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Original Article

Citrate metabolism in blood transfusions and its relationship due to metabolic alkalosis and respiratory acidosis

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Abstract: Metabolic alkalosis commonly results from excessive hydrochloric acid (HCl), potassium (K^+) and water (H_2O) loss from the stomach or through the urine. The plasma anion gap increases in non-hypoproteinemic metabolic alkalosis due to an increased negative charge equivalent on albumin and the free ionized calcium (Ca^{++}) content of plasma decreases. The mean citrate load in all patients was 8740±7027 mg from 6937±6603 mL of transfused blood products. The citrate load was significantly higher in patients with alkalosis (9164±4870 vs. 7809±3967, $P < 0.05$). The estimated mean total citrate administered via blood and blood products was calculated as 43.2±34.19 mg/kilogram/day. In non-massive and frequent blood transfusions, the elevated carbon dioxide output has been shown to occur. Due to citrate metabolism causes intracellular acidosis. As a result of intracellular acidosis compensation, decompensated metabolic alkalosis + respiratory acidosis and electrolyte imbalance may develop, blood transfusions may result in certain complications.

Keywords: Citrate metabolism, metabolic alkalosis, respiratory acidosis, electrolyte imbalance

Introduction

Blood component transfusion has been considered to be a safe and low risk procedure. In the last few decades there has been recognition of hazards of transfusion of blood and its products. It is no longer considered to be a low or no risk procedure, and consequently an increasing need for stricter guidelines for transfusing blood products has been recognized, not just to check infections, but also to minimize other side effects of transfusion [1].

Citrate intoxication is a frequent complication after massive blood transfusions and often presents itself as metabolic alkalosis. The reason this term comes about is due to the conversion of citrate, which is applied as an anticoagulant in blood bags, to bicarbonate, and this conversion happens, predominantly in the liver [2-4]. Stored blood is anticoagulated using citrate (3 g/unit of RBC), which chelates calcium. In a healthy adult, the liver metabolizes 3 g of citrate in 5 min. Infusion rates greater than 1 unit of RBC/5 min, or liver dysfunction, drive citrate elevation and lower plasma ionized calcium [5].

Acute metabolic acidosis, induced by the infusion of hydrochloric acid, decreased proximal fluid reabsorption and increased the fractional delivery of sodium and calcium to the distal tubule, but not to the final urine [6]. Corwin et al. [7] have reported that at least 30% of the transfusion requirement for patients in an ICU is due to blood sampling and testing. Acidosis increases plasma potassium concentrations by inducing outflow from the cell into the extracellular compartment through hydrogen exchange (altered internal balance) [8].

The metabolic alkalosis (MA) is reported as a well-known impediment of massive blood transfusion, but it is not stated as a complication of non-massive blood transfusions. Patients with MA had a larger fluid deficit (-3991±4324 vs. -1018±4863, $P < 0.05$), cumulative furosemide dose (406±356 vs. 243±189, $P < 0.02$), and

citrate load from blood transfusions (9164± 4870 vs. 7809±3967, $P < 0.05$). There was no difference in serum lactate concentration (3.15±1.63 vs. 3.11±1.91) in patients with and without MA. The duration of ICU stay was longer in patients with MA (14.9±15.3 vs. 5.3±3.9 days, $P < 0.004$) [9, 10].

Citric acid forms weakly dissociated salts with divalent cations and its untoward effects are generally attributed to the depression of ionization of such cations in the extracellular fluid, particularly calcium. The excitable tissues of the body are susceptible to such a depression, the effects on cardiac muscle being the most important [4]. Fresh frozen plasma has traditionally been used for a variety of reasons, including volume replacement, treatment of disseminated intravascular coagulopathy, during the treatment of a bleeding neonate, for prevention of intraventricular hemorrhage and in sepsis [11].

