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REVIEW
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Hypocalcemia in trauma patients: A narrative review

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ABSTRACT:

Hypothermia, acidosis, and coagulopathy together make up the trauma triad of death, which has been acknowledged as a key factor in the demise of trauma patients. Hypocalcemia has recently been added as the fourth element of the "diamond of death" in trauma. However, the effects of hypocalcemia in trauma patients have received insufficient attention from systematic reviews. The primary focus of this review will be the impact of hypocalcemia on the mortality rates among trauma victims. Regardless of a large transfusion, hypocalcemia can occur in trauma patients; this condition is known as "trauma-induced hypocalcemia". Hypocalcemia driven by trauma is multifaceted and linked to the fatal triad, which may worsen or even result in death. Our review showed an association between hypocalcemia and increased mortality. Recent data have introduced hypocalcemia integrated with the trauma lethal triad for predicting the prognosis and mortality of critically traumatized patients. However, the benefit of prophylactic calcium supplementation requires further study to support it.

Keywords: Hypocalcemia; Trauma; Diamond of death; Mortality

INTRODUCTION

The trauma triad of death, describing the combination of hypothermia, acidosis, and coagulopathy, has been recognized as a significant cause of death in trauma patients. This triad resulted in worsening hemorrhages and eventual death [1]. Recent data have introduced a fourth component, hypocalcemia, which plays a key role in the outcome of trauma patients [2].

This narrative evaluation of the relevant literature assesses the impact of hypocalcemia on trauma patients' mortality. The authors searched for published studies in Ovid, Embase, and Cochrane databases before August 2022 using the keywords “trauma”, “hypocalcemia”, and “mortality”. The causes and risk factors that predispose trauma patients to hypocalcemia will also be covered in the review.

Calcium: the definition and physiology

Calcium is the most abundant mineral in the body, accounting for approximately 1.5 to 2% of the total body weight. Ninety-nine percent of total body calcium is located in the bones and teeth. Normally, cytosolic calcium is low deficient, with a ratio of extracellular to intercellular ionized calcium of 10,000:1. Forty percent of serum calcium is protein bound, primarily albumin. An additional 10% to 15% is

complexed with serum anions such as bicarbonate, phosphate, and citrate. The remaining 45% to 50% is the physiologically active, ionized fraction [3].

Normal serum calcium is 8.8 to 10.3 mg/dL (2.2 to 2.6 mmol/L), and normal ionized calcium is 4.0 to 5.2 mg/dL (1.0 to 1.3 mmol/L). Any level below these ranges is considered hypocalcemia. A decreased albumin level affects the lowering of total serum calcium without affecting serum ionized calcium. The correction formula is widely used to adjust total calcium by albumin and pH. However, it has shown poor prediction of calcium status, especially in critically ill patients [3].

Serum-ionized calcium is controlled by the action of parathyroid hormone (PTH) via the calcium-sensing receptor (CaSR) and 1,25 $(OH)_2$ vitamin D. Calcitonin also responds to a high level of ionized calcium. However, its role seems not to be physiologically important in humans [4].

Calcium and its function

Calcium has a wide range of effects on various systems, including the electrolyte disturbance, cardiovascular system, gastrointestinal system, coagulation system, and central nervous system. The electrical rhythm that is displayed with delayed ventricular repolarization can be disturbed by hypocalcemia, which will also lengthen the QT interval and ST segment. Hypocalcemia can decrease cardiac performance, produce hypoperfusion, and ultimately result in acidosis [3].

Increased central, peripheral, and neuronal excitability can result from hypocalcemia. The tingling of the mouth and the tips of the fingers has been noted as a sign of hypocalcemia. A physical examination can be used to check for positive Chvostek's and/or Trousseau's signs. Additionally, individuals with hypocalcemia may experience convulsive seizures or a range of psychiatric symptoms, including psychoneurosis, psychosis, and an organic brain syndrome [3].

Moreover, calcium plays a significant role in the coagulation and hemostasis processes. Data from in vitro experiments showed that thrombin production and clot formation are impossible at ionized calcium concentrations below 0.25 mmol/L [5,6,7].

Risk factors for hypocalcemia in trauma

In the past, hypocalcemia after a traumatic event was believed to be caused primarily by citrated blood transfusions. The incidence of hypocalcemia in trauma patients on arrival at the hospital is approximately 16.4% up to 55% [4,8,9]. Multiple studies have shown evidence that trauma patients with hypocalcemia received more units of blood transfusion. Additionally, the incidence of hypocalcemia was seen commonly in trauma patients who required massive transfusions. Nowadays, multiple studies show the relationship between hypocalcemia and many factors such as hypothermia, acidosis, and coagulopathy, these factors are known as the trauma-lethal triad [1]. This study will evaluate available data related to hypocalcemia after trauma and show that hypocalcemia in trauma is multifactorial.

