Influence of different syringe pumps and infusion rates on red cells during paediatric simulated transfusion

Short title: Influence of syringe pumps on red blood cells

Larissa Perez Pardo[1]
Maria Angélica Sorgini Peterlini[2]
Lyvonne Nicole Tume[3]
Mavilde da Luz Gonçalves Pedreira[4]

[1] RN, MNSc, Adjunct Professor of the undergraduate course in Nursing at Paulista University, Sao Paulo, Brazil and PhD candidate in Paulista Nursing School. Universidade Federal de São Paulo – UNIFESP, Brazil. E-mail: larissappardo@hotmail.com/ Telephone number: +55 11 98398-7518.

[2] RN, PhD, Associate professor at the Universidade Federal de São Paulo - UNIFESP, Brazil. Coordinator of the Nursing Postgraduate Program at the Paulista School of Nursing at Unifesp, Sao Paulo, Brazil. E-mail: maria.angelica@unifesp.br/ Telephone number: +55 11 5576-4430.

[3] RN, PhD, Associate Professor in Child Health at the University of Salford, Manchester, England. E-mail: lyvonnetume@gmail.com

[4] RN, PhD, Titular head Professor at the Universidade Federal de São Paulo, Brazil, Coordinator of the Postgraduate and Research Chamber to the Paulista School of Nursing and Support of the Discipline of Clinical Care, Surgical and Pediatric Nursing Department, Sao Paulo, Brazil. E-mail: mpedreira@unifesp.br/ Telephone number: +55 11 5576-4430.

Correspondent Author:
Larissa Perez Pardo
Rua Napoleão de Barros, 754, Vila Clementino – Sao Paulo, SP – Brazil
larissappardo@hotmail.com
+55 11 983987518

Key words: Blood transfusion, Infusion pumps, Syringe, Haemolysis, Nursing

Data availability statement

The data supporting the results of this study will be made available by the corresponding author, [LPP], upon request.

Funding

This work was supported by National Council for Research Development (CNPq) [grant number: 308281/2015-2] and a scholarship from Coordination for the Improvement of Higher Education Personnel Foundation (CAPES) to the first author.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval Statement

This research was approved by the Research Ethics Committee of the Universidade Federal de São Paulo. Ethical approval number: CAAE: 04061812.0.0000.5505

Patient Consent Statement

Waiver of the donor's free and informed consent form was requested, as blood donation is a voluntary and altruistic act. Every donor signs a consent provided by law, in which he agrees that his blood can be used for therapeutic purposes, examinations and laboratory tests required by law and current technical standards.

Therefore, it was not possible to identify the donor's origin, as the blood units did not contain the donor's identification and, thus, the donor's image and privacy were protected.

Acknowledgement

COLSAN – Blood Collection Beneficent Association for technical support.

Alex Paixão dos Santos Nascimento for creating the figures used in the study method.

Ana Geisa Santos de Angelo and Maria Paula de Oliveira Pires for research support.

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Abstract

Background: Critically ill patients frequently need blood transfusions. For safety, blood must be delivered via syringe infusion pumps, yet this can cause red cell damage and increase the rate of haemolysis.

Aims and objectives: To evaluate biochemical and haemolytic markers of red blood cells transfused in three different, common type of syringe infusion pumps with two different infusion rates (10 and 100 ml/h).

Methods: A lab-based study using aliquots of 16 red blood cells bags was undertaken. Haemolysis markers (total haemoglobin(g/dl), haematocrit(%), free haemoglobin(g/dl), potassium(mmol/L), lactate dehydrogenase(U/L), osmolality(mOsm/kg), pH, degree of haemolysis(%)) were measured before and after red blood cells infusion and exposure. Three different syringe infusion pumps brands (A, B and C) were compared with two different infusion rates (10 and 100 ml/h).

Results: The total haemoglobin fell significantly in all red blood cells units during manipulation (Pre-infusion: 26.44±5.74; Post-exposure: 22.62±4.00; p=0.026). The degree of haemolysis significantly increased by 40% after manipulation of the red blood cells. Syringe infusion pump A caused a threefold increase in potassium levels (3.78±6.10) when compared to B (-0.14±1.46) and C (1.63± 1.98) (p=0.015). This pump also produced the worst changes, with an increase in free haemoglobin (0.05±0.05; p=0.038) and more haemolysis (0.08±0.07; p=0.033). There were significant differences and an increase in the degree of haemolysis (p=0.004) in the infusion rate of 100 mL/h.

