Effects of Blood Transfusion Sets on Red Blood Cell Hemolysis

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ABSTRACT

This experimental randomized study compared the effects of macrodrop and microdrop blood transfusion sets on red blood cell (RBC) hemolysis. Twenty units of packed RBCs from different donors were infused through 48 infusion sets from 2 manufacturers at infusion rates of 10 and 100 mL/h. Pre- and postinfusion analysis was performed to determine total hemoglobin (g/dL), hematocrit (%), free hemoglobin (g/dL), potassium (mmol/L), haptoglobin (g/L), and degree of hemolysis (%). The results demonstrated that the level of free hemoglobin ($P < .001$) and degree of hemolysis ($P < .001$) increased postinfusion. A higher degree of hemolysis was noted when the RBCs were infused at a rate of 10 mL/h through a microdrop blood transfusion set.

Key words: blood transfusions, haptoglobin, hemocrit, hemoglobin, hemolysis, intravenous infusions, nursing, red blood cells

More than 100 million units of blood are collected worldwide each year, and approximately 14 million units of whole blood and red blood cells (RBCs) are collected in the United States alone.[1,2]

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Regardless of the clinical condition of the patient receiving a blood transfusion, it is important that infusion practice is based on evidence that both guarantees the effectiveness of the intervention and includes nurses in the decision-making.[3,4]

Technological advances in transfusion medicine, for example, fractionation of whole blood into blood components, irradiation, washing, and filtration of the units, have led to reductions in morbidity and mortality in many clinical situations. Despite the advantages, the transfusion of blood components involves risk: on average, 1% to 2% of procedures lead to transfusion reactions, either immune or nonimmune.[1,3,5]

Data from 25 countries indicate that the average rate of transfusion reactions in 2016 was 660 per 100 000 procedures, with 3% being classified as severe reactions. Mortality associated with blood transfusion was 0.26 deaths per 100 000 transfusions.[6] In Brazil, 2.2% of the transfusion reactions are reported to be severe.[7] In the United States, 239.5 reactions have been registered per 100 000 transfusions (205.5 per 100 000 were associated with RBCs).[8] In a time series analysis from 2009 to 2015, the rate of transfusion reactions was higher among children, with 538 per 100 000 transfusions and 31 nonimmune transfusion reactions per 100 000 transfusions.[9]

Nonimmunologic reactions can be associated with extracorporeal hemolysis due to the manipulation in the blood bank and during infusion. For RBC transfusions, a broad range of intravenous infusion devices (eg, infusion pumps, macrodrop and microdrop administration sets,

and compression devices) can be used on the basis of evidence-based protocols and on the clinician's choice of a technology that meets the clinical needs of the patient. Infusion systems with different properties and characteristics are available on the market for RBC administration, and studies have raised questions about the potential influence of this equipment on hemolysis.[10,11]

After cellular damage, proteins and electrolytes are released into blood plasma, thus triggering a series of biochemical reactions. RBC membrane damage increases plasma hemoglobin and potassium levels and decreases the concentration of haptoglobin, a protein synthesized by hepatocytes that binds to free hemoglobin.[12-14]

Increased levels of potassium in post-transfused blood pose a significant risk to neonates and children, particularly in those with low blood volumes. Hyperkalemia is associated with arrhythmias and cardiorespiratory arrest.[15] Olson et al[16] documented an increase in serum potassium levels of up to 0.08 mmol/L post-transfusion in children.

During administration, distortion of the RBC membrane occurs, and shear stress results due to the RBCs being transfused through administration sets with various diameters. The effect of hemolysis of RBCs from administration sets used with electronic infusion devices has been demonstrated in several studies.[17-19] No studies on the effect on blood quality from gravity-dependent macrodrop and microdrop infusion systems can be found in the literature.

The administration sets most frequently used in the authors' clinical practice for RBC transfusions are gravity dependent and either a macrodrop or microdrop set. The effects on the blood of these administration sets based on the drop size are not well known. Clinical decision-making regarding the use of one administration set or another takes into account flow control accuracy, with a microdrop set often chosen for pediatric and neonatal patients.[10,17] Therefore, this study focused on comparing the effects of macrodrop and microdrop transfusion sets on hemolysis biomarker levels and the degree of hemolysis, depending on the type of set and infusion rate.

METHODS

The protocol of this experimental in vitro study was approved by the Research Ethics Committee. Experiments were conducted in a temperature-controlled laboratory at 21.9°C (range, 20°C-24°C) and average relative humidity of 64% (range, 49%-77%).