KEY MESSAGES:

- Trauma patients with hypocalcemia have been associated with increased mortality.
- Trauma-induced hypocalcemia is multifactorial.
- No current guideline on the specific timing of calcium measurement in trauma patients, so clinicians should be aware of trauma-induced hypocalcemia.
- The European guideline suggests to instantly correcting serum calcium less than 7.5 mg/dL or serum ionized calcium below 0.9 mmol/L in trauma patients who received a blood transfusion.

1. The relationship between hypocalcemia and trauma-lethal triad

Hemorrhagic shock causes a triad of death, describing the combination of hypothermia, acidosis, and coagulopathy. Acidosis surges serum-ionized calcium by competing with proteins (mostly albumin). It also contributes to coagulopathic bleeding in trauma patients. Meng et al. found that the lowering of pH from 7.4 to 7.2 reduces the activity of the coagulation proteases by more than half. Transfusion-induced hypocalcemia is associated with decreasing serum pH, which sequentially worsens coagulopathy in trauma patients [10].

Hypothermia causes worsening hepatic function in citrate metabolism; thus, the ionized calcium level was reduced due to binding with citrate. Hypothermia also directly interferes with the hemostatic process by slowing the activity of coagulation enzymes. In hypothermic patients, bleeding can be corrected by raising the core temperature as a result of improved platelet function and coagulation enzyme activity [11]. Calcium has an important function in the coagulation cascade. It is a necessary cofactor for clotting. In vitro, data demonstrate that thrombin generation and clot formation cannot occur with ionized calcium less than 0.25 mmol/L [5,6,7].

Ditzel et al. first described the term lethal diamond, thus the relationship of calcium with the other three components has been addressed [12]. The relationship between hypocalcemia and the lethal triad is demonstrated in Figure 1.

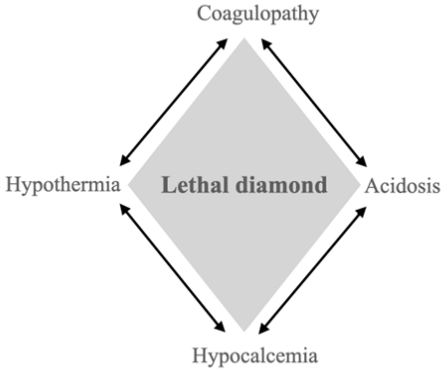

Figure 1. The lethal diamond.

2. The association of hypocalcemia and lactic acidosis

The disruption of the aerobic mitochondrial pathway caused by lower mean arterial blood pressure during hemorrhagic shock proceeds to lactate accumulation. Kuhna et al. demonstrated the phenomenon of lactate binding a significant amount of ionized calcium. The study found a significant correlation between hypocalcemia and lactate levels on day 3 with $p<0.001$ and a coefficient of $r=0.467$ (weak correlation) with $R^2=0.218$. High serum lactate and hypocalcemia are associated with poor outcomes. Lactate in lactic acidosis trauma patients binds and chelates to calcium; thus, it can cause worse hypocalcemia. Both hyperlactatemia and hypocalcemia are related and affect each other [13]. The relationship between acidosis and hypocalcemia is physiologically paradoxical. Acidosis causes the release of calcium from skeletal storage and competes with ionized calcium for binding to the imidazole group on albumin. Thus, acidosis increases the percentage of total serum calcium in the ionized form [14]. The correlation between total serum calcium and albumin decreases in animal models of hemorrhagic shock was indicated by decreasing calcium-albumin binding [15].

3. Calcium and transfusion

Ionized calcium plays a crucial role in the process of hemostasis and the coagulation cascade. It was required for platelet adhesion and the functions of clotting factors II, VII, IX, X, protein C, and protein S [2]. Figure 2 shows the locations in the coagulation cascade where ionized calcium is used [16].

Both whole blood and red blood cells are stored using citrate. Citrate is the anticoagulant substrate. It works by chelating calcium in the blood. In normal physiologic conditions, three grams of citrate can be metabolized into bicarbonate in the liver within 5 minutes. However, worsening hepatic function in traumatic shock patients and a blood component transfusion rate greater than 1 unit over 5 minutes were demonstrated to cause a decrease in ionized calcium levels by the free-floating citrate [17].

