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ORIGINAL

Biochemical changes in the patient's plasma after red blood cell transfusion

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ABSTRACT

Introduction. The study aimed at in vivo *assessment of the impact of administered red blood cells (RBCs) concentrates on the plasma levels of K+, lactate, pH, Na+, Ca++ and glucose, depending on the volume and age of administered products. Biochemical changes occurring during the storage of these products were studied* in vitro *simultaneously.*

Materials and methods. Arterial blood samples were collected in vivo *from patients before and after RBCs transfusion and plasma levels of biochemical parameters were determined. A group of 80 RBCs samples was analyzed simultaneously, with the samples being equally distributed throughout the recommended storage time of 1–35 days.*

Results. The age of RBCs concentrate results in increased potassium and lactate levels and decreased pH, sodium and glucose levels in the RBCs samples. The concentrations were in the following ranges: potassium 4.0–40.5 mmol/L; lactate 4.1–28.0 mmol/L; pH 7.0–6.65; sodium 137–116 mmol/L; glucose 29.0–14.0 mmol/L. A prospectively selected group of 46 patients were administered a total of 354 RBCs units. The mean age of RBCs concentrates was 16.18 days. The number of administered RBCs units ranged from 2 to 38, a mean of 7.7 RBCs units/patient. The administration of 1 RBCs unit was associated with a mean in vivo *increase of the potassium level by 0.07 mmol/L and lactate level by 0.13 mmol/L.*

Conclusion. The administration of larger amounts of RBCs concentrates may lead to an increase in the patient's plasma levels of potassium and lactate. This increase is proportional to the age and volume of RBCs.

Key words: red blood cells, transfusion, hyperkalemia, lactate

Introduction

Acute bleeding is frequently associated with the need for transfusion of blood derivatives, especially red blood cells (RBCs). The administration of transfusion products containing cellular elements poses many risks and potential adverse effects. Due to the gradual decomposition of RBCs and as a result of the accumulation of products of cellular metabolism, i.e. anaerobic glycolysis, the biochemical composition of RBC concentrates changes. In particular, there is an increase in K^+ and lactate levels and a simultaneous decrease in pH, glucose and Na^+ levels. The storage time has no impact on Ca^{++} levels in the RBC concentrate.

The changes are proportional to the storage time. (1) Large-volume RBC transfusion may contribute to changes in the patients' plasma biochemical parameters (hyperkalemia) and may therefore be related not only to the volume of RBC products but also to storage duration. (2) Other changes include a reduction in red blood cell deformability, altered red blood cell adhesiveness and aggregability, and a reduction in 2,3-diphosphoglycerate and ATP. Bioactive compounds with proinflammatory effects also accumulate in the storage medium. These changes reduce posttransfusion viability of red blood cells. The clinical effects beyond posttransfusion viability are uncertain, but a growing body of evidence suggests that the storage lesion may reduce tissue oxygen availability, have proinflammatory and immunomodulatory effects, and influence morbidity and mortality. (3)

Objectives

The study aimed at *in vivo* assessment of the impact of administered RBC concentrates on the levels of selected biochemical parameters (K^+, lactate, pH, Na^+, Ca^{++}, glucose), depending on the volume and age of administered products. At the same time, biochemical changes occurring during the storage of these products were studied *in vitro*.

Materials and Methods

Given the methods of data collection, ethics committee approval for the study protocol was not needed.

In a prospectively selected group of 46 patients needing RBC replacement and transfused with RBCs with various storage times, arterial blood samples were analyzed. The plasma levels of K^+, lactate, pH, Na^+, Ca^{++} and glucose were measured before and after the administration of RBC products. The samples were obtained by collecting 0.5 mL of blood from the patients' arterial catheters using the Marquest Quik Arterial Blood Gas (ABG) sampler. The samples were analyzed on a Nova Biomedical Stat Profile CCX combined acid-base analyzer. Excluded were patients with renal failure (furosemide diuresis, urea $>$ 20 mmol/L, creatinine $>$ 300 μmol/L, dialysis), manifest hepatic insufficiency (liver transaminases elevated to more than double the normal value, bilirubin $>$ 25 μmol/L) and those receiving noradrenaline at a dose $>$ 0.1 μg/kg/min to support their circulation. Also excluded were patients who were administered sodium bicarbonate during the study period or potassium chloride to treat their initial hypokalemia.