Samples

A total of 48 administration sets from 2 different manufacturers (A and B) were tested, including 24 macrodrop sets (12 from A and 12 from B) and 24 microdrop sets (12 from A and 12 from B). All of the sets contained a 180-micron filter approved for RBC transfusions. To simulate pediatric RBC transfusion practices, the flow rates selected for the study were 10 and 100 mL/h. The RBC samples were randomized by macrodrop or microdrop set manufacturer, as well as infusion rate.

The 48 administration sets were filled with aliquots of RBCs from 20 bags of packed RBCs (all type A+) from different donors, preserved with a citrate-phosphate-dextrose-adenine solution (CPDA-1) and stored at 2°C to 6°C.[20] The packed RBCs were obtained as surplus stock from a blood bank (COLSAN, São Paulo, Brazil) that contributed to the study and were used in 2 or 3 experiments according to the total volume of a bag.

The bags of RBCs had a minimum volume of 204 mL, a maximum volume of 350 mL, with the mean ± SD of 281 ± 48.89 mL. The RBCs were stored for 16.08 ± 7.28 days, with a minimum of 3 days and a maximum of 27 days.

Experimental Design

The RBCs were transported from the blood bank to the laboratory under controlled conditions and stored in accordance with quality control recommendations. All of the experiments were initiated by removing RBCs from a refrigerator and measuring initial temperature using an infrared thermometer, and additional measurements were performed every 15 minutes for 1 hour or when the RBCs reached the minimal temperature of 18°C. The first 5 mL of the blood sample labeled "pre-infusion" was collected directly into a dry tube to determine hemolysis marker levels, and the administration set was attached to the bag of RBCs.

The RBC bags were connected to an administration set (randomly selected) with aseptic technique, placed 80 cm above the distal port of the primary administration set, and primed with the RBCs. To control the infusion rate, the clamp was adjusted to 20 cm from the drip chamber for all of the sets tested in the experiment. After RBC infusion into the closed system, a sample was collected for analysis.

Due to the variation in the diameters of the administration sets, the internal volume was checked before the start of the experiments and was found to be in a range of 9 to 12 mL (10.5 ± 1.1 mL). On the basis of the criteria adopted in clinical practice, the hang-time period of the blood was 2 hours and 48.00 ± 39.22 minutes.

After the infusion of the 15- to 20-mL priming volumes (per each set's internal volume), a "postinfusion" sample was collected. This sample represented the effect of the type of administration set and the infusion rate on the hemolysis markers. The studied infusion rate (10 or 100 mL/h) was adjusted and controlled every 15 minutes to ensure that the infusion remained at the selected rate during the entire experiment.

All of the procedures in the laboratory were performed by nurses with the technical support of a pharmacist and biomedical researchers for the RBC marker analysis. The following markers were studied: total hemoglobin (g/dL), hematocrit (%), free hemoglobin (g/dL), potassium (mmol/L), haptoglobin (g/L), and the degree of hemolysis (%).

TABLE 1

Hemolysis Markers in RBCs According to Pre- and Postinfusion Analyses

Markers	Preinfusion (n = 48)		Postinfusion (n = 48)		*P* Value
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Total Hb (g/dL)	28.09 ± 3.48	21.16–37.03	27.13 ± 4.56	18.98–36.81	.062[a]
Free Hb (g/dL)	0.18 ± 0.19	0.03–0.63	0.21 ± 0.25	0.04–0.90	<.001[b]
Ht (%)	72.42 ± 6.32	60.00–85.00	72.50 ± 6.49	60.00–85.00	.608[b]
Degree of hemolysis (%)	0.16 ± 0.16	0.03–0.55	0.20 ± 0.22	0.03–0.90	<.001[b]
Potassium (mmol/L)	38.28 ± 5.27	17.92–47.84	38.31 ± 5.34	17.36–47.36	.802[b]
Hp (g/L)	0.80 ± 0.64	0.28–3.32	0.69 ± 0.43	0.28–2.42	.211[b]

[a]Student *t* test.
[b]Mann–Whitney test.
Abbreviations: dL, deciliter; free Hb, free hemoglobin; g, grams; Hp, haptoglobin; Ht, hematocrit; L, liter; max, maximum; min, minimum; mmol, millimole; RBC, red blood cells; SD, standard deviation; total Hb, total hemoglobin.

