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ORIGINAL ARTICLE

EX VIVO ANALYSIS OF PACKED RED BLOOD CELL HEMOLYSIS DURING TRANSFUSION BY PNEUMATIC PRESSURE BAGS

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ABSTRACT

Objective: to investigate markers of red cell hemolysis in stored blood infused by pneumatic pressure bags under a pressure of 300 mmHg. **Methods:** *ex vivo* experimental study simulating the clinical practice of massive packed red blood cell transfusion by pressure bags. The experiments were carried out under controlled conditions in a laboratory and the levels of hemolysis markers [total hemoglobin (g/dL), hematocrit (%), free hemoglobin (g/dL), potassium (mmol/L), lactate dehydrogenase (U/L) and degree of hemolysis (%)] were assessed before device inflation (control), and immediately, one and two hours after inflation under a pressure of 300 mmHg. Data were analyzed with parametric and non-parametric tests and the significance level was set at 5%. **Results:** the analysis showed increased free hemoglobin level (p=0.004) and hemolysis ratio (p=0.004) immediately after compression, increased lactate dehydrogenase one hour after compression (p=0.020), and decreased total hemoglobin (p=0.002) two hours after compression, without significant variations in potassium or hematocrit levels. **Conclusion**: the use of pressure bags for infusion of red blood cells caused alterations in hemolysis markers mainly after two hours of compression.

Keywords. Hemolysis. Blood Transfusion. Emergency. Patient Safety. Red Blood Cells.

INTRODUCTION

Blood transfusion is a well-known therapeutic intervention for saving lives and is one of the most common procedures performed in trauma patients. Also, transfusion of packed red blood cells (pRBCs) for surgical and critically ill patients is essential for health maintenance and the only treatment strategy in certain life-threatening situations[1]. Additionally, there are evidences of the relevance of protocols addressing massive transfusion for major bleeding in trauma, demonstrating the benefits in reducing mortality[2,3].

Although significant advances have been achieved regarding safety of blood products, the relevant change in transfusion technologies — including the use of different catheters and manual or electronic infusion devices — have raised concern in relation to mechanical trauma that such devices may cause in cell integrity [1,4,5].

In emergency situations in which there is massive hemorrhage, devices for liquid infusion with a 300 mmHg pressure bag are used for rapid administration of parenteral fluids, including pRBCs[5,6]. During surgery of patients with high risk of hemorrhage, pRBCs can be subjected to pressure for prolonged periods of

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time until infusion.

Studies are controversial as to whether high external pressure application results in increased levels of hemolysis in the transfused blood[5-9]. The pressure exerted by the device may increase the shear stress and the turbulent flow during the infusion, facilitating the rupture of the erythrocyte membrane[6]. Transfusion of hemolyzed blood products may result in fever, renal failure, hypotension, and disseminated intravascular coagulation[5,6].

Once any additional pressure exerted on the red blood cell membrane has the potential to cause hemolysis, and practice guidelines do not provide indications regarding the optimal pressure or the maximum time such pressure can be applied, studies are necessary to clarify how much additional pressure can influence the pRBC quality.

Thus, the objective of this study was to investigate the markers of hemolysis in pRBCs infused by inflatable pneumatic systems under a pressure of 300 mmHg immediately, one hour and two hours after inflation.

METHODS

Study design

This is an *ex vivo* experimental study simulating the clinical practice of massive pRBCs transfusion by pressure bags, under controlled humidity and temperature conditions.

The study was carried out in the Laboratory of Nursing Experiments (Laboratório de Experimentos de Enfermagem, LEEnf) of the Escola Paulista de Enfermagem da Universidade Federal de São Paulo, Brazil, by professors and graduate and undergraduate students.

Ethical considerations

The study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (number 56518, CAAE 04061812.0.0000.5505).

Samples

The experiments were randomly carried out with nine pRBC bags, A positive blood type, preserved with citrate-phosphate-dextrose-adenine (CPDA-1) anticoagulant solution, with an average storage time of 15.3 (±9.8) days, donated by the Associação Beneficente de Coleta de Sangue (COLSAN) in São Paulo, Brazil, due to excess storage (Type A positive) or close expiration date.

Three pneumatic systems, also called pressure bags, were used for infusion of pRBCs. They consisted of a reusable transparent polyurethane clear-cuff pressure bag with a hook for attachment to serum support; a manual inflatable rubber bulb, a metal manometer in mmHg scale (accuracy ± 0.5 mmHg), a transparent PVC tube, and a polyethylene valve.