Conclusions: Syringe infusion pumps may cause significant red blood cell damage during infusion, with increases in free haemoglobin, potassium and the degree of haemolysis. Some pumps types, with a cassette mechanism, caused more damage.

Relevance to clinical practice: In many ICUs, bedside nurses are able to consider infusion pump choice and understanding the impact of different pump types on RBC during a transfusion provides the nurses with more information to enhance decision-making and improve the quality of the transfusion.

Keywords: Infusion pumps; Syringe; Transfusion; Haemolysis; Paediatric Nursing.

Introduction

The transfusion of packed red blood cell (RBC) is common in critical care units, with the main objective to correct anaemia and increase the supply of oxygen to the tissues.[1] About 85% of patients admitted to an intensive care unit receive at least one blood transfusion after a week of hospitalization.[2] Although blood transfusion is a multiprofessional procedure, nurses usually assume responsibility for the administration and associated patient monitoring.[3]

Intravenous fluid administration should be delivered in a controlled manner to prevent accidental fluid overload.[4,5] Blood transfusion for neonates, children and patients with volume restrictions, presents particular risks and challenges and many countries mandate the use of controlled infusion devices, such as syringe infusion pumps (SIP).[6] SIP are electronic devices that control the volume of fluid being infused and are more accurate when compared to manual infusion systems. Additionally, they allow the controlled infusion of small volumes and low rates.[6] A wide variety of infusion devices are available, and the choice of device may affect the outcome of the procedure.

Despite their benefits, studies have shown that SIPs can cause red cell damage during blood administration, increasing the rate of haemolysis.[7]

Haemolysis is defined as the rupture of the RBC membrane, and can be classified as immune and nonimmune.[8] Nonimmune haemolysis occurs after manipulation and exposure of the cell by devices and equipment, which expose the components of the erythrocyte membrane to a shear stress, evolving to the loss of cell integrity and releasing haemoglobin and potassium into the plasma. This has potentially deleterious effects, mainly for the renal and cardiovascular systems.[6,9] The American Association of Blood

Banks (AABB) and the European guidelines limit the degree of haemolysis for each unit of packed RBC to 0.8%.[10]

In the renal system, free haemoglobin in plasma can cause obstruction and damage to the renal tubules and hemoglobinuria.[11,12] It may also inhibit nitric oxide (NO) in the bloodstream, leading to increased pulmonary and systemic vascular resistance, increased thrombus formation, fibrin deposition, and increased platelet aggregation.[13] It is known that levels from 0.01 g/dl already inhibit NO in the system.[13] The impact may be more deleterious on the pathology of critically ill children's. The release of potassium in plasma poses a risk of developing arrhythmias, muscle weakness, cardiorespiratory arrest and even death, especially in patients with volume restriction, associated heart problems, neonates and critically ill children.[14]

The objective of this study was to evaluate the biochemical and haemolysis markers of RBC transfused in three different brands of SIP with two different infusion rates. If differences exist, this may inform nurses' choice of SIP.

Design and Methods

A lab-based experimental study was conducted with 16 aliquots of A positive RBC units from different donors and of different blood ages.

The RBC units used had a mean of 15.59±7.42 days of storage, (minimum 3 days – maximum 30 days) and were categorized according to the storage time. The study used 4 (25.0%) RBC packs with a short storage time (up to 10 days), 7 (43.75%) RBC with medium storage time (from 11 to 21 days) and 5 (31.25%) RBC packs with long storage time (from 21 to 35 days).

Experimental procedures

RBC units were randomly (random Latin squares) allocated to study groups (by SIP, infusion rate and blood storage period). Three commonly used SIP brands were chosen to test (A, B and C) which have different pumping mechanisms, and three pumps of each of these brands were used, totalling nine pumps. The pumps were numbered and calibrated prior to the experiments.

SIP A had a cassette mechanism and a syringe can be coupled to the infusion set. The cassette mechanism consists of the infusion by means of piston drive. Such equipment has cassettes generally inserted into medial portion of the infusion set (Figure 1).

SIP B and C are devices in which the volume administered to the patient is stored through one or more syringes, and the syringe plunger is pushed by a movable piston controlled by the equipment, with flow selection by the operator and indicated in volume per unit of time on the equipment (Figure 1).

The RBC units were removed from the refrigerator (METALFRIO®) and subjected to room temperature, mimicking clinical practice, being temperature controlled by an infrared thermometer (MINIPA®) every 15 minutes during the experiments and the environments exposure time was inferior of 4 hours.