Hemolysis Marker Analysis

To measure the hematocrit percentage, the RBC samples were dispensed in capillary tubes with heparin and centrifuged at 11,500 revolutions per minute for 4 minutes using a Micro Hematocrit Centrifuge (CelmMH, São Paulo, Brazil). After that, the analysis was performed using the equipment to determine the hematocrit percentage of each sample. This measurement was then visually confirmed by 2 researchers.[21-23] Total hemoglobin (grams per deciliter) was analyzed by a colorimetric method and spectrophotometry at 540 nm (Bioespectra, Parana, Brazil).[22,23] To measure free hemoglobin (grams per deciliter), centrifugation of a blood sample in a tube with a clot activator and separator gel was carried out at 3600 rpm for 10 minutes (in the same centrifuge), to collect the supernatant. The analysis was based on spectrophotometry at the wavelengths 370, 415, 510, 577, and 600 nm.[22,23]

The potassium level was measured in millimoles per liter using the colorimetric system after preparation of solution with tetraphenylborate reagent. The final solution was subjected to spectrophotometry at 580 nm.[24,25]

To verify the haptoglobin level (grams per liter) in the supernatant serum of the centrifuged RBC, nephelometry by immunoreactions was employed using Minineph Plus-Binding Site (Birmingham, United Kingdom).[14,26,27] The degree of hemolysis was determined via the following mathematical formula: (100 − Ht) × Hbl (g/dL) / Hbt (g/dL),[23] where Ht is hematocrit; free Hb, free hemoglobin; and total Hb, total hemoglobin.

Statistical Analysis

Data were deposited in an electronic database and analyzed in the R software, version 3.12 (R Foundation for Statistical Computing, Vienna, Austria); they are represented as mean and standard deviation, standard error, median, interquartile range, minimum, and maximum.

Absolute or relative differences between preinfusion and postinfusion markers were employed to analyze variance attributed to the administration set type and infusion rate. To verify normality of the data distribution, the Anderson–Darling normality test was performed. In cases where the test confirmed normality, the Student *t* test or ANOVA was carried out. The Mann–Whitney, Levene, and Kruskal–Wallis tests, as well as the Tukey nonparametric test, were performed when normality was absent. The significance level was set as $P \leq .05$.

RESULTS

Table 1 shows the levels of the hemolysis markers presented according to the preinfusion and postinfusion analyses in all 48 studied administration sets. The data revealed that free hemoglobin levels and degree of hemolysis increased significantly postinfusion ($P < .001$). Total hemoglobin ($P = .062$) and haptoglobin ($P = .211$) levels decreased after infusion, but the differences were not statistically significant. The mean hematocrit and potassium levels showed no significant differences between preinfusion and postinfusion data.

An analysis of the influence of the type of administration set did not reveal significant differences in the changes in hemolysis markers among the administration sets, except for the degree of hemolysis. A significantly greater degree of hemolysis was observed in the microdrop group compared with the macrodrop sets ($P = .049$; Table 2).

In relative variance analyses, the authors were able to determine that total hemoglobin levels tended to decrease in both sets, with a reduction of 3% in the microdrop set and 2% in the macrodrop set. Free hemoglobin increased by 25% in the microdrop group and by 12% in the macrodrop group; both changes lacked statistical significance. No differences were observed in the changes of hematocrit levels; the degree of hemolysis increased significantly at 26% in microdrop administration sets as compared with the increase of 15% in macrodrop administration sets (Table 2).

TABLE 2

Preinfusion and Postinfusion Hemolysis Markers According to Administration Sets

Markers	Drop Systems (n = 48)		Microdrop Systems (n = 48)		*P* Value
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Total Hb (g/dL)	−0.64 ± 2.93	−6.08–5.00	−1.28 ± 4.00	−9.88–5.60	.534[a]
Free Hb (g/dL)	0.02 ± 0.02	−0.01–0.05	0.06 ± 0.09	0.00–0.27	.128[b]
Ht (%)	0.29 ± 1.20	−2.00–3.00	−0.12 ± 0.85	−2.00–2.00	.296[b]
Degree of hemolysis (%)	0.02 ± 0.02	−0.01–0.09	0.06 ± 0.09	−0.01–0.35	.049[b]
Potassium (mmol/L)	−0.42 ± 2.22	−6.18–2.63	0.48 ± 2.68	−2.98–9.50	.789[b]
Hp (g/L)	−0.22 ± 0.74	−2.72–0.84	0.00 ± 0.17	−0.31–0.60	.910[b]

[a]Student *t* test.
[b]Mann–Whitney test.
Abbreviations: dL, deciliter; free Hb, free hemoglobin; g, grams; Hp, haptoglobin; Ht, hematocrit; L, liter; max, maximum; min, minimum; mmol, millimole; SD, standard deviation; Total Hb, total hemoglobin.