Levels of hemolysis markers were assessed in four phases: direct control of the pRBCs bag (C) before manipulation; immediately after being subjected to pressurization at 300mmHg (E1); one hour after compression (E2), and two hours after compression (E3).

The collection phases of hemolysis markers were chosen based on the protocols for the pressure bag for pRBCs infusion in emergency situations, when rapid administration of blood is indicated. These protocols are also indicated to patients undergoing surgical interventions and receiving critical care in which there may be prolonged exposure of blood components.

Experimental design

In the beginning of the experiments, the pRBC bag was removed from the refrigerator and exposed to room temperature. Then, to obtain the first blood sample - Control (C) - the lateral seal of the bag was broken and blood was collected in a dry test tube. Then the bag was connected to the intravenous set (specific device for blood transfusion with 180-micron filter), the air was removed by free flow, and the bag was introduced in the pneumatic pressure system, inflating it until 300 mmHg of pressure. The infusion set was placed on a serum support at a height of 80 cm from the bench (mimicking the patient's bed height in clinical practice). The sample E1 was collected after priming: one and a half of the internal volume of the intravenous set was disregarded to ensure the blood was obtained from the bag under pressure.

The infusion system was maintained closed

and pressurized, with periodic checks of the pressure level at 1 hour and 2 hours of compression, when blood samples were collected, respectively, for the E2 and E3 tests. Before collections of all samples, one and a half of the internal volume of the intravenous set was disregarded .

Hemolysis marker analysis

The influence of the pressure exerted by the bag on the pRBCs was assessed by analyzing the total hemoglobin (g/dL), hematocrit (%), free hemoglobin (g/dL), potassium (mmol/L), lactate dehydrogenase (LDH; U/L), and degree of hemolysis (%).

Hematocrit was measured by pouring the pRBC sample into a non-heparinized capillary tube and centrifuging it in a microhematocrit centrifuge model MH (Celm®) for four minutesat 3.600 rpm, and then the reading was performed.

A total amount of 1 mL of the sample was collected in a disposable test tube and subjected to spectrophotometry (Biospectra®) by colorimetry with reading at 540 nm, based on the Methemoglobin-Cyanide methodology for analysis of total hemoglobin (g/dL).

The measurement of free hemoglobin (g/dL) was performed based on the pRBC sample collected in a clot activator tube at an approximate volume of 5 mL. This sample was subjected to centrifugation at 3.600 rpm for 15 minutes in the bench centrifuge (model K14-4000 by KASVI®) for collection of the supernatant, subsequently subjected to spectrophotometry with 370, 415, 510, 577, and 600 nm wavelengths.

The degree of hemolysis (%) was calculated based on the results obtained in the previously described analyses with the equation: [free hemoglobin (g/dL) × 100 – hematocrit (%)]/total hemoglobin (g/dL)[10,11].

The potassium dosage was made based on the blood sample collected in a clot activator tube, subjected to centrifugation at 3.600 rpm for 15 minutes in the bench centrifuge (model K14-4000, KASVI®). The colorimetric method was used to determine potassium in serum with the modified Tetraphenylborate methodology (Doles®) in spectrophotometry at 580 nm.

The LDH enzyme was dosed in U/L by the kinetic method, and the analysis was performed by spectrophotometry at the 340 nm wavelength in the 1st, 2nd, 3rd and 4th minute after the mixture of 40 µL of serum and 2 mL of the reagent (KOVALENT®).

Statistical Analysis

Descriptive and inferential statistics were presented in tables. Continuous variables were calculated by the mean and median, maximum and minimum values, and standard deviation. The Anderson-Darling and Kolmogorov-Sminorv tests were used to check the normality of the distribution of the data. The parametric *t*-test, Friedman test or Analysis of variance (ANOVA), and the nonparametric Mann-Whitney, Levene, Kruskal-Wallis and Tukey tests were applied. The R 3.1.2. (R Team®, 2012) software was used in the analysis. Results with error probability of less than 5% were considered statistically significant.

RESULTS

A total of nine pRBC bags were analyzed. Mimicking situations of clinical practice, the markers of hemolysis were analyzed in four moments, totaling 36 analyses, which are shown in Table 1.

Table 1. Markers of red cell hemolysis in stored blood infused by pneumatic pressure bags: control before infusion (C), immediately after priming and pressure (E1), and after one hour (E2) and two hours (E3) of pressurization.

