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Hypocalcemia in trauma patients receiving massive transfusion

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ARTICLE INFO

Article history:
Received 10 September 2015
Received in revised form
11 November 2015
Accepted 22 December 2015
Available online 30 December 2015

Keywords:
Blood coagulation
Blood transfusion
Calcium
Hypocalcemia
Resuscitation
Trauma

ABSTRACT

Background: Massive transfusion protocol (MTP) is increasingly used in civilian trauma resuscitation. Calcium is vital for coagulation, but hypocalcemia commonly occurs during massive transfusion due to citrate and serum calcium chelation. This study was conducted to determine the incidence of hypocalcemia and severe hypocalcemia in trauma patients who receive massive transfusion and to compare characteristics of patients with severe *versus* nonsevere hypocalcemia.

Materials and methods: This was a retrospective study of trauma patients who received massive transfusion between January 2009 and November 2013. The primary outcome was the incidence of hypocalcemia (ionized calcium [iCa] < 1.12 mmol/L) and severe hypocalcemia (iCa < 0.90 mmol/L). Secondary outcomes included calcium monitoring, calcium replacement, and correction of coagulopathy.

Results: There were 156 patients included; 152 (97%) experienced hypocalcemia, and 111 (71%) had severe hypocalcemia. Patients were stratified into iCa ≥ 0.90 ($n = 45$) and iCa < 0.90 ($n = 111$). There were no differences in demographics or baseline laboratories except the severe hypocalcemia group had higher baseline activated partial thromboplastin time (29.7 [23.7–50.9] *versus* 25.8 [22.3–35.9], $P = 0.003$), higher lactic acid (5.8 [4.1–9.8] *versus* 4.0 [3.1–7.8], $P = 0.019$), lower platelets (176 [108–237] *versus* 208 [169–272], $P = 0.003$), and lower pH (7.14 [6.98–7.28] *versus* 7.23 [7.14–7.33], $P = 0.019$). Mortality was higher in the severe hypocalcemia group (49% *versus* 24%, $P = 0.007$). Patients in the iCa < 0.90 group received more blood products (34 [23–58] *versus* 22 [18–30] units, $P < 0.001$), and calcium chloride (4 [2–7] *versus* 3 [1–4] g, $P = 0.002$), but there was no difference in duration of MTP or final iCa. Neither group reached a median iCa > 1.12.

Conclusions: Hypocalcemia is common during MTP, and vigilant monitoring is warranted. Research is needed to effectively manage hypocalcemia during massive transfusion.

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2015.12.036

1. Introduction

The triad of coagulopathy, hypothermia, and acidosis can perpetuate ongoing hemorrhagic shock in trauma patients leading to increased mortality. Coagulopathy in exsanguinating patients is multifactorial, and the prevention of secondary coagulopathy during massive transfusion is crucial. Many studies have evaluated the effect of targeted ratios of blood products on mortality and coagulopathy [1–8], but the incidence and effects of electrolyte abnormalities, specifically hypocalcemia, have not been clearly defined in patients requiring massive transfusion of blood products.

Calcium plays a significant role in coagulation, platelet adhesion, and contractility of myocardial and smooth muscle cells. It is required by clotting factors II, VII, IX and X, as well as proteins C and S for activation at the damaged endothelium. In addition, calcium plays a role in stabilizing fibrinogen and platelets in the developing thrombus [9].

Hypocalcemia is known to be common during massive transfusion of blood products due to chelation of serum calcium and citrate. Packed red blood cells (PRBCs) and fresh frozen plasma (FFP) contain approximately 3 g of citrate anticoagulant per unit as a preservative [9]. This interaction is usually insignificant due to the rapid clearance of citrate by the liver. In a healthy individual, 3 g of citrate can be metabolized in 5 min, but in a patient with hemorrhagic shock, the combination of rapidly infused blood products and decreased hepatic clearance due to hypoperfusion and hypothermia may impair the clearance of citrate [10,11].