However, some studies reported an incidence of hypocalcemia even before transfusion. Webster et al. found that hypocalcemia patients were diagnosed in 55% (33/50) of patients on arrival to the emergency department before receiving blood and in 89% (33/37) of patients after receiving any amount of blood product [8]. Vasudeva et al. assessed the association between the presence of hypocalcemia at admission (iCa <1.11 mmol/L) and acute traumatic coagulopathy (INR > 1.5) in trauma patients with a shock index of 1 or higher. There were 50% of patients with admission ionized hypocalcemia prior to any blood product transfusion, of whom 2.6% had severe hypocalcemia (iCa < 0.8 mmol/L). Hypocalcemia was significantly associated with coagulopathy on arrival to the emergency department (OR, 5.5; 95%CI, 2.8 to 10.8; $p < 0.001$) [4]. Giancarelli et al. retrospectively evaluated the incidence of hypocalcemia (iCa < 1.12 mmol/L) and severe hypocalcemia (iCa < 0.90 mmol/L) in trauma patients. This study

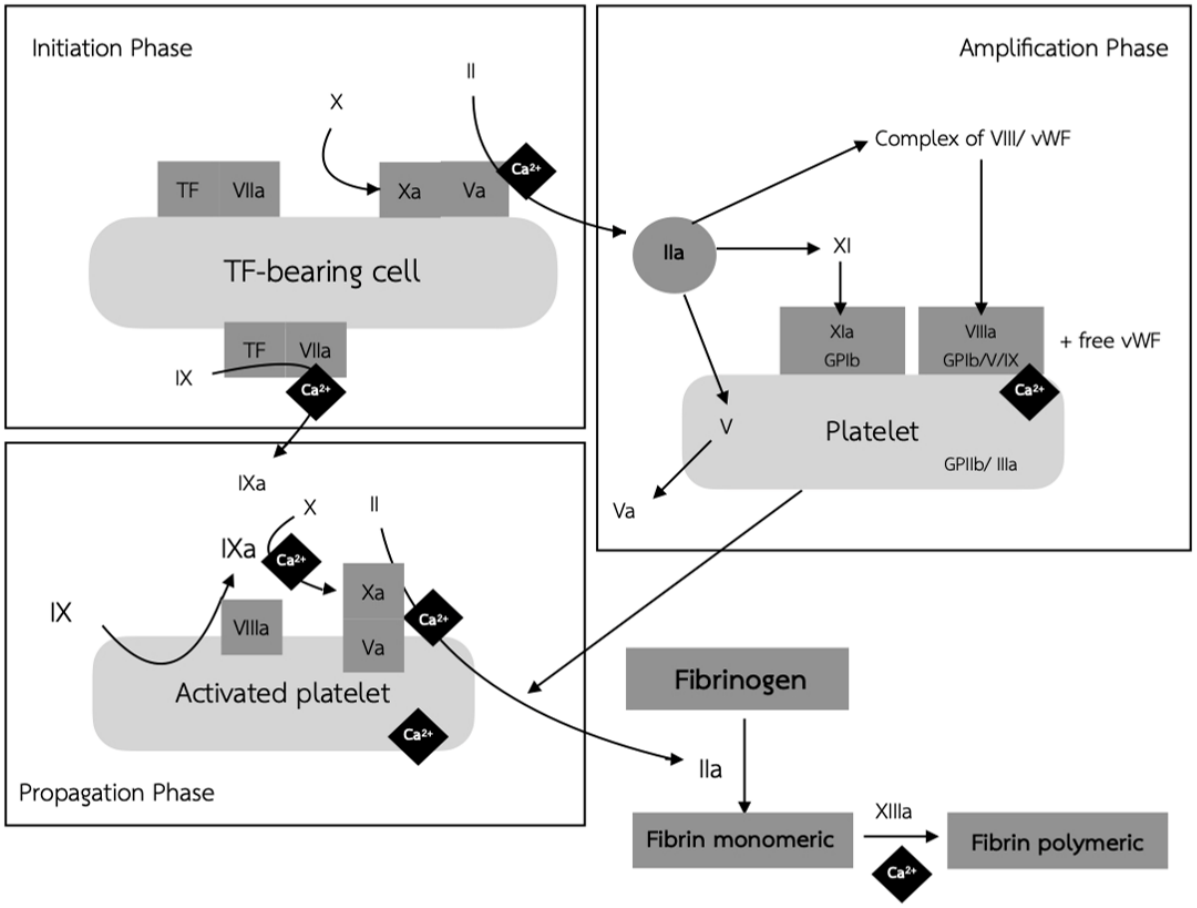

Figure 2. The locations in the coagulation cascade where ionized calcium is used.

showed that 97% of patients who received the massive transfusion protocol had hypocalcemia, and 71% of these patients had severe hypocalcemia. Furthermore, this study showed that severely hypocalcemia was associated with higher mortality (49% vs. 24%, p = 0.007) [18]. Byerly et al. identified independent risk factors for severe hypocalcemia (iCa ≤ 3.6 mg/dL) in trauma patients. They found a significantly higher risk of severe hypocalcemia in trauma patients who received pRBC plus FFP of 4 units during administration [AOR, 18.706; AUC, 0.897 (0.884 to 0.909)]. Therefore, severe hypocalcemia was an independent predictor of mortality [19].