Hemolysis Markers	**Study phases**						
	C						
	Mean	SD‖	SE¶	Median	IQ**	Min††	Max‡‡
Total Hemoglobin (g/dL*)	29.64	5.93	1.98	27.79	3.73	23.53	42.1
Free Hemoglobin (g/dL*)	0.08	0.06	0.02	0.04	0.1	0.03	0.18
Hematocrit (%)	74.67	5.34	1.78	75	4	66	86
Hemolysis (%)	0.06	0.05	0.02	0.04	0.05	0.03	0.18

Potassium (mmol/L†)	35.62	9.86	3.29	35.79	13.54	24.05	55.45
LDH‡ (U/L§)	518.68	417.96	139.32	315.7	763.63	110.63	1157.59
	E1						
Total Hemoglobin (g/dL*)	25.86	2.43	0.81	26.99	3.14	22.09	28.49
Free Hemoglobin (g/dL*)	0.13	0.09	0.03	0.12	0.15	0.03	0.28
Hematocrit (%)	74.33	5.39	1.8	75	2	66	86
Hemolysis (%)	0.13	0.09	0.03	0.11	0.16	0.03	0.27
Potassium (mmol/L†)	36.08	9.22	3.07	35.63	12.65	26.55	55.09
LDH‡ (U/L§)	2212.33	4961.29	1653.76	407.45	822.99	218.56	15404.78
	E2						
Total Hemoglobin (g/dL*)	25.27	3.39	1.13	24.63	1.32	21.35	32.71
Free Hemoglobin (g/dL*)	0.17	0.11	0.04	0.24	0.19	0.05	0.3
Hematocrit (%)	73.11	5.67	1.89	73	5	67	86
Hemolysis (%)	0.19	0.14	0.05	0.11	0.26	0.05	0.39
Potassium (mmol/L†)	35.92	9.35	3.12	34.59	12.12	26.45	55.75
LDH‡ (U/L§)	2176.66	4673.42	1557.81	466.81	701.57	250.94	14603.38
	E3						
Total Hemoglobin (g/dL*)	25.69	3.14	1.05	24.84	1.27	22.75	32.47
Free Hemoglobin (g/dL*)	0.21	0.14	0.05	0.28	0.26	0.06	0.38
Hematocrit (%)	73.89	5.93	1.98	74	5	67	87
Hemolysis (%)	0.21	0.15	0.05	0.12	0.28	0.06	0.41
Potassium (mmol/L†)	35.72	9.81	3.27	33.91	13.2	25.72	56.04
LDH‡ (U/L§)	2004.55	4474.23	1491.41	491.1	793.31	10.67	13891.02

Legend: *g/dL=grams per deciliter; †mmol/L=millimoles per liter; ‡LDH= lactate dehydrogenase; §U/L=unit per liter; ||SD=Standard Deviation; ¶SE=Standard Error; **IQ=Interquartile Range; ††Min= Minimum Value; ‡‡Max=Maximum Value

The descriptive analysis demonstrated a decrease in mean total hemoglobin and hematocrit and an increase in free hemoglobin, degree of hemolysis and LDH levels, with less variation in potassium levels. Table 2 shows the inferential comparison between levels of hemolysis markers in the studied phases of data collection.

Table 2. Comparison of markers of red cell hemolysis in stored blood infused by pneumatic pressure bags between the studied periods - before infusion (C), after priming and pressure (E1), and after one hour (E2) and two hours (E3) of pressurization.

Hemolysis markers	Hypothesis	P
Total Hemoglobin (g/dL*)	E1=C	0.055‖
	E2=C	0.055¶
	E3=C	0.020¶
Free Hemoglobin (g/dL*)	E1=C	0.004¶
	E2=C	0.004¶
	E3=C	0.004¶
Hematocrit (%)	E1=C	0.674‖
	E2=C	0.228‖
	E3=C	0.458‖
Hemolysis (%)	E1=C	0.004¶
	E2=C	0.004¶
	E3=C	0.004¶
Potassium (mmol/L†)	E1=C	0.355‖
	E2=C	0.521‖
	E3=C	0.830‖
LDH‡ (U/L§)	E1=C	0.109¶
	E2=C	0.020¶
	E3=C	0.203¶

Legend: *g/dL=grams per deciliter; †mmol/L=millimoles per liter; ‡LDH= lactate dehydrogenase; §U/L=unit per liter; ||Paired t-test; ¶Paired Mann-Whitney test

The levels of free hemoglobin (p=0.004) and hemolysis ratio (p=0.004) had a significant increase when phases C and E1 were compared to C and E2. Some significant changes were

observed in free hemoglobin (p=0.004), hemolysis (p=0.004) and LDH (p=0.020). The comparison between C and E3 shows a significant variation in the levels of free hemoglobin (p=0.004), hemolysis (p=0.004) and total hemoglobin (p=0.020), as shown in Table 2.

