and heart defects.

It is well known that red blood cells do not keep well over the entire storage time. The common reasoning therefore is that the patients' benefit from such a transfusion is compromised to some degree.¹ The urgency of any blood transfusions should outweigh in vitro degeneration and its possible associated risks while expecting in vivo regeneration. There is no alternative in case of acute bleeding, but while idling on the edges of recommended Hb levels, the shelf life of eligible blood units, as well as their BGAs as a feasible and readily available tools to measure the products'

extracellular composition, should be accounted for to adjust the goal, volume, and duration of transfusion accordingly.

A follow-up study analyzing more pRBC units should stratify for body weight and underlying heart defects, so as to promote better understanding of the possible influence of pRBC age on the most vulnerable patients: neonates and infants with LCOS after CPB surgery.

Meanwhile, in close collaboration with the Institute for Transfusion Medicine and Gene Therapy, a novel approach to fresh pRBC has been introduced at the University Clinic of Freiburg without changing our actual storage strategies: we recruit blood donors in advance specifically for certain complex congenital heart operations to guarantee the shortest possible pRBC storage time before transfusion.

Another strategy being discussed is the washing of pRBC prior to its administration in ICU. While striving for completely transfusion-free congenital heart surgery, washing (CATSmart, Fresenius Kabi, Graz, Austria) pRBC is a standard procedure in the operating room for CPB priming solutions and during surgery to normalize supernatant potassium, lactate and improve pH levels. This method results in pRBC solutions which are more in line with desired physiological levels and could potentially reduce the risk of arrhythmia and cardiac arrest²³ due to high potassium levels amongst other transfusion-related adverse effects.

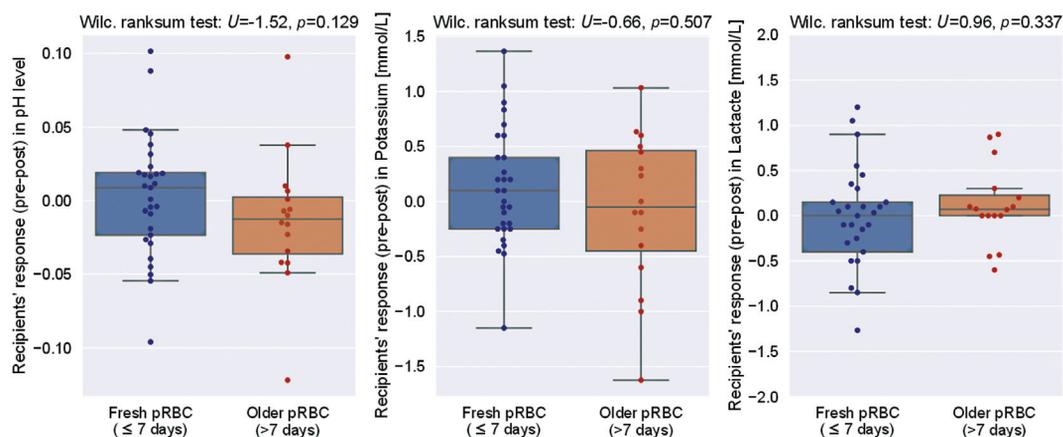


Fig. 4 Box-whisker plots showing patients' BGA response after transfusion stratified for pRBC storage time.

Stored red cells are a valuable clinical good and their eligibility has to be evaluated with great care, as none of them should be discarded lightly. Fresh pRBC solutions should be favored to guarantee the most beneficial transfusions to all patients, neonates, and children in particular.

Conclusion

Our study results show a statistically highly significant increase in potassium and lactate, as well as a respective drop in pH levels over the duration of storing pRBC ($p < 0.0001$). While we verified no significantly detrimental effect from pRBC on children's BGAs within 4 hours after transfusion, we emphasize that these analyses were under constant monitoring and counteracting therapy in the PICCU.

The washing of pRBC – wherever possible outside of the operating room – prior to mass transfusion in critically ill patients could be considered as a preventive measure to counteract a possible metabolic imbalance due to pRBC with a low pH and high levels of potassium and lactate.

A larger sample size would allow for further analysis concerning the possible influence of children's body weight and the underlying heart defect with special emphasis on neonates and cyanotic heart defects.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

The authors thank Carole Cürten for language editing.