Because citrate is rapidly utilized under normal conditions it has been regarded as a perfectly safe anticoagulant for blood and the danger of citric acid intoxication resulting from transfusion of blood has been thought in the past to be negligible. There is now good evidence that with the massive amounts of blood now used, and the speed with which it must often be administered, and with the increasing number of patients with liver disease undergoing surgery, citrate concentrations may often rise to toxic levels. It is now well recognized that tremendous increases in citrate concentration can occur during exchange transfusions in erythroblastotic infants; tetany and deaths have been reported [2].

During liver transplantation the glucose metabolism is affected by a crucial disturbance. The blood glucose level is exceedingly hard to control by conventional clinical protocols during this phase [12, 13]. Liver transplant is one of the surgical procedures that required transfusion of large volumes of blood products resulting towards complex alterations of the internal milieu leading to life-threatening intraoperative events [14]. While the orthotopic liver transplantation, metabolic alkalosis associated with massive blood transfusions developed in 40-64% of the cases on approximately the third and fourth days after transplantation [15].

While blood transfusion is usually a life-saving procedure, it implies various complications as it is a kind of tissue implantation. Blood transfusions can be a life-saving procedure, but it has risks, including infectious and non-infectious complications. Non-immunological complications include circulatory overload, transfusion dependent sepsis, hemosiderosis, anticoagulant complications, gas embolism, cold-induced thrombopathy and viral transmission. Transfusion associated complications are classified as immunological complication and non-immunological complications [16, 17].

Neonates are at risk of developing heart failure due to hypocalcaemia during transfusion, because cardiac function (relaxation and contraction) depends largely on plasma concentrations of ionized calcium [18]. When neonates present liver failure leading to lower citrate metabolism and the risk is very high, death may ensue [19]. Citrate toxicity may be prevented in these cases if the transfusion rate is kept below 1 ml/kg/min [18].

Therefore, the work proposed to count at the connection between carbon dioxide output, which was due to the effect of citrate metabolism and serum electrolytes in patients who are followed up with an identification of aplastic anemia or blood cancer patients.

Material and methods

The charts of 267 patients who underwent 189 consecutive orthotropic liver transplantations at the Jining NO. 1 People's Hospital, Transplant Program from 2009 to 2013 and the approval was obtained from the institutional Ethics Committee. Metabolic alkalosis was defined as (i) a base excess value higher than -2.5 and/or an actual bicarbonate level ≥ 26 mmol/l in successive controls and (ii) presence of one metabolic alkalosis in more than two successive blood gas measurements [10]. Patient demographic data and laboratory information were collected during the pre-, intra-, and 20 days' post-operative period. Metabolic alkalosis was defined as a primary increase in serum bicarbonate greater than 28 mEq/dL and/or a base excess of greater than -2.5 on at least two consecutive observations [20, 21]. Metabolic acidosis was defined as a primary decrease in the serum bicarbonate of less than 20 mEq/dL and/or a base deficit of less than -2.5 [20-22].

Table 1. Main causes of metabolic alkalosis

H+ loss through GI Tract	Vomiting
	High output fistula
Renal H+ loss	Mineralocorticoid loss (Primary)
	Diuretic usage (Thiazide or Loop)
	Post hypercapnic alkalosis
	Hypercalcaemia
	Milk-Alkali Syndrome
Apparent H+ loss through intracellular shift	Hypokalaemia
Alkali administration	Citrate
	Cocaine abuse
'Contraction' alkalosis	Over-diuresis
	Villous adenoma
	Factitious diarrhea
Rare genetic causes	Bartter's Syndrome
	Gitelman's Syndrome
Other	Substance abuse
	Antibiotics

Table 2. Clinical features of the alkalosis group compared with the non-alkalosis group

	Alkalosis group	Non-alkalosis group	*P*
Fluid balance (mL)	-3991±4324	-1018±4863	0.05
Furosemide (mg)	406±356	243±189	0.02
Duration of ng suction (days)	3.7±6.2	3.9±10.2	Non-significant
Intra-op veno-venous bypass	51%	39%	Non-significant
Citrate load (mg)	9164±4870	7809±3967	0.05

In patients with abnormal $PaCO_2$, appropriate corrections in serum bicarbonate were made. Citrate load was assessed by assuming that each unit of blood contained 630 mg of citrate (Department of Hematology, Jining NO. 1 People's Hospital, China) and that fresh frozen plasma (FFP) contained 60% of the citrate and packed red blood cells 40% [23]. Urinary electrolytes were studied serially in 22 patients with MA and 35 patients with normal acid base status. Patients taking loop diuretics 2 days prior to transplantation and those with a serum creatinine greater than 1.4 mg/dL or who were on dialysis were excluded from this analysis. Those taking spironolactone were included.