As for infusion rates, the degree of hemolysis was significantly higher ($P = .042$) at 10 mL/h. The level of total hemoglobin was lower at 10 mL/h, thus representing a reduction of 5% after RBC infusion; at 100 mL/h, no differences were observed. While the level of free hemoglobin manifested a greater increase at the infusion rate of 10 mL/h versus the infusion rate of 100 mL/h, the difference was not statistically significant. The hematocrit and potassium levels barely changed. The haptoglobin levels slightly decreased at both infusion rates, but the difference was not statistically significant (Table 3).

Figure 1 shows relative differences in the degree of hemolysis depending on the administration set type and infusion rate. The infusion rate of 10 mL/h yielded a 2-fold greater increase in the degree of hemolysis, nearly 33%, whereas at the rate of 100 mL/h, the increase was 15%.

The comparisons of administration sets between manufacturers A and B uncovered no statistically significant differences: total hemoglobin levels decreased in samples subjected to infusion via the sets from both manufacturers (A: –1.38 ± 3.06; B: –0.54 ± 3.88; $P = .409$); free hemoglobin levels showed a similar increase (A: 0.04 ± 0.07; B: 0.04 ± 0.07; $P = .315$); sets from manufacturer A (0.05 ± 0.06) and B (0.04 ± 0.08) led to an increase in the degree of hemolysis ($P = .116$). Potassium concentration (A: 0.23 ± 2.77; B: –0.17 ± 2.18; $P = .680$) and haptoglobin concentration (A: –0.04 ± 0.3; B: –0.18 ± 0.71; $P = .984$) were lower postinfusion for both manufacturers, indicating no significant differences.

TABLE 3

Preinfusion and Postinfusion Hemolysis Markers According to Infusion Rates

Markers	Infusion Rate, 10 mL/h (n = 48)		Infusion Rate, 100 mL/h (n = 48)		*P* Value
	Mean ± SD	Min-Max	Mean ± SD	Min-Max	
Total Hb (g/dL)	−1.93 ± 2.66	−7.06–2.45	0.01 ± 3.97	−9.88–5.60	.054[a]
Free Hb (g/dL)	0.06 ± 0.09	−0.01–0.27	0.02 ± 0.03	0.00–0.14	.325[b]
Ht (%)	0.17 ± 1.40	−2.00–3.00	0.00 ± 0.51	−1.00–1.00	.953[b]
Degree of hemolysis (%)	0.06 ± 0.09	0.00–0.35	0.02 ± 0.03	−0.01–0.09	.042[b]
Potassium (mmol/L)	0.03 ± 3.16	−6.18–9.50	0.03 ± 1.60	−3.65–2.63	.543[b]
Hp (g/L)	−0.13 ± 0.64	−2.72–0.84	−0.10 ± 0.43	−2.09–0.12	.563[b]

[a]Student *t* test.
[b]Mann–Whitney test.
Abbreviations: dL, deciliter; free Hb, free hemoglobin; g, grams; Hp, haptoglobin; Ht, hematocrit; L, liter; max, maximum; min, minimum; mmol, millimole; SD, standard deviation; Total Hb, total hemoglobin.