Insert Figure 1

Measurement and sampling points

When the RBC reached the target temperature of 18°C, the first sample, called Pre-infusion (T1), was collected. Thereafter, a gravity-drive infusion device was attached to the RBC bag and positioned on a support device 80cm above the distal line of the equipment outlet, to promote filtration of micro coagulants prior to aspirating the blood into the syringe. Then a 3-way connector was attached to the distal portion of the set to

promote aspiration of the blood into the syringe and extension set. After manual filling of the syringe and extension set, the second sample was collected and corresponded to Syringe Control (T2), where 5ml of blood was collected in the same way as T1. The syringe was then positioned on the selected infusion pump. The rate, 10 or 100mL/h, was programmed and RBC infusion was started. After the infusion corresponding to one and a half times the internal volume of the extension set (1.5 ml) at the chosen rate, the third sample, called Post-infusion (T3), was collected. Two hours after the infusion, a new sample called Post-exposure (T4) was collected in order to evaluate the influence of the infusion time and exposure of the RBC aliquot in the device. All samples were analysed for total haemoglobin (g/dL), haematocrit (%), free haemoglobin (g/dL), potassium (mmol/L), lactate dehydrogenase (LDH)(U/L), pH, the degree of haemolysis (%) and osmolality (OsM)(mOsm/kg), both across the sampling points and between T1 and T4.

Data analysis

Data were entered into an electronic database and analysed by software R 3.1.2. (R team®, 2012). Absolute differences were compared between T1 and T4 for this, using Anderson-Darling's normality test to verify the normality of data distribution. Normally distributed data was analysed used Student's t-test or ANOVA inferentially. Levene and Kruskal-Wallis tests were used on non-parametric data. Finally, we compared values across the four sampling points (T1, T2, T3 and T4). The change in haemolysis indicators through the steps of the experiment, was tested using the Friedman test. The Dunn (post-hoc) test for multiple comparisons was applied for the comparison between the different steps of the experiment. The level of significance adopted in the analyses was 0.05. Two-tailed tests were always used.

Ethical issues

The study was approved by our hospital ethics and research committee. The brands of the electronic devices were not disclosed in order to have a non-commercial partnership with the industries that collaborated with the research. The nine electronic devices studies, as well as the disposable infusions sets and syringes, were provided by the manufactures. It was agreed at the beginning, that each SIP manufacturer would receive the results, but the pump names would not be disclosed.

Results

Changes in RBC with manipulation across all devices

When the absolute difference across samples were compared, all three devices caused significant ($p=<0.005$) haemolysis of RBC, which increased by 40% from baseline level (T1: 0.09±0.05; T4: 0.15±0.07). The total haemoglobin fell significantly in all RBC units (across all infusion devices) after manipulation and infusion of the RBC (T1: 26.44±5.74; T4: 22.62±4.00; $p=0.026$). The absolute difference in levels of free haemoglobin did not show significant variations after the passage of blood through the infusion device. Potassium levels did not change significantly across the duration of sampling points, and there was little change in pH, LDH and osmolality across the sampling points. However, when comparing values across the four sampling points, there were significant changes in both haemolysis and total haemoglobin levels (Figure 2).

Insert Figure 2

Comparison of Infusion Devices

The infusion devices performed differently. When examining the absolute difference between T1 and T4 samples, one infusion device SIP A (which uses a cassette mechanism with a coupled syringe) produced significantly worse haemolysis (increase of 47% from baseline; SIPA: 0.08±0.07; SIPB: 0.05±0.05; SIPC: 0.04±0.06; p=0.033) and more increases in potassium (p=0.015), free haemoglobin (p=0.038) and LDH levels (0.016) (Table 1). SIP A produced the worst change, with a median increase of 47% in free haemoglobin, while SIP C produced the least modification, with a 12% increase (p=0.005). Osmolality significantly decreased with SIP A and B but increased with SIP C (p=0.017).

Comparing T1 to T4 samples across the three SIPs, there were also significant differences in the degree of haemolysis ($p<0.001$), potassium levels ($p<0.001$) and osmolality (p=0.049), with SIP A causing the most change (Figure 3). No significant alterations were seen with total haemoglobin, free haemoglobin, haematocrit, LDH and pH between the three SIPs.

Insert Table 1

Insert Figure 3

Impact of the infusion rate on RBC

No significant differences were found between infusion rates when compared the absolute difference between T1 and T4 samples.

Comparing pre infusion to post exposure samples across the two infusion rates, there were significant differences with increase in degree of haemolysis (p=0.004) in the infusion rate of 100 mL/h and drop of pH ($p<0.001$) in the infusion rate of 10 mL/h.