Determination of blood amount for transfusion

Patients who had hemoglobin levels lower than 7 g/dl were administered 10 ml/kg erythrocyte suspension. Random thrombocyte suspension (1 unit/10 kg) was distributed to some patients who had thrombocyte levels between 10 and 20,000/mm^3 (depending on the term and diagnosis) and to all patients who had thrombocyte levels lower than 10,000/mm^3. The dose of erythrocyte suspension for newborns ranged between 5 and 10 ml/kg. Each unit of apheresis thrombocyte suspension was taken for granted to be equivalent to 6-8 units of random thrombocyte suspension. 10 ml/kg of FFP transfusion was performed for patients who had severe sepsis, widespread intravascular coagulation and who had Hemophilia A. The collected granulocyte unit was administered in severe and non-recovering neutropenia (granulocyte number < 100/mm^3) [24, 25].

Statistical analysis

Student's *t*-test for comparing two variables and repeated measures of one-way ANOVA followed by Fisher's least-significant difference method to compare more than two variables was used. The *P*-value was set at < 0.05 for significance. Chi-square test was used to analyze the categorical variables. Stepwise regression analysis was constructed to identify the model that best predicts serum bicarbonate post-transplant. The candidate variables used were fluid balance, citrate load, diuretic dose, serum creatinine, plasma K^+, Cl^-, bilirubin, and serum glutamic-oxalacetic transminase (SGOT).

Results

One hundred and eighty-nine orthotropic liver transplantation were performed in 267 patients at the Jining NO. 1 People's Hospital, Transplant Program. There are list of causes of metabolic alkalosis (**Table 1**). The etiology of liver failure was alcoholism in 37 (31.1%), hepatitis B and C in 33 (27.7%), primary biliary cirrhosis in 27 (22.7%) and other causes in 22 (18.5%). The clinical features of patients with metabolic acidosis and alkalosis in comparison with those

