ORIGINAL RESEARCH PAPER

Clinical Laboratory

CHANGES IN BLOOD DURING STORAGE FOR TRANSFUSION

KEY WORDS: Potassium, calcium, bicarbonate, blood transfusion

Athanasios V. Bakaloudis	General Practitioner, Consultant. Renal Department General Hospital of Komotini, Greece.
Marianna G. Andreadou	Microbiologist, Director.Blood Donation Department, General Hospital of Komotini, Greece.
Irini M. Kalogiannidou	Nephrologist, Consultant, Antoniou Dialysis Center "Dimokrition", Greece.
Nazli O. Osman	General Practitioner. Renal Department General Hospital of Komotini, Greece.
Konstantinos S. Mavromatidis*	Nephrologist, Director, Antoniou Renal Department General Hospital of Komotini, Greece. *Corresponding Author

ABSTRACT

Introduction: Over the past 20 years, extensive research has been conducted on blood transfusion and the hazards arising from them, as well as on safest maximum storage duration for blood derivatives. Blood transfusion rates in patients with and-stage renal disease may have declined markedly after the discovery and use of erythropoietin in the mid-1980s, but is still remains a standard of care. Since several biochemical changes take place in stored blood, physicians should be alert when transfusing blood in end-stage renal disease patients, who are, theoretically at least, at higher risk of complications.

Methods and Results: This study were designed to investigate changes in storer blood over time (every 10 days from 0 to 40 days). Changes in sodium, potassium, chloride, total calcium, lactate, pH, partial pressure of carbon dioxide, bicarbonate and hematocrit, as well as the degree of hemolysis, were recorded. The findings show a significant increase in potassium, lactate, partial pressure of carbon dioxide and hematocrit and a reduction in chloride, pH and bicarbonate. The serum levels of sodium initially increased (up to day 20) and then declined.

Conclusions: In conclusion, stored blood undergoes significant changes, which can be life-threatening, especially when the transfusions are massive or in patients with end-stage renal disease, who are more sensitive to significant K^+ or acid overload.

INTRODUCTION

The body's cells take their energy needs from the oxidative phosphorylation of glucose, but red blood cells, which do not have mitochondria, metabolize glucose anaerobically to create adenosine triphosphate (ATP), 2,3 diphosphoglyceric acid (2,3-DPG) and nicotinamide adenine dinucleotide (NADH), which are essential for their survival (1). The normal lifespan of red blood cells is 120 days; every second. 2,400,000 new red blood cells are added to the circulation and the same amount of old red blood cells are removed (2).

Under blood storage conditions, the functioning of red blood cells is altered due to changes in their metabolism, increased oxidative stress and damage to their cell membranes (3). It has reported that oxidative stress is the predominant mechanism by which free hemoglobin (Hb) is harmful for endothelial function and smooth muscle tone (4). According to the Food and Drug Administration, blood that is suitable for transfusion can be stored for the maximum of 42 days, although the average storage time for transfused blood in the US is 15 days (5). Or a little longer (6). In some European countries, the average storage period is 35 days (7). Recently, however, one study found that blood storage for more than 14 days contained few intact red blood cells (which are reported to survive for 32 days), while another has found that 23% of red blood cells were destroyed after 21 days of storage (2). Finally, others estimate that 30% of transfused red blood cells are removed from the circulation (destroyed) within 24 hours after the transfusion (8).

Some argue that transfusion complications are greater and more severe when blood is stored for a long time (9) and that the risk of such complications, which are often fatal, is higher in critically ill patients (such as patients with massive bleeding, renal failure and cardiovascular disorders) (10) and those who undergo open surgery because the extracorporeal circulation (9). Studies have linked transfusions with increased incidence of infection, multiple organ failure and increased morbidity and mortality (11). In this prospective study, wanted to identify the changes in stored blood over the time.

MATERIAL AND METHODS

MATERIAL

The blood donation department of our hospital collects about 4,000 bags of blood per year, of which about 30 are unsuitable for use due to their expiration date and about 20-30 prove to be infectious after being checked and are, therefore, also considered inappropriate for use. In the present study, stored blood was examined to identify changes in levels of ions and molecules significant to the recipients. Blood from donors of group O, A and B (Rhesus +) was used for the study (i.e., the most common blood types were preferred). A total of 40 units of blood were taken from an equal number of blood donors. Plasma and the white layer (white blood cells) were removed by centrifugation (with cryocentrology) before storage. In the specific bags used for the protocol, the plasma remaining in each bag after centrifugation was estimated at 60-80 ml.