DISCUSSION

The results demonstrated increased in levels markers of hemolysis in pRBC after infusion. The time of exposure of pRBCs to pressure—maintained at 300 mmHg —influenced the degrees of hemolysis markers, a result with relevant clinical significance considering protocols for practices in emergency and surgical procedures.

In this study, when the maximum values were assessed, a degree of hemolysis above 0.8% was found; however, the mean values were in accordance with the quality control recommendations for blood banks. Standardization proposes that 1.0% of the blood components produced by hemotherapy services must undergo quality control in laboratory[11]. This standardization also establishes a maximum hemolysis level of 0.8% for pRBCs, and the calculation of free hemoglobin and hematocrit. The other hemolysis markers investigated in this study are not included in the main protocols of pRBC quality control[11-14].

Free hemoglobin level is the most specific marker, and the acceptable levels of free hemoglobin in blood range between 5 and 10 mg/dL, but values higher than those have been measured in the manipulation of pRBCs[15].

A study states that a free hemoglobin level of 100 mg/dL is the maximum limit to avoid body damage[16]. Free hemoglobin in the blood causes — even at lower levels depending on the patient's clinical situation — the inhibition of nitric oxide release, resulting in systemic and pulmonary vasoconstriction, which increases platelet aggregation and the risk of thrombosis. Moreover, excess of free hemoglobin in the bloodstream may result in kidney injury during the glomerular filtration process[15-17].

Our data demonstrated a constant increase of free hemoglobin levels with the time of exposure to pressure and variation of free hemoglobin levels even in the control samples, probably due to the large variation of storage time of the studied pRBCs.[18]

This result is in line with the risk analysis of the transfusion process, since pRBC bags which already had altered levels of free hemoglobin showed increased values in some experiments carried out with the studied infusion systems. Therefore, there is no consensus regarding the reference value for free hemoglobin, since different results, guidelines and type of solution are presented by authors, making comparisons difficult[15,19].

Studies on hemolysis during blood transfusion have mainly addressed electronic devices of infusion, and catheters' calibers and types of, and some processes of erythrocyte manipulation, such as washing, reduction of leukocytes, and cell irradiation. Moreover, some studies have shown significant changes in hemolysis ratio and other parameters such as free hemoglobin and hemolysis level[19-23].

Infusion devices can lead to hemolysis during pRBC transfusions, and thus research on this topic is necessary. Comparing our results with previous findings reported in the literature, the levels of free hemoglobin and degree of hemolysis after pRBC infusion were worse when infusion pumps and manual infusion sets were used than when pneumatic pressure bags were used[23-26].

A study in South Africa that compared the effects of pneumatic pressurization and manual syringing on hemolysis in pRBCs showed that free hemoglobin concentrations ranged between 0.03 and 0.08 g/dL and degree of hemolysis range between 0.09 and 0.17% in the control. After pressurization experiments, free hemoglobin levels changed to 0.05 and 0.09 g/dL and hemolysis levels to 0.12 and 0.22%. After syringing, free hemoglobin was found to be between 0.38 and 0.92 g/dL and hemolysis between 1.03 and 2.15%; cannula sizes did not affect hemolysis[25]. The storage time in this experiment was 12.3 ± 4.3 days. Another study evaluated hemolysis markers after pRBC transfusion in infusion sets of drop and microdrop, the degree of hemolysis showed maximum values of 0.90% after infusion using these devices[27].

Variations between 0.03 and 0.38 g/dL in free hemoglobin and between 0.03 and 0.41% in the

degree of hemolysis were observed in the present study, with an average storage time of 15.3±9.8 days. Also, despite the high storage time, the level of potassium did not present significant variations resulting from to the proposed intervention.

Therefore, despite causing significant changes in free hemoglobin and hemolysis, the use of pressurizers during blood transfusion should not cause too much concern, as it happens in the use of syringe pressure. However, the procedure may become risky depending on other factors, such as the patient's clinical condition and RBC storage time.