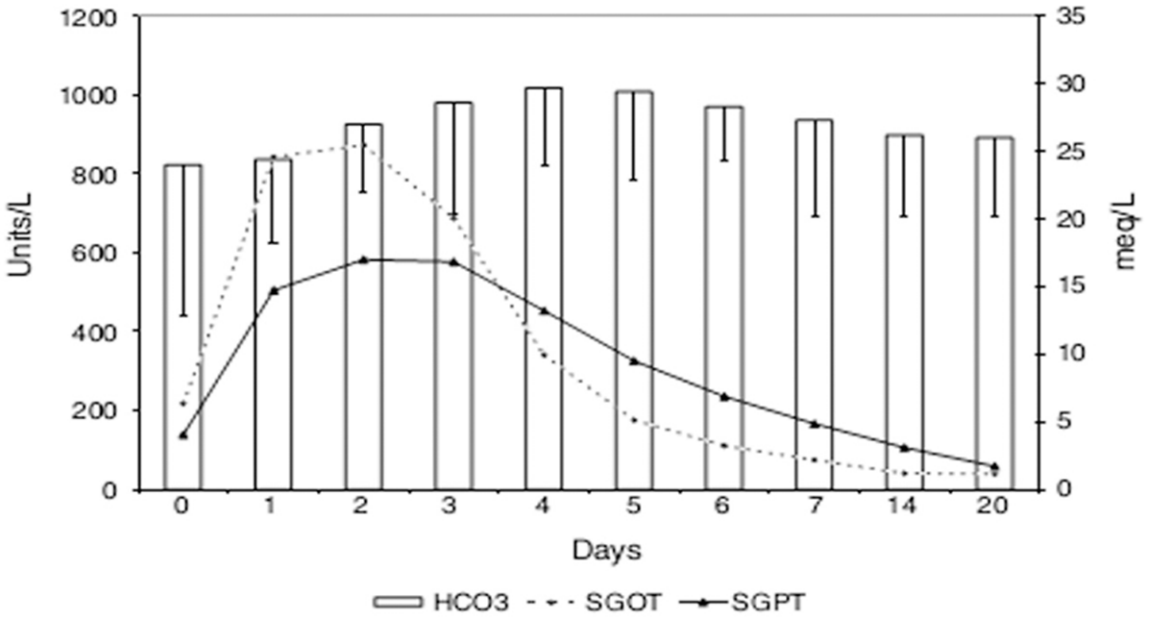

Figure 1. Hepatic transaminase concentrations in relation to the serum bicarbonate levels over 20 days after orthotropic liver transplantation. Serum bicarbonate (HCO_3) in mEq/L, serum glutamic-oxaloacetic transaminase (SGOT) in U/L (-), and serum glutamic-pyruvic transaminase (SGPT) in U/L (-).

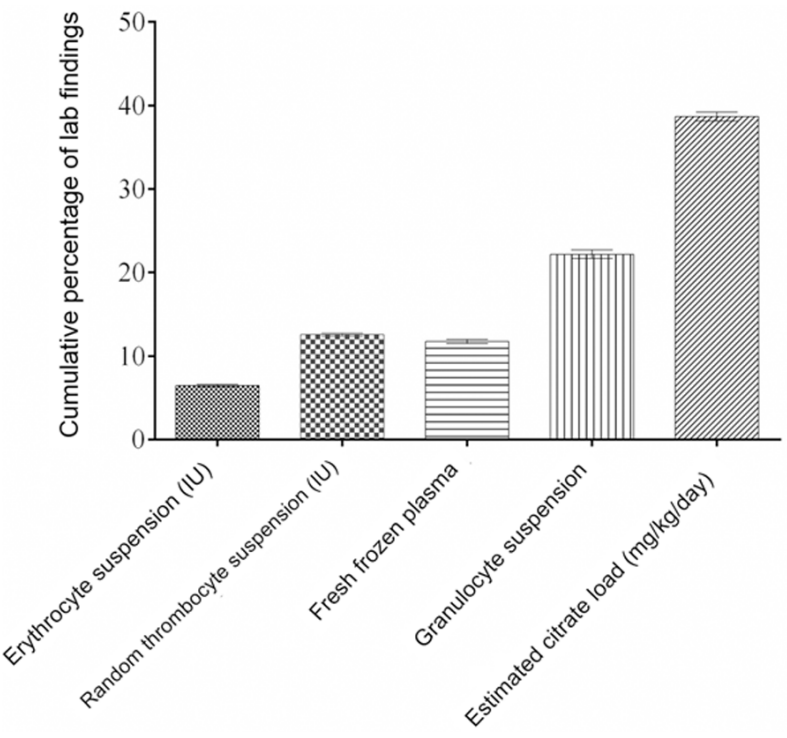

Figure 2. The total quantity of lineage and blood products given to the patients in 15 days prior to the highest actual bicarbonate level. The values were subjected ANOVA with statistical significance $P > 0.05$.

with normal acid-based status are given in **Table 2**. The mean citrate load in all patients was 8740±7027 mg from 6937±6603 mL of transfused blood products. The citrate load was significantly higher in patients with alkalosis (9164±4870 vs. 7809±3967, $P < 0.05$). After censoring the outliers the median citrate load and blood product volume were higher in alkalotic patients (citrate load 304.9 vs. 279.1 and blood product volume 5672 vs. 5192). Patients with MA had a significantly higher fluid deficit (-3991±4324 vs. -1018±4863, $P < 0.05$) and received a higher cumulative dose of furosemide (406±356 mg vs. 243±189, $P < 0.02$). The mean fluid balance during the follow-up period was -256±82.7 mL/day for the entire group.