The impact of blood storage time on infused RBC

In general, total haemoglobin levels reduced after RBC manipulation, and this reduction was more pronounced in the RBC from units stored up to 10 days (short storage time), with no significant difference and probably associated to the higher level of total haemoglobin in RBC with short storage time (p=0.140). The absolute difference between T1 and T4 samples found significantly higher potassium levels (p=0.048) in samples of the medium stored time compared to the short storage bags (short: 0.12±1.19; medium: 2.65±5.47; long: 1.84±2.73). The pH also increased in the short-time storage bags (0.09±0.10) compared to the other storage time categories (p=0.034). Comparing pre infusion to post exposure samples across the three storage times, there were significant differences with increase in potassium (p=0.018).

Discussion

This is the first study to compare the effect of infusion pumps with a cassette and mobile piston on the RBC quality during and after blood infusion in a controlled set.

We observed a significant increase in free haemoglobin, potassium, LDH and the degree of haemolysis after the manipulation of RBC and infusion by SIPs, regardless of the type and the rate of infusion. This is consistent with a previous study which evaluated one brand of SIP (SIP C) at three different infusion rates (5, 10 and 20 ml/h).[7] This study also found a significant increase in potassium levels, LDH, free haemoglobin and the degree of haemolysis, in addition to a significant drop in total hemoglobin.[7] Frey and Eber[15], also compared the effect of three different SIP brands(with different pump mechanisms) on haemolysis during RBC infusion, and showed that the pump with a mechanism in which the plunger of the syringe is pushed by a piston caused greater

cellular damage in the RBC than the pump with a peristaltic mechanism, as demonstrated by a significant increase in free haemoglobin, potassium and LDH levels.[15]

Pumps with the syringe mechanism coupled to the cassette system caused greater cellular damage in all samples. The reason for this is unclear but may be related to the mechanism of delivery. The cassette mechanisms utilize reservoirs of known volumes in the medial portion of the device, with cylindrical reservoirs which are filled by the blood to be infused. The syringe is coupled to the equipment that delivers the fluid into the infusion pump. A piston moves in and out of each filling cylinder, delivering the blood to the patient. This contrasts with the pump system, where blood passes through structures that have a smaller diameter than the syringe, influencing the deformability and increased exposure of the RBC in the device.[16] A further study found that pumps with a cassette mechanism caused a greater increase in the degree of haemolysis during transfusion than pumps with a syringe mechanism.[17]

We found no statistically significant differences in RBC damage between the two infusion rates commonly used in paediatric practice. Previous studies comparing blood transfusion in infusion pumps at the rate of 5, 10.6 ml/h, 20 and 50 ml/h, showed that lower rates (5 and 10.6 ml/h) did cause significantly higher increase in levels of free haemoglobin and potassium when compared to the higher rates (20 and 50 ml/h).[17,18]

The RBC storage time was shown to be a variable that influenced cellular damage. In our study, samples with RBC stored for a medium duration (11-20 days) were more prone to increased potassium levels and decreased pH. The results are similar to another study, which demonstrated that RBC units with a longer storage times (over 25 days) had increased levels of potassium, free haemoglobin, as well as increased fragility of the cell membrane after manipulation by infusion pumps.[15,19,20] However, we did not find worse damage in the longest stored RBC (categorized as >20 days).

There are no previous studies that evaluate and compare the time of exposure of blood in the infusion system. This is important because it replicates clinical practice in paediatrics. Neonates and children receive infusions at small volumes per hour, and for this reason, the RBC are exposed for longer in the infusion system (manipulation and temperature). In our study these post-exposure samples showed greater damage to the cell, with significant increases in potassium, free haemoglobin and the degree of haemolysis when compared to the other samples. This may be clinically important, since the blood being infused into the patient will be exposed for a longer time to in the infusion system and will potentially alter the temperature of the infused RBC.

One alternative to the use of infusion pumps is to delivery RBC by manual macrodrops or microdrops infusion sets. A study demonstrated that also this equipment leads to haemolysis and microdrops sets increased the degree of haemolysis, after infusion, 3 times higher when compared to macrodrops sets. The biomarker free haemoglobin increased by 25% in the microdrop sets and by 12% in the macrodrop group.[21]

Despite the benefits of using a SIP, it is clear that all cause cell damage during blood transfusion. However, our study has shown that differences related to the mechanism of delivery may exist, which could reduce the degree of haemolysis. This may have important clinical implications for neonates and children due to their smaller body size, and rapid increase in haemolysis rate per kilogram of weight.[22] Children's kidneys are more immature, with a lower rate of glomerular filtration and, as a result, they may be predisposed to more complications than those of adults.[23,24]

In our study, free haemoglobin levels also significantly increased across the four sampling points and this may cause deleterious effects in critically ill neonates and

children.[25] Excess potassium in the plasma may also cause adverse effects in critically ill children.[26-28]

Although we found all infusion pumps caused cell damage, the degree of haemolysis did not exceed the limits allowed by the AABB and European guidelines recommendations, which recommend 0.8%[10]. However, the effects of this on patients' clinical outcomes are currently unknown.