At the same time, samples of RBCs administered to patients were prospectively studied. From a total of 354 RBC units (bags) administered to the patients, 80 units were sampled according to the length of storage in the blood bank to equally cover the entire recommended shelf time. The obtained data were plotted to show the dependence of the studied biochemical parameters (K^+, lactate, pH, Na^+, Ca^{++} and glucose) in stored RBC products on their age. All the analyzed samples of RBC units met the following criteria: volume of 280$\pm$50 mL, Hb $>$ 43 g/U, HCT 50-70%, white blood cells (WBC) $< 1.2\times10^9$/L, platelet count $< 20\times10^9$/L, plasma proteins $<$ 2 g/L. Although the expiration time of RBC products was up to 42 days, they were recommended to be used no later than 35 days from collection. (4) The study was carried out in the inpatient ward of the Department of Anesthesiology, Resuscitation and Intensive Medicine, University Hospital Olomouc. The RBC concentrates were stored in the blood bank under normal conditions at 2-6 °C and were delivered to the patient's bed in an insulated box. Within 2 minutes from the removal and careful mixing of the content of the transfusion bag, a 0.5 mL sample of the RBC concentrate was taken using the Marquest Quik ABG sampler and analyzed on a Nova Biomedical Stat Profile CCX combined acid-base analyzer. The obtained samples were used to determine the dependence of changes in the studied parameters on the age of products. To preserve 1 RBC concentrate unit of the studied samples, 20 mL of SAGM (Sodium chloride-Adenine-Glucose-Mannitol) solution and 100 mL of CPD (Citrate-Phosphate-Dextrose) solution were used (for the composition of both solutions see table 1).

The impact of frequency of administration and length of previous storage of RBC units on the plasma levels of biochemical parameters was assessed *in vivo*.

The results were analyzed by the parametric paired t-test and non-parametric paired Wilcoxon test. Correlation between the number of administered RBC units and increase in potassium and lactate levels was demonstrated by the Spearman correlation coefficient. Regression analysis was used to fit curves showing the dependence of plasma concentrations of individual biochemical parameters on the amount of RBCs administered.

Results

The *in vitro* group comprised 80 RBC unit samples stored for 1–35 days. The analyzed samples were equally distributed throughout the interval so that on each day of storage in the blood bank, two samples were examined.

1. There was a steady increase in K^+ levels in the RBC concentrate depending on the storage time (table 2, figure 1).
2. There was a gradual decrease in the pH of the RBC concentrate depending on the storage time (table 2, figure 2).
3. There was a steady increase in lactate levels in the RBC concentrate depending on the storage time (table 2, figure 3).
4. There was a decrease in Na^+ levels depending on the storage time (table 2, figure 4).
5. The storage time had no impact on Ca^{++} levels in the RBC concentrate (table 2).

The *in vivo* group comprised 46 patients, of whom 31 (67.4%) were males with a mean age of 56.97 years and 15 (32.6%) were females with a mean age of 57.66 years. The stratification of the group according to diagnosis was as follows: surgical bleeding in 18 patients (39%) and traumatic bleeding in 28 patients (61%). The patients were administered a total of 354 RBC units, a mean of 7.71 RBC units/patient, a median of 6.3 RBC units/patients, range 2–38 RBC units/patient. The mean storage time prior to administration was 16.18 days, a median of 15.8 days. Women received a mean of 6.33 RBC units/patient (a mean storage time of 15.78

Table 1. Composition of RBC (red blood cell) preservation solutions.

100 mL of CPD solution contain	
citric acid (anhydrous)	0.299 g
sodium citrate (dihydrate)	2.63 g
monobasic sodium phosphate (monohydrate)	0.222 g
dextrose (monohydrate)	2.55 g
water for injections	q.s.
100 mL of SAGM solution contain	
dextrose (monohydrate)	0.900 g
sodium chloride	0.877 g
mannitol	0.525 g
adenine	0.0139 g

days) and males were given 8.38 RBC units/patient on average (a mean storage time of 16.33 days).