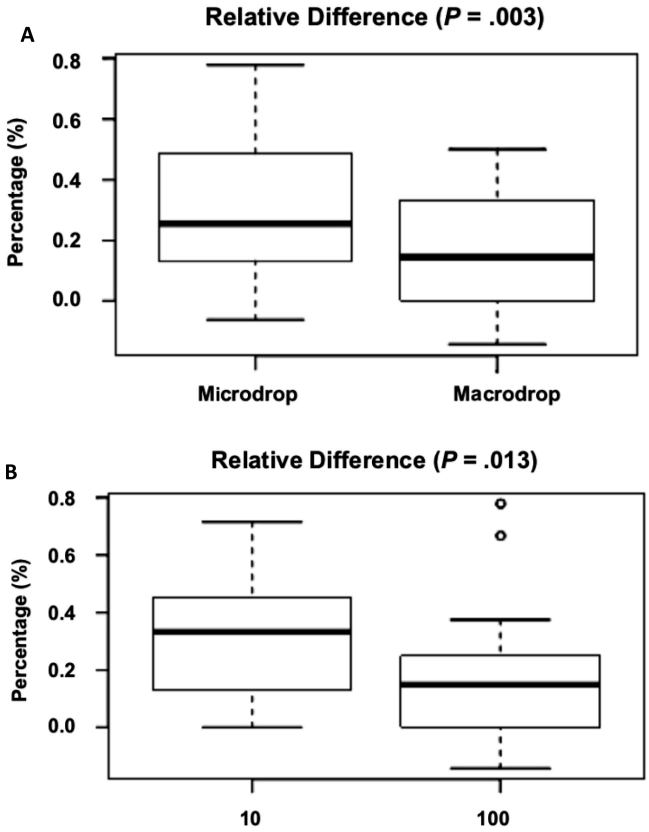

Figure 1. Relative differences in levels of hemolysis biomarkers and in the degree of hemolysis between red blood cell samples preinfusion and postinfusion, depending on the A) infusion set type and B) infusion rate.

LIMITATIONS

This study was limited by the number of RBC units and the hemolysis markers studied. Additionally, hemolysis was influenced by storage time; RBC units with a longer period of storage composed 30% of the analyzed packed RBCs.

DISCUSSION

Hemolysis

Studies that are aimed at analyzing extracorporeal hemolysis have verified the effects of catheters and infusion pumps on the quality of RBC transfusions. In the literature, the authors found no studies on hemolysis related to macrodrop and microdrop administration sets. The results of our study indicate that the effect on hemolysis was related to the type of administration set, with the microdrop administration set at the infusion rate of 10 mL/h yielding a greater degree of hemolysis in our experiments.

Some studies that have assessed blood quality after transfusion via infusion pumps and catheters with different gauges and lengths did not produce similar results. Some showed damage to RBCs from administration through infusion pumps and shear stress from catheters, whereas others did not detect such a phenomenon.[10,27-30] Two studies—one involving different types of infusion pumps (shuttle- and piston-type pumps), the other testing different gauges of catheters (16- to 22-gauge)—revealed significant differences in the degree of hemolysis after the infusion of RBCs.[10,27]

For RBC transfusions, gravity-dependent blood transfusion sets with drop sizes of various diameters are used. Considering the results obtained in this study, it is possible that extravascular damage to erythrocytes is related to the reduction in the internal caliber of the system structures, mainly due to use of microdrop sets; the reduction of the radius increases shear stress, which causes a loss of surface area in the erythrocyte membrane, which causes a reduction in the deformation ability of the cell, greater fragility of the membrane, and possible rupture of an RBC.[29]

In support of the present study, researchers who analyzed different infusion rates found that during RBC infusions at lower infusion rates (10 and 20 mL/h) via infusion pumps, there is a greater change in the osmotic fragility of the erythrocyte membrane and a greater increase in the levels of free hemoglobin and potassium compared with higher rates (70 mL/h).[10,30] Other investigators who evaluated higher infusion rates—100 to 999 mL/h during RBC transfusions via infusion pumps—have noted no significant changes in the analyzed hemolysis markers.[31-37]

This study detected an increase in the degree of hemolysis after the infusion of RBCs via the microdrop set at 10 mL/h, reaching a level of 0.90%. These high levels of hemolysis could lead to a transfusion contraindication according to blood bank quality control recommendations.[38]

Free Hemoglobin

In addition to the degree of hemolysis, free hemoglobin is a relevant marker of damage to erythrocytes. The bags of packed RBCs tested in this study contained mean levels of 0.18 g/dL, with an increase to 0.21 g/dL after the flow of erythrocytes through the administration set. Researchers who have described the influence of a peripheral catheter gauge on hemolysis have registered the levels of free hemoglobin of 0.1 g/dL after infusion via 18-gauge catheters and 0.3 g/dL with 24-gauge catheters.[31]

Free hemoglobin, even at levels less than 0.01 g/dL, neutralizes nitric oxide, which causes systemic and pulmonary vasoconstriction, in addition to increasing platelet aggregation and the risk of thrombosis. Moreover, excess free hemoglobin can cause renal injury during the blood-filtering process.[39-41]

One in vitro experimental study has evaluated the effect of infusion pumps on the quality of transfused blood at different infusion rates and retrospectively analyzed hemoglobinuria in children receiving the transfusion in a hospital. The results indicate that lower infusion rates, more commonly applied in pediatrics and neonatology, lead to more negative effects on RBC quality, as evidenced by increased free

hemoglobin levels. The data also showed that 9.6% of the patients had hemoglobinuria related to blood transfusion.[42]