4. Calcium and other electrolytes

4.1 Calcium and other electrolytes

Ionized calcium and ionized magnesium are essential cations in intracellular metabolism and mitochondrial acid-base balance [20]. Frankel et al. showed a 43% incidence of hypomagnesemia in injured patients, and the several common factors that predispose to hypomagnesemia were metabolic acidosis, hypocalcemia (iCa < 1 mmol/L), and drug-induced loss such as diuretics and citrate [21]. Carpenter et al. examined the effect of hemorrhagic shock in animal models on serum calcium and magnesium. This study manifested that ionized calcium levels decreased after the injury as a result of intracellular shifting, in contrast to ionized magnesium levels that increased during the first phase of hemorrhagic shock and subsequently fell during the resuscitation phase due to intracellular shifting for energy production. The decrease in ionized magnesium levels was presumably associated with hypocalcemia in traumatic shock [15].

4.2 Calcium and phosphate

Inorganic phosphate concentration increases threefold post-injury and may chelate and reduce biologically active ionized calcium. Kim et al. studies in blunt trauma patients found that nonsurvival patients had a significantly higher phosphate level than the survival group, and patients with hyperphosphatemia were associated with increased 30-day mortality (adjusted OR, 2.453; 95% CI, 1.164 to 5.171; p<0.018) [22]. Explanation of the association between hyperphosphatemia and mortality consequent results from phosphate chelating ionized calcium causing hypocalcemia in these patients. Hypocalcemia is a crucial factor in the mortality of trauma patients.

Outcomes of hypocalcemia in trauma

Traumatic bleeding itself causes patients to have hypocalcemic status; however, the treatment of hemorrhagic shock with blood transfusion is also precipitating this condition to be worse.

Transfusion-induced hypocalcemia has been reported in various studies and is associated with clinically worsening outcomes in trauma patients [4,5,23-26]. Moore et al. studied the incidence of hypocalcemia (iCa ≤ 1.0 mmol/L) in prehospital traumatic hemorrhagic shock patients to support the use of prehospital plasma. Prehospital plasma recipients had significantly higher rates of hypocalcemia compared with the control group (52.6% vs. 35.7%, p=0.03). Hypocalcemia was an independent predictor of mortality and massive transfusions [27]. Helsloot et al. showed mortality at 6 hours after arrival at the Emergency Department in major trauma patients was independently associated with iCa < 0.90 mmol/L (OR 2.69, 95%CI 1.67-4.34; P<0.001), iCa 1.30-1.39 mmol/L (OR 1.56, 95%CI 1.04-2.32; P=0.03), and iCa ≥ 1.40 mmol/L (OR 2.87, 95% CI 1.57-5.26; P< 0.001) [9].

Role of calcium replacement

There is evidence that hypocalcemia is linked to poorer outcomes for trauma patients; however, there is little data to support the idea that replacing lost calcium will lead to better results. The European guideline on the management of major bleeding and coagulopathy recommended that ionized calcium levels be monitored and kept within the normal range due to the pathophysiology of calcium in various roles in trauma patients. Serum ionized calcium levels below 0.9 mmol/L or serum calcium levels less than 7.5 mg/dL need to be rectified right away [28].

Calcium chloride is the suggested calcium agent; 270 mg of elemental calcium are included in 10 ml of a 10% solution. By contrast, just 90 mg of elemental calcium are present in 10 mL of 10% calcium gluconate. In the case of abnormal liver function, where delayed release of ionized calcium is due to reduced citrate metabolism, calcium chloride may also be preferable to calcium gluconate [28].

CONCLUSION

Trauma-induced hypocalcemia is multifactorial. Trauma patients with hypocalcemia have been associated with increased mortality. Recent data have introduced hypocalcemia integrated with the trauma lethal triad for predicting the prognosis and mortality of critically traumatized patients. The European guideline on the management of major bleeding and coagulopathy suggests that ionized calcium levels should be monitored and maintained within the normal range. Hypocalcemia should be corrected instantly [28]. However, the benefit of prophylactic calcium supplementation requires further study to support.

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