6. Increased potassium levels were noted in 34 (74%) patients (a mean of 8.47 RBC units/patient, a mean storage time of 16.32 days). In 7 (15%) patients, the increase led to hyperkalemia (a mean of 11.85 RBC units/patient, a mean storage time of 16.78 days). Severe hyperkalemia was observed in 1 patient who had received 38 RBC units (a mean storage time of 18.62 days), with the potassium level rising from 4.0 mmol/L to 7.3 mmol/L (table 3). Four (9%) patients had their potassium levels unchanged (a mean of 2.75 RBC units/patient, a mean storage time of 14.63 days). Potassium levels decreased in 9 (20%) patients (a mean of 6.0 RBC units/patient, a mean storage time of 11.74 days).

It was calculated that in the studied group, the administration of a mean of 7.71 RBC units/patient resulted in an increase in the potassium level by 0.54 mmol/L. That is, the administration of 1 RBC unit was associated with a mean *in vivo* increase of the potassium level by 0.07 mmol/L.

Statistical analysis revealed moderate positive correlation between the number of administered RBC units and the changes in K^+ levels. The increase was statistically significant ($P = 0.0002$) (table 4, figure 5).

7. There was a statistically significant difference in lactate levels between genders. Increased lactate levels were observed in 28 (61%) patients. Of those, 21 (46%) were males (a mean of 10.72 RBC units/patient, a mean storage time of 15.46 days) and 6 (13%) were females (a mean of 8.83 RBC units/patient, a mean storage time of 15.05 days). There was a decrease in lactate levels in 8 (17%) males (a mean of 4.88 RBC units/patient, a mean storage time of 15.79 days) and 9 (20%) females (a mean of 4.66 RBC units/patient, a mean storage time of 16.09 days). Two (5%) males were shown to have no changes in lactate levels (a mean of 2 RBC units/patient, a mean storage time of 20 days). It was calculated that the administration of 1 RBC unit was *in vivo* associated with a mean increase in lactate levels by 0.2 mmol/L in males and with a mean decrease by 0.06 mmol/L in females. Statistical analysis showed moderate positive correlation between the number of administered RBC units and the changes in lactate levels. The increase was statistically significant ($P = 0.01$) (table 4). The non-parametric Mann-Whitney test showed significantly smaller changes in lactate levels in females than in males. On average, lactate levels rose by 1.52 mmol/L (a median of 1.0 mmol/L) in males and dropped by 0.16 mmol/L (a median of -0.1 mmol/L) in females.

8. No statistically significant changes were observed in pH, Na^+, Ca^{++} and glucose levels (table 4). When comparing the changes in plasma levels following the administration of RBCs, the only difference between males and females was that in lactate levels. There were no differences between genders in the other studied parameters.

Discussion

The results showing an increase in plasma potassium levels are in accordance with those reported by Aboudara et al. in 2008. (5) The study focused on hyperkalemia (> 5.5 mmol/L) in a group of 131 non-crush trauma patients undergoing cardiopulmonary resuscitation during the initial 12 hours after admission to a hospital. Of those, 96 (73.3%) patients received RBCs (a mean of 11.2 RBC units/patient, range 1-55 RBC units/patient). Interestingly, 38.5% of transfusion patients developed hyperkalemia, as compared with only 2.9% of patients without transfusion. The study documented a more dramatic rise in potassium levels in transfusion (from 3.7 mmol/L to 5.3 mmol/L) than in non-tranfusion patients (from 3.6 mmol/L to 4.0 mmol/L).

Similar conclusions were published by Smith et al. in 2006. They retrospectively reviewed the Mayo Clinic records of patients who developed intraoperative cardiac arrest associated with hyperkalemia during large volume or fast RBC transfusion in 1988–2006. Sixteen patients were identified (11 adult, 5 pediatric) who received from 1 (in a 2.7 kg neonate) to 54 RBC units. The mean potassium concentration during cardiac arrest was 7.2 ± 1.4 mmol/L (range 5.9–9.2 mmol/L). The mean resuscitation duration was 32 minutes (range 2–127 mins) and the in-hospital survival rate was 12.5%. (6)