An important aspect to address is the time of exposure of the pRBCs to pressure. Our study demonstrated that the level of free hemoglobin presented constant increases across time, and the level of total hemoglobin decreased after two hours; thus, we recommend the infusion of pRBCs immediately after initiation of pressurization.

The study has a limitation regarding the analysis of the impact of the identified variations on patient outcomes during pRBC transfusions. The identification of a more appropriate device to be used in pRBC transfusion is fundamental because the patient's clinical condition may have deleterious effects on the high free hemoglobin and hemolysis levels of pRBCs and massive transfusions can significantly decrease mortality in trauma patients,. So, this is an open field for technological advancement that will contribute to patient safety during rapid massive transfusion procedures in emergency situations.

CONCLUSION

The use of inflatable pneumatic systems under a pressure of 300 mmHg for pRBC infusion caused alterations in hemolysis markers, mainly increasing free hemoglobin and hemolysis and decreasing total hemoglobin after two hours of compression. The exposure time significantly increased LDH levels.

ANÁLISE EX VIVO DE HEMÓLISE DE CONCENTRADOS DE GLÓBULOS VERMELHOS DURANTE INFUSÃO POR BOLSAS PRESSURIZADORAS

RESUMO

Objetivo: verificar o nível de marcadores de hemólise de concentrados de glóbulos vermelhos infundidos por bolsas pressurizadoras sob pressão de 300 mmHg. **Método**: estudo experimental *ex vivo* simulando a prática clínica de transfusão maciça de concentrados de glóbulos vermelhos por bolsas de pressão pneumática. Os experimentos foram conduzidos em condições controladas em laboratório e os níveis dos marcadores de hemólise (hemoglobina total (g/dL), hematócrito (%), hemoglobina livre (g/dL), potássio (mmol/L), lactato desidrogenase (U/L) e o grau de hemólise (%) foram avaliados antes da insuflação do dispositivo (controle) e imediatamente, uma e duas horas após a insuflação sob pressão de 300 mmHg. Os dados foram analisados de acordo com testes paramétricos e não paramétricos e o nível de significância adotado foi de 5%. **Resultados**: A análise demonstrou aumento no nível de hemoglobina livre (p=0,004) e grau de hemólise (p=0,004) imediatamente após a compressão, aumento da lactato desidrogenase com uma hora de compressão (p=0,020) e diminuição da hemoglobina total (p=0,002) após duas horas de compressão, sem variações significativas nos níveis de potássio ou hematócrito. **Conclusão**: O uso de sistema pneumático inflável para infusão de hemácias provocou alterações nos marcadores de hemólise principalmente após duas horas de compressão.

Palavras-chave. Hemólise. Transfusão de Sangue. Emergência. Segurança do Paciente. Eritrócitos.

ANÁLISIS *EX VIVO* DE HEMÓLISIS DE CONCENTRADOS DE GLÓBULOS ROJOS EN INFUSIÓN POR BOLSAS PRESURIZADAS

RESUMEN

Objetivo: comprobar el nivel de marcadores de hemólisis de concentrados de glóbulos rojos infundidos por bolsas presurizadas bajo presión de 300 mmHg. **Método**: estudio experimental *ex vivo* que simula la práctica clínica de transfusión masiva de concentrados de glóbulos rojos por bolsas presurizadas. Los experimentos se realizaron en condiciones controladas en laboratorio y los niveles de marcadores de hemólisis hemoglobina total (g/dL), hematocrito (%), hemoglobina libre (g/dL), potasio (mmol/L), lactato deshidrogenasa (U/L) y el grado de hemólisis (%) fueron evaluados antes de inflar el dispositivo (control) e inmediatamente, una y dos horas después. Los datos fueron analizados de acuerdo con pruebas paramétricas y no paramétricas y el nivel de significación adoptado fue de 5%. **Resultados**: el análisis demostró un aumento en el nivel de hemoglobina libre (p=0,004) y grado de hemólisis (p=0,004) inmediatamente después de la compresión, aumento de lactato

deshidrogenasa con una hora de compresión (p=0,020) y disminución de la hemoglobina total (p=0,002) tras dos horas de compresión, sin variaciones significativas en los niveles de potasio o hematocrito. **Conclusión**: el uso de bolsas presurizadas para infusión de hematíes provocó alteraciones en los marcadores de hemólisis, sobre todo, después de dos horas de compresión.

Palabras clave: Hemólisis. Transfusión de Sangre. Emergencia. Seguridad del Paciente. Eritrocitos.

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