References

- Barbosa FT, Jucá MJ, Castro AA, Duarte JL, Barbosa LT. Artificial oxygen carriers as a possible alternative to red cells in clinical practice. *Sao Paulo Med J* 2009;127(02):97–100
- Mazine A, Rached-D'Astous S, Ducruet T, Lacroix J, Poirier NPediatric Acute Lung Injury and Sepsis Investigators Network. Blood transfusions after pediatric cardiac operations: a North American Multicenter Prospective Study. *Ann Thorac Surg* 2015;100(02):671–677
- Valentine SL, Bembea MM, Muszynski JA, et al; Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Consensus recommendations for RBC transfusion practice in critically ill children from the pediatric critical care transfusion and anemia expertise initiative. *Pediatr Crit Care Med* 2018;19(09):884–898
- Cholette JM, Willems A, Valentine SL, Bateman ST, Schwartz SMPediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI) Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Recommendations on RBC transfusion in infants and children with acquired and congenital heart disease from the pediatric critical care transfusion and anemia expertise initiative. *Pediatr Crit Care Med* 2018;19(9S, suppl 1):S137–S148
- Lion N, Crettaz D, Rubin O, Tissot J-D. Stored red blood cells: a changing universe waiting for its map(s). *J Proteomics* 2010;73(03):374–385
- Flatt JF, Bawazir WM, Bruce LJ. The involvement of cation leaks in the storage lesion of red blood cells. *Front Physiol* 2014;5:214
- Bennett-Guerrero E, Veldman TH, Doctor A, et al. Evolution of adverse changes in stored RBCs. *Proc Natl Acad Sci U S A* 2007;104(43):17063–17068
- Du X, Chen H, Song X, et al. Risk factors for low cardiac output syndrome in children with congenital heart disease undergoing cardiac surgery: a retrospective cohort study. *BMC Pediatr* 2020;20(01):87
- Şahutoğlu C, Yaşar A, Kocabaş S, Aşkar FZ, Ayık MF, Atay Y. Correlation between serum lactate levels and outcome in pediatric patients undergoing congenital heart surgery. *Türk Gogus Kalp Damar Cerrahisi Derg* 2018;26(03):375–385
- D'Alessandro A, D'Amici GM, Vaglio S, Zolla L. Time-course investigation of SAGM-stored leukocyte-filtered red blood cell concentrates: from metabolism to proteomics. *Haematologica* 2012;97(01):107–115
- Hess JR. Red cell changes during storage. *Transfus Apheresis Sci* 2010;43(01):51–59
- Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. *Lancet* 2008;372(9647):1411–1426
- Safeukui I, Buffet PA, Deplaine G, et al. Quantitative assessment of sensing and sequestration of spherocytic erythrocytes by the human spleen. *Blood* 2012;120(02):424–430
- Hod EA, Spitalnik SL. Stored red blood cell transfusions: iron, inflammation, immunity, and infection. *Transfus Clin Biol* 2012;19(03):84–89
- Bardyn M, Rappaz B, Jaferzadeh K, et al. Red blood cells ageing markers: a multi-parametric analysis. *Blood Transfus* 2017;15(03):239–248
- Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. *N Engl J Med* 2015;372(15):1419–1429
- Fergusson DA, Hébert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: the ARIPI randomized trial. *JAMA* 2012;308(14):1443–1451
- Fergusson D, Hébert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. *JAMA* 2003;289(15):1950–1956
- Khan SY, Kelher MR, Heal JM, et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. *Blood* 2006;108(07):2455–2462
- Heddle NM, Klama LN, Griffith L, Roberts R, Shukla G, Kelton JG. A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusions. *Transfusion* 1993;33(10):794–797
- Savorgnan F, Bhat PN, Checchia PA, et al. RBC transfusion induced ST segment variability following the Norwood procedure. *Crit Care Explor* 2021;3(05):e0417
- Muraki R, Hiraoka A, Nagata K, et al. Novel method for estimating the total blood volume: the importance of adjustment using the ideal body weight and age for the accurate prediction of haemodilution during cardiopulmonary bypass. *Interact Cardiovasc Thorac Surg* 2018;27(06):802–807
- Hall TL, Barnes A, Miller JR, Bethencourt DM, Nestor L. Neonatal mortality following transfusion of red cells with high plasma potassium levels. *Transfusion* 1993;33(07):606–609