With respect to the potential increase in potassium levels, the risk is posed especially by long-stored RBC concentrates. In addition to decomposition of RBCs, increased potassium concentration in older RBC units is determined by cold-induced blockade of adenosine triphosphate (ATP). This leads to extracellular release of K^+ and entry of Na^+ ions into RBCs. The intracellular concentration of potassium ions ranges from 100 to 140 mmol/L. (7) The transcellular gradient for K^+ between the extracellular and intracellular spaces is mostly contributed to by Na^+/K^+-ATPase (sodium pump) which is inhibited under anaerobic conditions. Under physiological conditions, it pumps three sodium ions out of the cell for every two potassium ions pumped in. Higher potassium levels in fresh RBC concentrates may also result from muscle activity – repeated fist pumping during blood collection. This may increase serum K^+ concentration at the collection site in the donor's forearm by more than 1 mmol/L. (8) The potassium concentrations measured in stored RBCs suggest that the recommended maximum rate of 20 mmol/hour, (9,10) or 40 mmol/hour in severe hypokalemia, (11) may be exceeded. The maximum may be achieved by administration of a mean of 6 RBC units/hour (a mean age of RBCs of 14 days means potassium concentration of 23 mmol/L). With a mean hematocrit value in RBCs of 0.50 and a volume of a transplantation unit of 290 ± 20 mL, the total volume of extracellular fluid in a RBC unit is 145 mL and mean total potassium in 14-day-old RBCs is 3.33 mmol. If the RBC storage time is prolonged from 35 to 42 days, hemolysis of red blood cells increases by 30% on average. (12) The mean 24-hour posttransfusion

recovery of short-stored (1-10 days) RBCs was 86.4±17.8% as compared with 73.5±13.7% in long-stored (25-35 days) RBCs. (13) On the other hand, the administration of long-stored RBCs has no adverse impact on gastric tonometry or tissue oxygenation. (14) From the currently published data, it is difficult to determine whether there is a relationship between the age of transfused RBCs and morbidity or mortality in adult patients, with the exception of trauma patients receiving massive transfusion in whom the risk of older RBCs was confirmed. (15) Recent studies suggest that transfusion of RBCs older than 2 weeks is related to an increased risk of postoperative complications and higher mortality. (16-18) Metabolic changes in the recipient's organism, such as hyperkalemia, citrate toxicity, lactic acidosis or hypothermia, may lead to depression of left ventricular function. (2) Red blood cells older than 2 weeks increase both the risk of postoperative complications and mortality rates in cardiac surgery patients. (19,20) Transfusion of RBCs increases cerebral oxygenation in patients with severe brain injury, with the exception of transfusion of RBCs older than 19 days. (21) In reversing the neurocognitive deficit of acute anemia, however, RBCs stored for 3 weeks are as efficacious as those stored for 3.5 hours. Therefore, requiring fresh RBCs is not warranted in this case. (22) Since new alkaline additive solutions have prolonged the storage time to 10 weeks, (23) the risk of hyperkalemia may be eliminated by using potassium adsorption filters prior to administration of older RBC concentrates. In another study, potassium level was 60.6 ± 2.68 mmol/L just before filtration of 28-day-old RBC concentrates. After filtration, the level of K^+ was only 3.42±2.91 mmol/L. (24) At present, potassium adsorption filters are not commonly available in clinical practice. The question arises whether patients at risk of hyperkalemia (massive blood replacement, renal failure, pre-existing hyperkalemia) should be considered for administration of short-stored RBCs. Other complications related to the use of "old" RBCs in critically ill patients should also be borne in mind, such as transfusion-related immunomodulation, ability to transfer O_2, impaired deformability of RBCs and their impact on the already affected microcirculation, etc. Should preferential selection of "young" RBCs for these patients be arranged with the blood bank then? The age of RBCs administered in the first 6 hours of blood replacement was shown to be an independent risk factor for the development of posttraumatic multiorgan failure. Therefore, fresh blood should be required in the initial phase of volume resuscitation of traumatized patients. (25)

In the course of the study, a significant drop in potassium levels was noted in one of the cases. It occurred after the initiation of perioperative blood recuperation using the Cell Saver system.

The salvaged blood (returning to the patient) was hypokalemic (2.7 mmol/L of K^+). In the system, suctioned blood is washed with heparinized saline containing no potassium. Excess fluid with ions and tissue detritus is removed by centrifugation. When being returned to the patient, blood is not commonly biochemically monitored and decreased potassium levels may not be noticed.

In stored RBC concentrate, there is an increase in the levels of lactate, a product of anaerobic blood cell metabolism. The source of energy, glucose, is metabolized by glycolysis to lactate using two ATP molecules. When monitoring lactatemia in our study, a statistically significant difference between genders was observed, with lactate levels rising in males but falling in females. There is no satisfactory explanation for this finding. At the same time, there is a question about misinterpretation of lactate levels as a marker of shock and its successful therapy in patients with massive transfusion.