Haptoglobin

One of the physiological methods of protection from the harmful effects of free hemoglobin in humans is the presence of haptoglobin in blood plasma. Haptoglobin is a protein that binds to free hemoglobin, inhibiting it and carrying it to the endothelial reticular system so that it can be disposed of without causing harm to the body.[12] Previous research addressed the use of haptoglobin in packed RBCs as a protection factor—it could inhibit the deleterious action of free hemoglobin excess before transfusion. Studies have uncovered a decrease in the neutralization of nitric oxide and in cell oxidation, a large amount of the hemoglobin–haptoglobin complex, and an improvement in stored-RBC quality, which confirms the protective function of haptoglobin.[43,44]

Researchers who have analyzed haptoglobin properties as a biomarker of hemolysis suggest that a reduction in this protein's concentration is associated with cases of hemolysis after blood transfusion.[12,14] In the current study, there was a decrease in haptoglobin concentration after the passage of blood through the administration sets. The reduction in the haptoglobin level can be a consequence of formation of the hemoglobin–haptoglobin complex due to hemolysis. Nevertheless, the level of haptoglobin in bags of stored RBCs likely depends on the donor's characteristics. Furthermore, during preparation of plasma, proteins, including haptoglobin, can be filtered out; this can explain the drop in its concentration.

Potassium

Another hemolysis marker is extracellular potassium. The concentration of potassium in a bag of RBCs typically increases depending on storage time and the preservative solutions used. This is because without active potassium and sodium pumps, this ion cannot be recaptured by the cell and remains free in the supernatant, with its concentration growing by nearly 1 mmol/L after each storage day.[45] A study conducted in 2014 indicates that RBCs with the CPDA-1 preservative solution yield an increase in extracellular potassium of 20 mmol/L in the first week of storage and 40 mmol/L after 2 weeks.[25]

The mean level of potassium in this study was 38.31 mmol/L in postinfusion samples. Some batches of packed RBCs after long storage (15–28 days) indicated levels of up to 47.8 mmol/L in preinfusion samples. The data in the literature on extracellular potassium in bags of RBCs have shown levels of up to 60 mmol/L at the end of a storage period (maximum storage of 35 days), with the ideal level of extracellular potassium in a freshly packed RBC bag of 5 mmol/L.[45]

An experimental study[46] evaluated blood transfusion via a syringe pump, simulating the transfusion practice in neonates. Results showed that, after infusion, there was a significant increase of potassium and free hemoglobin levels in the analyzed samples.

Clinical Significance

Children and neonates commonly need transfusions in small volume requiring a microdrop administration set to ensure accuracy. We identified a relation between the microdrop sets and RBC hemolysis. Furthermore, regarding the studied infusion rates of RBCs of 10 mL/h and 100 mL/h, our experiments indicate that slower infusion rates and use of microdrop sets caused more RBC damage and an increased hemolysis grade. The control of volume accuracy during intravenous infusion in pediatric patients can be achieved with infusion pumps indicated by the manufacturer to RBC transfusion. Burettes are also options and are commercially available with various size drop sets.

The study findings on hemolysis markers after administration of erythrocytes by macrodrop and microdrop transfusion sets indicated that macrodrop transfusion sets lead to fewer alterations in the RBCs. In addition, this fundamental study was inspired by bedside inquiries, showing that nurses' critical appraisal of technologies can contribute to improvements. Bedside-to-bench translation research is essential for the safety, reliability, and effectiveness of the care provided by nurses and thus directly affects patient, family, and societal outcomes.[47,48]

This is a unique study, indicating the need for further comparative research on other gravity-dependent transfusion sets. Despite the fact that many transfusions are administered via infusion pumps, comparisons on the level of hemolysis according to the use of electronic or manual flow-control devices are relevant. A larger sample of packed RBCs and different administration sets must be analyzed to validate the influence on hemolysis biomarkers.

CONCLUSIONS

Hemolysis markers underwent changes after RBCs were transfused through gravity-dependent macrodrop and microdrop administration sets with significant increases in free hemoglobin levels and in the degree of hemolysis. The microdrop administration set at an infusion rate of 10 mL/h yielded significant increases in the degree of hemolysis in the RBC samples. No significant changes in hematocrit, potassium, or haptoglobin levels were observed.

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