Limitations

This study has a few limitations that warrant mentioning. We were not able to control for the length of storage time of the RBC we received from the blood bank. Therefore, we had differing amount of RBC packs between the three storage times. In addition, this study was laboratory based, meaning we did not examine the outcome and potential implications of transfused RBC given by different SIPs in critically ill children, this should be the next phase of research in this area.

Relevance to clinical practice

Infusion pumps are among the most commonly used devices in healthcare and are used in 90% of patients admitted to intensive care units to increase patient safety.[29,30]

The critical care nurse needs to be aware of these effects when choosing the infusion device to administer RBC. In addition, senior nurses may have influence over hospital administrators when making decisions about infusion device purchasing and these effects should be taken into consideration. Therefore, knowledge of the impact of the SIP on RBC, is of paramount importance. Clinicians and clinical engineers involved in the decision-making around pump selection also need to be aware of these findings to minimize RBC damage.

Conclusions

This lab-based study showed that syringe infusion pumps cause significant changes in biochemical and haemolysis markers of red blood cell during infusion, with increases in free haemoglobin and potassium. There was a statistically significant change in the degree of haemolysis after infusion and blood exposure, but the values remained within the acceptable standards of degree of haemolysis (minus 0.8%). Importantly, some pumps, namely those with a cassette mechanism, caused more RBC damage. This research is highly relevant to intensive care nurses, as it provides evidence to guide the nurses' choice infusion device at the time of transfusion.

What is already known

- Previous studies exist regarding haemolysis due to different mechanisms of syringe infusion pumps.
- They show damage to red blood cells during infusion with the use of infusion pumps with different infusion mechanisms (syringe, peristaltic and rotary).

What this study adds

- The choice of infusion pump for blood transfusion may have an impact on the degree of haemolysis, since syringe infusion pumps with cassette mechanism cause greater haemolysis and increased markers of haemolysis after infusion and exposure of red blood cell.
- The infusion rate did not directly influence the quality of red blood cells during transfusion.

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Table 1 - Absolute difference in levels of biochemical markers and degree of haemolysis between Pre-infusion and Post-exposure, according to SIP brands.

Markers	SIP A (n=18)		SIP B (n=18)		SIP C (n=18)		P value
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	
Total HB (g/dL)	-5.34±6.16	-18.45 – 1.19	-3.93±5.61	-11.89 – 10.61	-2.18±5.99	-18.18 – 3.91	0.122[a]
Free HB (g/dL)	0.05±0.05	0 – 0.19	0.03±0.03	-0.02 – 0.09	0.02±0.03	-0.02 – 0.08	0.038[a]
HT (%)	-1.06±2.65	-5 – 5	-1.28±3.59	-11 – 3	-1.67±3.07	-8 – 3	0.656[a]
Degree of Haemolysis (%)	0.08±0.07	0.01 – 0.28	0.05±0.05	-0.06 – 0.17	0.04±0.06	-0.01-0.24	0.033[a]
Potassium (mmol/L)	3.78±6.10	-1.95-19.15	-0.14±1.46	-4.97 – 2.03	1.63±1.98	-1.18 – 7.56	0.015[c]
LDH (U/L)	108.83±559.85	-272.53 – 2285.49	134.47±299.77	-78.25 – 1276.31	38.23±210.68	-248.24 – 474.90	0.016[a]
pH	0.02±0.05	-0.09 – 0.17	0.06±0.08	-0.08 – 0.22	0.04±0.12	-0.27 – 0.20	0.039[c]
OsM (mOsm/kg)	-1.06±10.36	-12 – 35	-2.61±4.59	-10 – 5	2.11±4.86	-6 – 11	0.017[a]

Subtitle: SIP– Syringe Infusion Pump; Total HB – Total Haemoglobin; Free HB – Free Haemoglobin; HT – Haematocrit; LDH – Lactate Dehydrogenase; pH – Hydrogen ion potential; OsM – osmolality; a –Kruskal-Wallis test; c – Levene test.

Figure 1