We used triple blood collection bags from Macopharma, which is appropriate for storage of red blood cells for 42 days. Each contains 63 ml of anticoagulant solution (citrate-phosphate-dextrose, CPD) to receive 450±10 ml of whole blood. After centrifugation of whole blood and removal of 15-180 ml of plasma, 100 ml of additive solution (saline-adenine-glucose-mannitol, SAG-M) was added to the concentrated red blood cells.

The pH, bicarbonate (HCO_3^-), partial pressure of carbon dioxide ($PvCO_2$), hematocrit (Hct), sodium (Na^+), chloride (Cl^-

), total calcium (Ca^{2+}) and lactate in each blood unit (bag) were determined, as well as the degree of hemolysis at the beginning (day of blood sampling) and every 10 days until the 40th day storage.

METHODS

The blood units (concentrated red blood cells) were stored at 4 °C (the temperature was checked every 4 hours, and an alarm was installed that informed the staff of any changes in the storage temperature). No units were used after the end of the study.

Four samples for the study (every 10 days) were taken after good stirring (in a special stirrer) from the accompanying small bag of the package.

Levels of blood gases (and lactates) were determined on a Siemens RAPID 500 analyzer. Hct levels were tested on a Roche automatic hematology analyzer and levels of electrolytes (K^+, Na^+, Cl^-, Ca^{2+}) on an ion-selective analyzer, also from Roche. Mid hemolysis was considered when there was hemolysis in <0.8% of red blood cells and moderate when it was in <0.9%.

Statistical Analysis

Analysis of variance (ANOVA), sequential analysis (post hoc) and t-tests were used for statistical analysis of the results. Differences with a significant level <0.05 were considered significant.

RESULTS

The ANOVA test showed a significant decrease in pH, HCO_3^-, Cl^- and Ca^{2+} over time ($p<0.0001$ in all cases). Sequential analysis (post hoc) showed that these changes were statistically significant after 10 ($p<0.0001$), 20 ($p<0.0001$), 30 ($p<0.0001$) and 40 days ($p<0.0001$). While the pH decreased from 7.136±0.043 after 10 days, it remained at a similar level for the rest of the test period (after 40 days, it was 6.5±0.0). The HCO_3^- decreased from 24.33±1.78 mmol/L at the beginning of the study to 8.20±0.31 on day 40. The Cl^- was reduced from 97.4±1.7 mmol/L at the baseline to 89.3±2.7 mmol/L on day 40, and the total Ca^{2+} decreased from 2.46±0.12 mmol/L at the beginning of the study to 0.99±0.19 on day 40. An examination of the changes in pH, HCO_3^-, Cl^- and Ca^{2+} (comparisons between baseline and values after 10, 20, 30 and 40 days) showed a statistically significant difference in all cases ($p<0.001$) (Table 1).

Table 1: Changes in pH, HCO3-, CI- and Ca2+ during the study (recordings took place during blood storage after sampling)

	Beginning	After 10 days	After 20 days	After 30 days	After 40 days
pH	7.136 ± 0.043	6.714 ± 0.032	6.072 ± 0.084	6.550 ± 0.033	6.714 ± 0.315
HCO_3^- (mmol/L)	24.33 ± 1.78	14.7 ± 0.9	13.5 ± 1.7	10.7 ± 1.6	8.20 ± 0.31
Cl^- (mmol/L)	97.4 ± 1.7	93.9 ± 1.8	90.6 ± 2.5	88.8 ± 2.8	89.3 ± 2.7
Ca^{2+} (mmol/L)	2.46 ± 0.12	1.85 ± 0.12	1.2 ± 0.17	1.05 ± 0.17	0.99 ± 0.19

The ANOVA test also showed a significant increased in K^+, lactates, PvCO2 and Hct over time ($p<0.001$ in all cases). Sequential analysis showed that the levels of these significantly increased after 10 ($p<0.0001$), 20 ($p<0.0001$), 30 ($p<0.0001$) and 40 days ($p<0.0001$). More specifically, K^+ increased from 4.4±0.1 mmom/L at baseline to 26.6±5.9 mmol/L on day 40. The lactate levels increased from 3.0±0.2 mmol/L at the start of the study to 20.1±1.3 mmol/L on day 40, and $PvCO_2$ increased from 76±4.7 mmHg at baseline to 114±13 mmHg on day 40. Finally, Hct levels increased from 42.1±2.1% at the start of the study to 52.4±4.3% on day 40. Comparisons between baseline and values after 10, 20, 30 and 40 days revealed a statistically significant difference in all cases ($p<0.0001$) (Table 2).