In all patients the mean serum bicarbonate increased from 24.4±4.5 mEq/L on the day of OLT to 29.7±4.8 mEq/L on the fourth post-OLT day (P

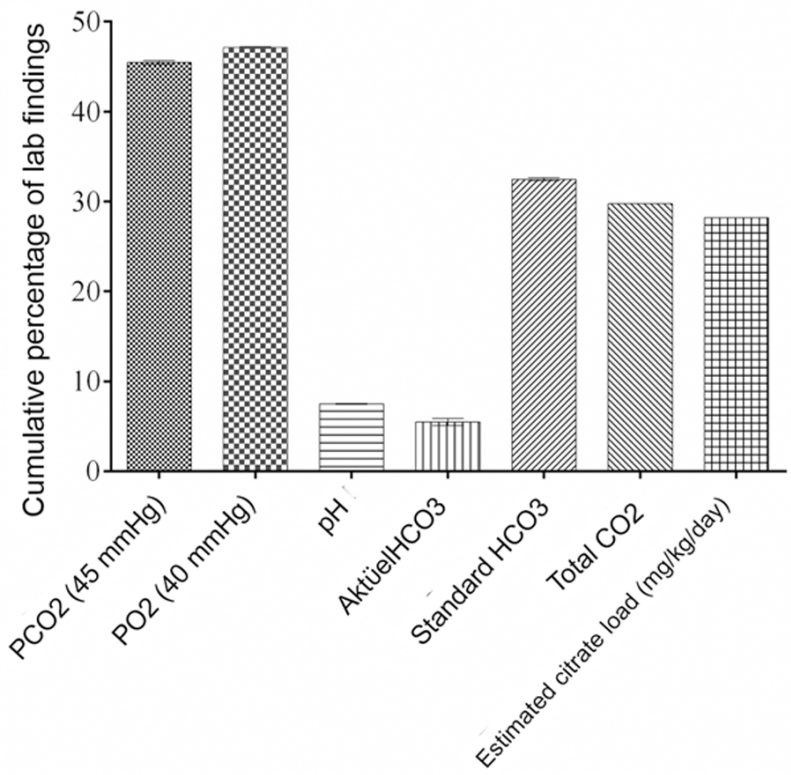

Figure 3. Cumulative estimation of Patient's blood gas results and estimated citrate amounts. Statistical significance ($P > 0.05$).

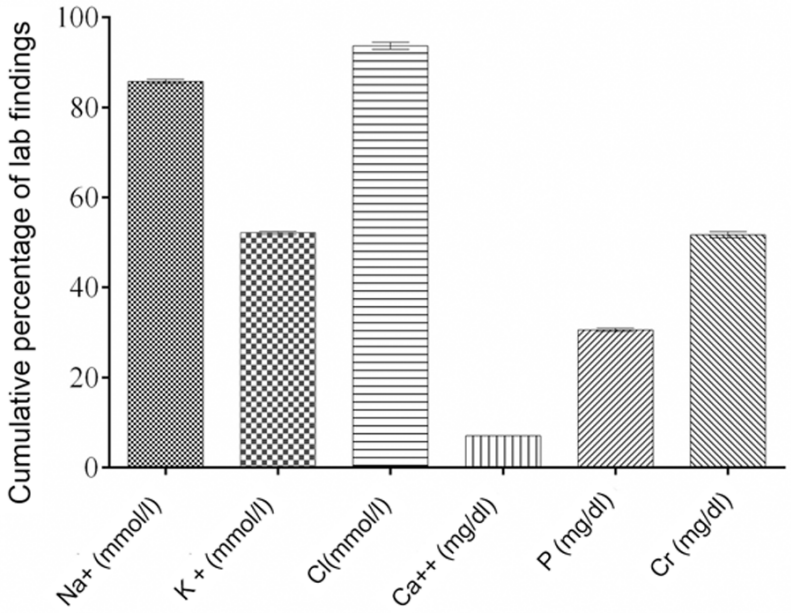

Figure 4. Urine electrolytes in patients with metabolic alkalosis. Statistical significance ($P > 0.05$).

