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Citrate metabolism and its complications in non-massive blood transfusions: Association with decompensated metabolic alkalosis + respiratory acidosis and serum electrolyte levels

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ABSTRACT

Background and objectives: Metabolic alkalosis, which is a non-massive blood transfusion complication, is not reported in the literature although metabolic alkalosis dependent on citrate metabolism is reported to be a massive blood transfusion complication. The aim of this study was to investigate the effect of elevated carbon dioxide production due to citrate metabolism and serum electrolyte imbalance in patients who received frequent non-massive blood transfusions.

Materials and methods: Fifteen inpatients who were diagnosed with different conditions and who received frequent blood transfusions (10–30 ml/kg/day) were prospectively evaluated. Patients who had initial metabolic alkalosis (bicarbonate > 26 mmol/l), who needed at least one intensive blood transfusion in one-to-three days for a period of at least 15 days, and whose total transfusion amount did not fit the massive blood transfusion definition (<80 ml/kg) were included in the study.

Results: The estimated mean total citrate administered via blood and blood products was calculated as 43.2 ± 34.19 mg/kg/day (a total of 647.70 mg/kg in 15 days). Decompensated metabolic alkalosis + respiratory acidosis developed as a result of citrate metabolism. There was a positive correlation between cumulative amount of citrate and the use of fresh frozen plasma, venous blood pH, ionized calcium, serum-blood gas sodium and mortality, whereas there was a negative correlation between cumulative amount of citrate and serum calcium levels, serum phosphorus levels and amount of urine chloride.

Conclusion: In non-massive, but frequent blood transfusions, elevated carbon dioxide production due to citrate metabolism causes intracellular acidosis. As a result of intracellular acidosis compensation, *decompensated metabolic alkalosis + respiratory acidosis* and electrolyte imbalance may develop. This situation may contribute to the increase in mortality. In conclusion, it should be noted that non-massive, but frequent blood transfusions may result in certain complications.

1. Introduction

Citrate intoxication is a frequent complication after massive blood transfusions and often presents itself as metabolic alkalosis. The reason this condition occurs is due to the conversion of citrate, which is used as an anticoagulant in blood bags, to bicarbonate, and this conversion occurs

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predominantly in the liver [1]. During 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 [2–5]. Also, metabolic alkalosis was detected in 49% and 52% of pediatric patients who underwent open heart surgery within 24.3 h and 2.7 ± 1.5 days, respectively [6,7].

Many patients, particularly hematology patients with bone marrow deficiency such as leukemia and aplastic anemia receive blood transfusions intensively even though it is not defined as massive. Patients who are followed up with a diagnosis of leukemia or aplastic anemia can be transfused with 10–30 ml/kg/day erythrocyte and thrombocyte suspension at a rate of approximately 15–20 unit/month in the first one or two months of admission. In cases with disseminated intravascular coagulation (DIC) which developed due to various causes, additional fresh frozen plasma (FFP) that contains the highest amount of citrate (14 mEq/l) can be administered to patients. The aforementioned amounts do not fit into the "massive blood transfusion" definition, but nevertheless correspond to a considerably extensive transfusion amount. This is because the amount of blood or blood product transfusion within 24 h does not exceed 80 ml/kg.

While blood transfusion is usually a life-saving procedure, it implies various complications as it is a kind of tissue implantation. Transfusion associated complications are classified as immunological complication and non-immunological complications. Non-immunological complications include circulation overload, transfusion-dependent sepsis, hemosiderosis, anticoagulant complications (citrate toxicity and metabolism), gas embolism, cold-induced thrombopathy and viral transmission [8].

According to our literature search, metabolic alkalosis is reported as a well-known complication of massive blood transfusion, but it is not mentioned as a complication for non-massive blood transfusions. While the amount of estimated citrate these patients received in a day (six to twenty-four hours) due to massive transfusion were 9164 ± 4870 mg citrate/day [2], the patients in this study were administered the same amount of citrate in approximately fifteen days using non-massive blood transfusion (647.70 mg/kg), and the difference between these types of transfusions (massive and non-massive) is the duration.

A correlation between the increase in the number of thrombocyte transfusions and the increase in mortality was reported in patients who have thrombocytopenia for various reasons and who are administered thrombocyte suspension in newborn intensive care units. The underlying reason for this correlation is not known [9]. The association between blood transfusion and age and mortality is not highly reported except for the newborn period.

This study aimed to examine the association between carbon dioxide production, which is elevated as a result of citrate metabolism and serum electrolytes in patients who were followed up with a diagnosis such as leukemia/aplastic anemia and who received non-massive blood transfusions.

2. Materials and methods

2.1. Study population

Fifteen patients who were monitored in Dr. Abdurrahman Yurtarslan Ankara Oncology Training and Research Hospital Pediatric Hematology Clinic with various diagnoses between March 2008–March 2011, and who received "frequent blood transfusion" (10–30 ml/kg/day) in the last 15 days of monitoring were prospectively evaluated: the measurements are indicated below. Approval was obtained from the institutional Ethics Committee.

2.2. Inclusion criteria

The inclusion criteria included the following: Being scheduled for transfusion; initial serum actual bicarbonate level > 26 mmol/l, which is analyzed one day after transfusion; no kidney failure; no diuretic and bicarbonate treatment; at least one intensive blood transfusion using erythrocyte, thrombocyte, granulocyte suspensions and/or FFP (approximately 10–30 ml/kg/day) during at least the last fifteen days and in less than three days; non-massive blood transfusion (less than 80 ml/kg); absence of any pathology that would explain observed electrolyte imbalance, such as insufficient uptake, excessive sweating, burns, central nervous system (CNS) diseases, hormonal disorders, loss from kidneys (including diuretic uptake) and gastrointestinal system.

2.3. Metabolic alkalosis definition

Metabolic alkalosis was defined as (i) a base excess (BE) 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 [2,10].

2.4. Analysis of blood gas

Venous blood was used during the blood gas measurements, as the patients had thrombocytopenia, and disseminated intravascular coagulation (DIC) and arterial blood drawing possess high risk for bleeding. As known, if the measurement of partial oxygen pressure is not required, venous blood gas analysis is usually sufficient to evaluate the acid–base equilibrium. The pH of venous blood is 0.04 units lower than arterial pH, whereas venous blood PCO_2 is higher than 5 mmHg. In addition, venous PO_2 and bicarbonate levels are also lower. However, venous bicarbonate measurement is considered as equally informative for arterial base deficit in intensive care patients [11]. In this study, patients who required transfusion in 3 days or a shorter time in the last 15 days, and will receive transfusion were chosen and venous blood samples were taken 24 h after the new transfusion. Blood and urine electrolytes were studied with co morbid blood gas. The highest actual bicarbonate level was determined among these blood samples. The amount of blood and blood products given to the patients in 15 days was indicated prior to the highest

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