Table 2: Changes in K^+, lactates, $PvCO_2$, Hct and Na^+ during the study (recordings took place during blood storage after sampling)

	Beginning	After 10 days	After 20 days	After 30 days	After 40 days
K^+	4.4 ± 0.1	15.2 ± 3.3	20.4 ± 4.6	23.9 ± 5.7	26.6 ± 6.0
Lactates	3.0 ± 0.2	11.1 ± 0.7	16.1 ± 0.8	17.8 ± 0.8	20.1 ± 1.3
$PvCO_2$	76.0 ± 4.7	118.0±12.6	129.3 ± 24.2	116.7 ± 15.5	114 ± 13
Hct	42.1 ± 2.1	55.4±5.2	54.7 ± 4.7	52.4 ± 4.4	52.4 ± 4.3
Na^+	141.3 ± 1.2	148.8±2.9	145.0 ± 4.4	142.0 ± 4.0	140.1 ± 4.1

Finally, the ANOVA test showed that Na^+ levels changes significantly initially ($p<0.0001$) but not throughout the study. In particular, sequential analysis showed that Na^+ levels increased at a significant rate after 10 ($p<0.0001$) and 20 days ($p<0.0001$) but not after 30 ($p<0.231$) or 40 days ($p<0.427$) (Table 2).

DISCUSSION

The modern material in which blood is stored are saline solutions containing citrate, glucose and mannitol (12). Whole blood is collected in triple bags. The first bag is empty for blood collection, and the second contains 63 ml of CPD solution, consisting of sodium citrate (prevents blood clothing, binds calcium, citric acid (regulates pH, achieving high concentration of hydrogen ions), sodium chloride and sodium bicarbonate (which provide isotonicity and ensure suitable osmolality). The third bag contains 100 ml SAG-M solution, which contains mannitol (increase the osmolality of the extracellular space, protects against hemolysis and supports the integrity of the red blood cell membrane) (13), adenine (contributes to the survival of red blood cells by activating ATP production), dextrose (an energy source for red blood cells) and sodium monophosphate (supports ATP production and enhances glycolysis) (14).

A blood bag is suitable for transfusion in the US (when is stored for a maximum of 42 days at 4 °C), if the 75% of its red blood cells are survive in the recipient's circulation for 24 hours after transfusion, and the existing hemolysis in the bag is less than 1% (0.8% in Europe) (15-17). Hemolysis can occur during collection of the sample or during transport, but it may also occur due to irreversible changes in the erythrocyte membrane during storage (18).

Hemolysis was not detected in any bag until the 30th day of blood storage. However, on the 40th day of blood storage, 37/40 bags were found to have <1% hemolysis and were deemed suitable for transfusion.

In stored blood, leakage causes the redistribution of monovalent cations, as well as a higher intracellular concentration of bases (and therefore water), which leads to cellular oedema (19). Thus, the changes in the concentration of ions in the stored blood in SAG-M solution has an increasing effect on their volume. This difference is partly due to the absence of Ca^{2+}.

Finally, during blood storage, a gradual increase in Hct was observed form day 0 to day 40. This is due to the fact that automated haematological analyzers do not determine Hct directly but do so indirectly by estimating the mean volume of red blood cells (MCVs), changes in which affect the Hct, which is also affected by the number of red blood cells (20), as observed in the present study.