Decreased levels of ionized calcium in citrate intoxication and thus clinical signs of hypocalcemia resulting from transfusion of citrate blood derivatives are rare. In such cases, 10 mL of 10% $CaCl_2$ may be administered. However, routine administration of calcium remains a matter of controversy. In the recipient's organism, citrate binds to calcium, resulting in decreased levels of ionized calcium. The clinical signs of citrate toxicity (depression of myocardial inotropy, prolonged QT interval, decreased vascular resistance) may occur if citrated blood products are administered at a rate of more than 100mL/minute or, in patients with hepatopathy, even at a lower rate. (26)

No changes in pH of patients due to transfusion of RBCs with low pH were recorded although acidification may result from both lactate, a metabolite of anaerobic glycolysis of RBCs, and low pH of citrate preservative solution. The lowered pH of stored blood is also likely to be caused by a gradual increase in pCO_2. However, transfusion may be followed by manifestations of metabolic alkalosis after citrate is converted to bicarbonate. Thus, the final shift in pH depends both on the rate and volume of transfusion and on the metabolic function of the liver. (26) The rate of administration of RBC concentrate is dependent on patient tolerance. The highest recommended rate is 100 mL/min while the slowest administration of 1 RBC unit may take as much as 4 hours (the risk of bacterial contamination). If slower application is needed (in patients with cardiac failure), the blood bank should be asked for providing smaller bags. (27)

The reason for decreased *in vitro* Na^+ concentration in RBCs is that the process of K^+/Na^+ exchange between the intracellular and extracellular spaces is inhibited during storage of RBCs. However, decreased sodium levels in RBCs have no effect on *in vivo* sodium concentration after transfusion. This is likely because the decrease in sodium levels in RBCs is not substantial.

The decrease of 2,3-diphosphoglycerate (DPG) in RBCs is proportional to the storage time. It results in the shift of the hemoglobin dissociation curve to the right and increased affinity of hemoglobin for oxygen, leading to decreased release of oxygen to tissues and a risk of tissue hypoxia. In addition to 2,3-DPG reduction, RBC storage leads

Table 2. Mean K+, pH, lactate, Ca++, Na+ and glucose concentrations in bags on storage days 1 to 35.

day	1	3	7	10	14	18	21	24	28	31	35
pH	7.00	6.95	6.93	6.91	6.85	6.83	6.78	6.75	6.71	6.68	6.65
K^+ (mmol/L)	4	10	12	22	23	29	31	32	33	38	40
lactate (mmol/L)	4.1	10.0	14.0	17.0	18.0	22.0	23.0	25.0	26.0	27.0	28.0
glucose (mmol/L)	29	28	27	26	25	24	23	20	18	16	14
Ca^{++} (mmol/L)	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Na^+ (mmol/L)	137	135	133	130	125	123	123	122	120	118	116

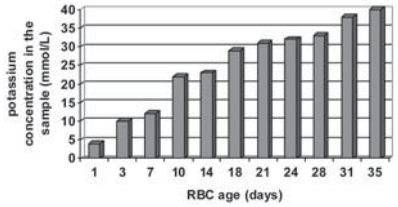

Figure 1. Mean K+ concentrations in RBC (red blood cell) concentrate depending on its age.

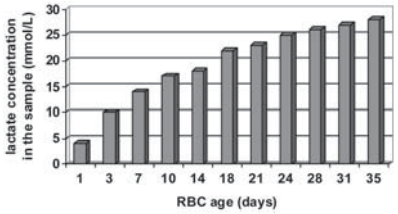

Figure 3. Lactate concentration (mmol/L) in RBC (red blood cell) concentrate depending on its age.

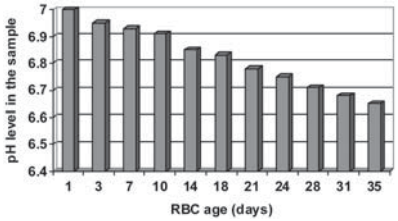

Figure 2. pH levels in RBC (red blood cell) concentrate depending on its age.