< 0.0001) (**Figure 1**). The serum SGOT (AST) and serum glutamic-pyruvic transminase (SGPT) (ALT) peaked on day 2 and significant improvement in hepatic transaminases had occurred by day 4 (**Figure 1**). Metabolic alkalosis was observed in 60 (51.2%) patients. The total quantity of lineage and blood products given to the patients in 15 days prior to the highest actual bicarbonate level determined, and the sum of the citrate transfused through these stock products are shown in **Figure 2**.

The only significant correlation was between the amount fresh frozen plasma and estimated citrate amount and estimated citrate amount increased with increasing quantity of fresh frozen plasma ($r = 0.738$ and $P = 0.002$). There was no substantial correlation between other blood/blood products and the estimated citrate amount ($P > 0.05$). PCO_2, pH, base excess, actual bicarbonate, standard bicarbonate and total carbon dioxide levels generally increased with increasing estimated citrate amount depending on the transfusion number, frequency and amount (**Figures 3** and **4**).

Discussion

Massive transfusion is arbitrarily and variously defined as transfusion of more than 10 units of RBCs, replacement of one blood volume in 24 h, a 50% blood volume loss within 3 h or a rate of loss of 150 ml min^{-1} or greater. The transfusion of large volumes of stored blood products, particularly RBCs, in massive transfusions may

lead to a number of complications. Among these are dilutional coagulopathy, circulatory overload, hyperkalaemia, hypoglycaemia, hypothermia and, rarely, citrate-induced hypocalcaemia [26]. Sodium citrate is the anticoagulant of choice used in blood collection. In massive transfusion, an excessive amount of citrate can produce a transient hypocalcaemia and hypomagnesaemia that may affect the cardiac rate and function. This is usually seen only in patients with liver failure and/or severe hypothermia where citrate metabolism is slowed [27]. In stored blood, potassium levels tend to be high. It has been seen that after storage for around 42 days, potassium levels may reach 50 meq/L in a RBC unit [28].

Citrate toxicity results when the citrate in the transfused blood begins to bind calcium in the patient's body. Clinically significant hypocalcaemia does not usually occur unless the rate of transfusion exceeds one unit every five minutes or so [29]. Mortality is high in massive transfusion and its etiology is multifactorial. The lethal triad of acidosis, hypothermia and coagulopathy has the highest mortality. The acidosis and hypothermia is managed with ease but the coagulopathy is critically difficult to correct.

Post-operative MA was treated with correction of fluid balance in the majority of OLT patients. However, in one-third with severe MA (serum bicarbonate 38.9±2.5) intra-venous 0.1 N hydrochloric acid and/or oral acetazolamide was administered in addition to volume repletion. The decision to treat and the method of MA treatment was made by individual physicians. As no treatment algorithm was used and as this is retrospective data, no firm guidelines regarding when and how MA should be corrected can be offered. Most patients were treated when the blood pH was greater than 7.5 and the serum bicarbonate was greater than 40 mEq/L.

The challenge for transfusion medicine research in the 21st century is that transfusions are widely used across virtually all clinical specialities, but we simply do not know which patients truly benefit from transfusions. Further research is critical to public health as red cell transfusions are one of the most common therapeutic modalities employed, relevant in virtually all medical specialities, and have large and pervasive impact on clinical outcomes and the costs of health care. In conclusion, there is an increase in carbon dioxide production as a result of citrate metabolism in non-massive, frequent blood transfusions; elevated carbon dioxide production causes intracellular acidosis; metabolic alkalosis + respiratory acidosis and electrolyte imbalance such as hypocalcemia, hypokalemia, hypochloremia, iso/hypernatremia develops as a result of the compensation of intracellular acidosis; this affected the increasing mortality rates in non-massive, frequent blood transfusions and therefore, patients who are frequently administered with blood and blood products in the clinics should be monitored regarding these aspects.

Disclosure of conflict of interest

None.

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