The Na^+ in the blood bags decreased according to some researchers, when the storage time is longer (21). In fact,

Ratcliffe et al. found a decrease in Na^+ from 170 mmol/L to 156 mmol/L (13) after 35 days of blood storage. The reduction is due to the low storage temperature, which inhibits Na^+-K^+-ATPase (22,23), thereby increasing the concentration of Na^+ intracellularly. Normally, this pump extract 3 Na^+ from intracellular space and injects 2 K^+ outside (24) ions. However, in their study, Opoku-Okrah et al. found that the K^+ in stored blood increased by 0.5 mmol/L per day and that Na^+ decreased by 0.59 mmol/L per day (25), meaning there was an equal change in the levels of these ions in the blood. These results were not found in the present study (Table 3); rather, an increase in Na^+ was noted after 10 and 20 days, following by a decrease.

Table 3: Changes of K^+ and Na+ after 10, 20, 30 and 40 days

Day	Beginning	After 10 days	After 20 days	After 30 days	After 40 days
K^+	4.4	15.2	20.4	24	26.6
Na^+	141	148	145	142	141
Change of (K^+-Na^+)		10.8 against 7	16 against 4	19.6 against 1	22.2 against 0

Potassium plays an important role in cellular metabolism, especially in the synthesis of albumin and glycogen and in the enzymatic process necessary for cellular energy production. It also helps to maintain the electrical neutrality and osmolality of cells. Other functions of K^+ include the regulation of acid-base balance, the stimulation of nerves and maintenance of a normal heart rhythm. It also contributes to the contraction of smooth and striated muscles. Moreover, a constant K^+ concentration is important for cell division and growth.

Hyperkalemia after blood transfusions has been reported in the literature. While it is considered transient and "clinically non-significant" (26), deaths in newborns and young children from arrhythmias or cardiac arrest have been reported (27). Washing the red blood cells and removing the supernatant from the blood bags (leukapheresis) reduces this toxicity in high-risk recipients (28). Other studies were conducted on patients with trauma (without crush syndrome) to examine the effect of transfusion with blood that had been stored for 30-34 days on serum K^+ (two groups were compared: those transfused with more than 7 blood bags and those transfused with less). They found that those with more than 5 times more likely to have hyperkalemia. Other researches (29-31) have found that mass transfusion is associated with an increased incidence of hyperkalemia, which is not so much related to the amount of blood donated as to the rate of blood transfusion (30) and the number of days for which the units were stored, as well as to the presence or absence of hypovolemia.

Up to 60 mmol K^+ (32) has been recorded in the supernatant in blood bags. Opoku-Okran et al. (25) studying K^+ levels in 28 samples of stored blood and found an average increase from day 0 to day 20. These findings are supported by other studies of human subjects (21,33,34) and experimental animals (35). Ratcliffe et al. studied 115 blood samples and found a particularly significant increase in K^+ on day 38 (from 7 mmol/L to 25 mmol/L (13), which corresponds to our findings (from 4.4±0.1 mmol/L at baseline to 26.6±5.9 mmol/L on day 40).

Of course, in patients with severe renal failure, even a small increase in serum K^+ can be dangerous, so the blood that they are given should be stored for less than 5 days (9).

Hyperkalemia has been reported in intensive care unit (ICU) patients who have received stored blood for less than 12 days. In fact, one of those who had a K^+ level of 9 mmol/L after receiving a transfusion of 7 units presented with heart failure and died. This was first study to reveal the factors responsible for hyperkalemia in severely ill ICU patients by determining K^+ levels immediately after administration of washed red cells (36). Heart attack has been reported in adults due to massive blood transfusions (21,37,38).

Washing red blood cells reduces the K^+ load, but in emergencies (severely injured patients), there is no time for such preparation, so there is a risk of hyperkalemia (39). In fact, it seems that transfusion large amounts of stored blood at a rapid increase the risk of hyperkalemia in a small percentage of patients (36).

It is known that the distribution of K^+ in the body and its storage in the intracellular space is regulated by particularly important hormones (insulin, thyroxine, catecholamines) (40,41). Its uptake by all cells is achieved by the action of Na^+-K^+-ATPase. This makes the cell membranes particular permeable to K^+, which enters in the intracellular space through its channels (24), while K^+ extracted from the cells through the K^+-H^+-antiporter and the K^+-Cl^--cotransporter.