Severe, ionized hypocalcemia has been defined as <0.9 mmol/L and is associated with increased mortality in critically ill adults, whereas levels of <0.8 mmol/L have been associated with adverse cardiac effects [12,13]. Therefore, a threshold ionized calcium (iCa) of <0.9 mmol/L has been proposed as a trigger for intravenous calcium supplementation in critically ill patients [13]; however, there are limited data regarding the timing and dosage of calcium supplementation needed after administration of blood products. Many institutions have incorporated calcium monitoring and replacement into a massive transfusion protocol (MTP). One institution reported providing 2 g of intravenous calcium gluconate empirically for every 2 to 4 units of PRBCs administered and monitoring iCa levels every 1 to 2 h during large-volume transfusions [9]. Another proposed replacement method is 1.35 mEq of calcium (290 mg of calcium gluconate or 96 mg of calcium chloride) for every 100 mL of blood received [13]. However, the effectiveness of these two strategies has not been reported.

Despite the known chelation of serum iCa with citrate and the serious consequences of severe hypocalcemia, the incidence and clinical significance of hypocalcemia in patients receiving massive transfusion has not been studied. The objective of this study was to describe the incidence and severity of hypocalcemia in trauma patients receiving massive transfusion.

2. Materials and methods

This retrospective chart review was approved by the Institutional Review Board at Orlando Regional Medical Center, a level 1 trauma center. All trauma patients aged ≥18 y who had activation of MTP were identified from the trauma database from January 1, 2009 through November 31, 2013.

MTP at our institution uses coolers containing 6 units of PRBC, 6 units of FFP, and one pack (equal to 6 units) of apheresis platelets. Activation of MTP was triggered by the presence of systolic blood pressure ≤ 90 mm Hg, heart rate ≥ 120 beats per min, positive focused sonography for trauma examination, or pH ≤ 7.24, and if transfusing at least 4 units of PRBC over 1 h, or anticipate ≥10 units over 24 h.

Patients were excluded if they had MTP activated for any indication other than trauma, did not receive massive transfusion, had no iCa available within 24 h of MTP initiation, or if blood bank records were unavailable. The trauma database included basic demographics, Injury Severity Scores, trauma type and pattern, baseline vitals, and patient outcome. All additional information was obtained from the electronic medical record. Blood product administration was collected for the duration of MTP activation, and iCa monitoring and calcium replacement were collected up to 24 h after MTP discontinuation.

The primary outcome of this study was to determine the incidence of hypocalcemia and severe hypocalcemia in trauma patients who received massive transfusion. Hypocalcemia was defined as an iCa < 1.12 mmol/L, and severe hypocalcemia was defined as an iCa < 0.90 mmol/L. Patients were further stratified into iCa < 0.90 mol/L and iCa ≥ 0.90 mmol/L to assess calcium monitoring and management of hypocalcemia during MTP and the correction of coagulopathy at the end of MTP. Calcium replacement is reported in grams of calcium chloride. Coagulopathy was defined as prothrombin time (PT) or activated partial thromboplastin time (aPTT) > 1.5 times the upper limit of normal.

All statistics were run using SPSS version 22.0 (IBM Corp, Armonk, NY). Dichotomous data were evaluated using the chi-square test, and continuous non-normally distributed data were compared using the Mann–Whitney *U* test. Data are presented as median with interquartile range for continuous variables or as number (N) and percentage for categorical variables. Two-tailed tests were used to determine statistical significance, and a *P* value of <0.05 was considered significant. A receiver-operating characteristics (ROC) analysis was performed to identify the cutoff value of total blood volume associated with development of severe hypocalcemia.

3. Results

A total of 172 patients were identified in the trauma database during the study period, and 156 were included in the final analysis. Sixteen patients were excluded: 10 were aged <18 y, five did not have an iCa available within 24 h of MTP initiation, and one patient did not have blood bank records available (Fig. 1). The overall incidence of hypocalcemia in this population was 97.4% ($n = 152$), and the incidence of severe hypocalcemia was 71% ($n = 111$).