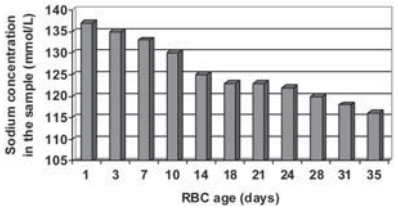

Figure 4. Sodium concentration (mmol/L) in RBC (red blood cell) concentrate depending on its age.

Table 3. Increased potassium levels following RBC (red blood cell) administration.

Hyperkalemia	no. of patients	increase in K^+ (mmol/L)	no. of RBC units	mean age of RBCs (days)
mild 5.5–6.0 K^+ (mmol/L)	2	+ 0.8 + 0.4	5,11	15.56
moderate 6.1–7.0 K^+ (mmol/L)	4	+ 2.6 + 0.9 + 2.2 + 1.0	6,9,10,14	19.44
severe > 7.0 K^+ (mmol/L)	1	+ 3.3	38	18.62

to decreased deformability of the red cells and reduced ATP. These changes shorten RBC survival after transplantation, decrease the availability of tissue oxygenation and have proinflammatory and immunomodulatory effects. In a study of aged packed RBCs used in critically injured trauma patients, there was a decrease in tissue oxygenation in patients receiving RBCs 21 days old or older as compared with patients receiving blood less than 21 days old. Thus, factors in stored RBCs may influence oxygen delivery. (28) Unfortunately, no randomized controlled studies are available that would confirm the impact of RBC storage time on morbidity and mortality. (3)

Iron overload may occur after repeated RBC transfusion. Under normal conditions, daily extraction of iron is approximately 1 mg. One RBC unit contains about 250 mg of iron. Full plasma transferrin saturation with iron is achieved after the administration of 10–15 RBC units. Unbound iron may cause organ damage by formation of its deposits in the myocardial, liver and pancreatic tissues. Another problem may be the pro-infective effects of iron. However, iron overload is not associated with administration of a single massive blood product. (26,29)

The so-called "storage lesions" are related not only to biochemical changes. Elevation of anti-inflammatory cytokines and molecular changes (deformation of the shape and elasticity of RBCs followed by impaired microcirculation) also occur during storage. Recuperation is capable of removing microaggregates larger than 17 μm but not those smaller than 7 μm. Currently, there is

Table 4. Changes in K+, pH, lactate, Na+, Ca++ and glucose concentrations *in vivo* after the administration of 2–38 (a mean of 7.7) RBC (red blood cell) units.

	baseline	baseline	baseline	final	final	final	
	range	median	mean±SD	range	median	mean±SD	significance
K^+ (mmol/L)	2.8–6.9	4.25	4.31±0.79	3.0–7.3	4.65	4.85±0.82	< 0.0001
pH	6.94–7.56	7.35	7.31±0.12	7.05–7.51	7.32	7.3±0.11	0.429
lactate (mmol/L)	0.4–15.2	3.05	4.1±3.38	0.7–16.2	3.35	5.08±4.45	0.01
glucose (mmol/L)	5–23	9.45	10.67±4.33	4.8–21.8	9.2	10.39±4.31	0.429
Ca^{++} (mmol/L)	0.16–1.24	0.97	0.96±0.21	0.76–1.26	0.99	0.98±0.14	0.225
Na^+ (mmol/L)	117–150	138	137±5.5	126–150	139	139±5.6	0.01

Table 5. Mean pH, K+, Ca++ and glucose concentrations in selected blood derivatives.

	RBCs (day 14)	FFP (day 14)	PLTs (day 1)	Cell Saver (fresh)
pH	6.85	7.40	7.30	7.31
K^+ (mmol/L)	23.0	3.0	3.0	2.7
Ca^{++} (mmol/L)	0.17	0.22	0.22	0.23
glucose (mmol/L)	25.00	20.00	21.10	0.44

Cell Saver, fresh blood from a salvage system; FFP, fresh frozen plasma; PLTs, apheresis leukocyte-depleted platelet concentrate; RBCs, red blood cells, resuspended, buffy coat removed.