During blood storage, there is a slow but steady movement of K^+ from the intracellular space to the plasma (based on the concentration gradient present). This is attributed to the inability of the Na^+-K^+-ATPase to act due to hypothermia during blood storage (9,21,42) and not to a reduction in intracellular ATP levels (21). It has even been found that K^+ in blood increased by 0.5-1 mmol/L for each day of storage (43), which is in accordance with our findings in the present study. Thus, in blood storage for 21 or 35 days, the increase in plasma K^+ was 21.4 and 60.7%, respectively (9,13,44). In our samples, we observed a progressive increase in K^+, which reaches an average of 26.6±5.9 mmol/L on day 40, which was 6 times the level of potassium at the beginning of the study.

Investigators consider among other factors the change of K^+ to the secondary, caused by metabolic activities of cells (15). In particular, K^+ excretion from cells increases when extracellular osmolality increases (as in diabetes mellitus hyperglycaemia) due the mannitol and glucose in the perspective solution, as well as metabolic acidosis (H^+ of extracellular space exchanged with K^+ of intracellular) (45). For each 0.1 unit decrease in pH, the K^+ plasma increase by 0.4 mmol/L (in the present study, this effect was small, since the pH increased from 7.136 to 6.650, a change that justifies a <3 mmol/L increase in K^+). However, blood stored in CPDA-1 (citrate-phosphate-dextrose with adenine) has been to have 10 times more plasma K^+ on the 42nd day of storage compared to the 1st day due to increased fragility and deformability and reduced viability and survival of red blood cells (46,47). Finally, large amounts of K^+ are released in the event of cell death.

Chloride levels increased during blood storage for the first 7 days and then decrease significantly (22). We found a gradual decrease in chloride levels from the day of blood sampling until day 40. This is probably due to the entry of K^+ intracellularly during blood storage.

Total calcium is reduced in stored blood (22), which is explained by the presence of citrates in the CPDA-1 solution (43,44). This is supported by our findings that Ca^{2+} levels were found three times lower between the first day of blood storage and the 40th day.

As mentioned, red blood cells do not have mitochondria and, therefore, derive their energy from anaerobic metabolism of glucose (thus producing metabolites such as ATP [the source of red blood cell energy], 2,3-DPG and NADH, which are necessary for their survival). The 2,3-DPG disappears from red blood cells after 2 weeks of blood storage (48). This deficiency increases the affinity of HB for O_2, but 24 hours after transfusion, its levels return to the normal. Nicotinamide adenine dinucleotide is considered an important factor that contributes to the conversion of oxyhaemoglobin to methaemoglobin (the last contains Fe^{3+}, and is not bound to O_2) (50). At blood storage temperatures, cellular metabolism is maintained at baseline levels, reaching 10 times lower than normal.

Glycolysis leads to an increase in lactate levels, which is mainly responsible for lowering pH (22). Lactate in stored blood has been reported to reach 8 mmol/L (13), 20 mmol/L (34), (which is supported by our finding) and even 25 mmol/L after 35 days of storage (13). In our case, the increase in $PvCO_2$ was likely responsible for the decrease in pH.

The hyperlactemia that we and others observed leads to a gradual decrease in ATP, 2,3-DPG and NADH. As a result, in 3rd to 6th week of storage, the blood's pH can reach 6.5, as we noted on day 40th of the present study (2,15). Thus, the pH is maintained at relatively normal levels during blood storage, although it shows a tendency to decrease (15,34,51). In fact, the literature shows a tendency of pH levels to reduce when metabolism is maintained without respiratory gas exchange (acidosis) (51).

Bicarbonates are significantly reduced in stored blood due to their consumption during the neutralization of lactates, which are produced during anaerobic glycolysis. This is despite the fact that in acidification, the Cl^--HCO_3^- pump moves the extracellular HCO_3^- to neutralize the H^+ (22). In our material, the HCO_3^- levels sub-tripled from an average 24.33±1.78 mmol/L at the beginning of the study to 8.20±0.31 mmol/L on the day 40th (from 3.04 mmol/L to 29.3 mmol/L).

Preserved blood $PvCO_2$ was significantly affected. Various studies (13,34,51) have noted an increase similar to that observed in our study, which was from 76±4.7 mmHg at the beginning to 114±13 mmHg on day 40. This change is attributed to the release of CO_2 which comes from red blood cell metabolism (35).

The present study indicates that changes occurred in stored blood, some of which are life-threatening (especially hyperkalemia) and others not. Given these results, red blood cell bags for transfusions in patients with end-stage renal disease should be used in some days after donation (maybe less than five).

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