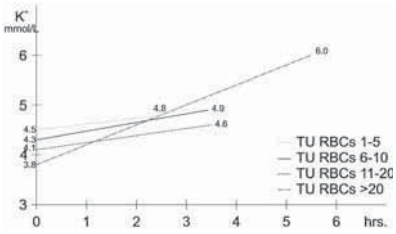

Figure 5. Changes in potassium levels after transfusion of various numbers of RBC (red blood cell) transfusion units (TU) (mean RBC age 16.18 days).

much interest in the immunomodulatory effect of transfused RBCs as a potential mechanism for increased morbidity and mortality of hospitalized patients after administration of RBCs. The mechanism is development of nosocomial infections, acute lung injury or later autoimmune diseases. (30,31) Given the above risks, transfusions should be carefully considered. According to the American Association of Blood Banks (AABB), the need for transfusion should be assessed with respect to parameters of the severity of the disease and clinical status rather than arbitrary hemoglobin levels. (32) There is no single value of hemoglobin concentration that justifies or requires transfusion. Evaluation of the patient's clinical situation should be a factor in the decision (33) since the organism is capable of adapting to anemia by increased cardiac output (in the absence of volume depletion), changes in microcirculation and increased concentration of 2,3-DPG (i.e. the shift of the hemoglobin dissociation curve to the right). (34) There is almost no evidence that routine administration of RBCs to non-bleeding patients with hemoglobin concentrations greater than 70 mg/L results in better outcome. (34) This study focused on assessing changes in biochemical parameters occurring in red blood cells, buffy coat removed. Therefore, the results do not apply to other blood products such as resuspended RBCs, leukocyte-depleted RBCs and resuspended apheresis RBCs. The other types of blood derivatives, such as fresh frozen plasma, apheresis platelets or apheresis leukocyte-depleted platelets, contain no cellular elements. As compared with RBC products, in particular potassium and pH values are significantly differ-

ent (table 5). Therefore, the potential impact of the other blood derivatives (fresh frozen plasma, platelet concentrate) on changes in plasma levels of the studied parameters is very likely to be negligible. When discussing the outcomes, the potential effect of many variables should be taken into account that play a role in the patient's internal environment during life-threatening conditions requiring massive transfusion. To varying degrees, they contribute to the development of hemorrhagic shock and may, to a certain extent, skew the results. Of particular importance is the ability of the buffer systems to compensate for the decrease in pH. Each 0.1 unit of pH change results in a 0.4 mmol/L change in the serum potassium level (a 0.6 mmol/L change according to some authors). (11) Potassium levels are increased by acidosis and decreased by alkalosis. The resulting change in the internal environment also depends on the ability of the respiratory system to counter the developing metabolic acidosis. The renal function status, ability of the kidneys to increase potassium excretion, either in spontaneously maintained diuresis or especially after the administration of loop or osmotic diuretics. (11) Other aspects to be taken into account are continued blood loss (i.e. loss of relatively hyperkalemic blood after transfusion), degree of tissue and organ hypoperfusion (increasing acidosis on its own) and the liver's ability to convert citrate to bicarbonate and lactate to glucose. What cannot be overlooked is the potential effect of potassium-containing replacement solutions (Plasma-Lyte 5 mmol/L, Ringer's acetate 5 mmol/L, Ringer's lactate 5 mmol/L, Ringerfundin 4 mmol/L, Tetraspan 4 mmol/L; Voluven and saline contain no potassium) or alkalizing solutions (Plasma-Lyte) or those maintaining neutral pH (Ringerfundin).

Conclusion

The detected changes in the plasma levels of biochemical parameters suggest the risk for developing hyperkalemia and hyperlactatemia, depending on the character of RBC products. The risk grows with increases in the volume of administered RBCs, duration of transfusion and storage time of the administered RBCs. The presented *in vivo* study confirms the published results and documents the influence of administration of long-stored RBCs, especially increased K^+ and lactate levels. Particularly possible hyperkalemia may be a life-threatening factor. Intermittent monitoring of the patient's biochemical parameters during massive transfusion is advisable. In small-volume transfusions, laboratory plasma levels should be monitored in patients with a limited ability to eliminate potassium load (renal insufficiency) or in those with pre-existing hyperkalemia. In the future, potassium adsorption filters are likely to be used. Although the storage time has a negative impact on the biochemical composition of RBCs, there is currently insufficient evidence to advocate for shorter storage times for RBCs. No randomized controlled trials studying the effect of storage time on morbidity and mortality have been published. By contrast, leukoreduction improves the quality of RBCs and may reduce the adverse effects (impaired tissue oxygen availability, proinflammatory and immunomodulatory effects). In some studies, it was shown to reduce morbidity and mortality.

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