A review of transfusion- and trauma-induced hypocalcemia: Is it time to change the lethal triad to the lethal diamond?

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Traumatic Coagulopathy and the Effects of Transfusion

The principles of managing patients suffering from hemorrhagic shock have evolved over time. It is well supported that patients who continue to suffer from shock or hypoperfusion are at greater risk of morbidity and mortality attributable to blood failure precipitated by hypothermia, coagulopathy, and acidosis.[1] These three conditions—hypothermia, coagulopathy, and acidosis—collectively known as the lethal triad, serve as the foundational physiologic insults that describe the mechanisms of action of disseminated intravascular coagulopathy and drive the current hemorrhagic shock resuscitation efforts.[2,3] Hypothermia, defined as a core temperature under 35°C, exerts deleterious effects on hemostasis by inhibiting thromboxane A_2, causing a reduction in local vasoconstriction and platelet aggregation at the site of injury in addition to altering the rate at which enzymatic process occurs throughout the clotting cascade. Moreover, hypothermia is associated with a leftward shift of the oxygen-hemoglobin dissociation curve and a reduction in myocardial contractility, both leading to reduced tissue oxygenation and an increased state of oxygen debt. These mechanisms described previously directly correlate with coagulopathy and acidosis as irreversible shock progresses throughout the lethal triad. Coagulopathy, traditionally regarded as an international normalized ratio (INR) of 1.5 or greater in an acute setting, may additionally be exacerbated by hemodilution of platelets and clotting factors through crystalloid infusions.[4,5] Lastly, acidosis or serum pH of less than 7.36 is associated with a reduction in coagulation factor activity and increases in fibrin degradation rate and coagulation times, further exacerbating the traumatic hemorrhage induced coagulopathy.[6] It is through these mechanisms by which each element of the lethal triad overlaps upon the others. Although the use of whole blood (WB) and blood products has assisted in decreasing mortality for patients suffering from the lethal triad, the authors of this review believe that there are still gaps in the management of trauma-induced coagulopathy. The goal of this literature review was to demonstrate through examination of previous studies the prevalence of hypocalcemia in trauma and the need to address this deficiency in management of severely injured patients. From this, we hope to promote targeted research in the management of hypocalcemia in trauma and support recently published guidelines in trauma management that accounts for this gap in trauma-induced coagulopathy. We believe that early identification and correction of hypocalcemia in this patient population could be a missing link to the management and prevention of trauma-induced coagulopathy and effectively change the descriptor from the lethal triad to the lethal diamond.

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This study was presented at the Annual Meeting of the Committee for Tactical Emergency Casualty Care, May 13–17, 2018, in Charlotte, NC, and at the 31st Annual Meeting of the Special Operations Medical Association's Special Operations Medical Scientific Assembly, May 6–10, 2019, in Charlotte, NC. The discussions generated by this presentation subsequently drove changes to the Joint Trauma System's Damage Control Resuscitation Clinical Practice Guideline.

R.M.D. and J.L.A. shared co-first authorship.

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PATIENTS AND METHODS

In this review, initial studies were identified by searching Ovid for English language articles using the following key words: *hypocalcemia in trauma*, *prehospital blood transfusion*, and *hypocalcemia* and *transfusion*. Additional studies were then identified from the reference lists of the most relevant studies and were reviewed by two members (R.M.D. and J.L.A.) of the research team for relevance.

Twenty-three records were ultimately identified through this method; five articles were excluded because of lacking information related to hypocalcemia, one was later excluded because of not adding any additional conclusions that had not been previously covered, and one additional article was excluded due to a new protocol.[22] Information on the studies used in this review can be found in Table 1.

RESULTS

Trauma-Related Hypocalcemia

Webster et al.[19] noted that 55% of trauma patients in a major trauma center in the United Kingdom were hypocalcemic (iCa, <1.12 mmol/L) on arrival to the emergency department (ED) before the administration of any blood products. Magnotti et al.[15] also noted hypocalcemia on arrival of trauma patients to the ED, in which 56% (332 of 591 patients) had an ionized calcium of less than 1.0 mmol/L upon admission. This group, identified in the study as lo-Cal (short for low-calcium), was associated with higher mortality (15.5% vs. 8.7%, $p = 0.036$) and increased need for multiple (≥5 units of packed red blood cells [PRBCs] in 24 hours; 17.1% vs. 7.1%, $p = 0.005$) and massive transfusions (≥10 units of PRBCs in 24 hours; 8.2% vs. 2.2%, $p = 0.017$). Magnotti et al.[15] concluded that low ionized calcium levels on admission to the ED were a useful independent predictor for the need for multiple transfusions on trauma patients.

Transfusion-Related Hypocalcemia

Giancarelli et al.[18] noted that 97% of trauma patients receiving massive transfusion experience hypocalcemia, with 71% of those experiencing severe hypocalcemia, with an ionized calcium level of less than 0.90 mmol/L. The *severe hypocalcemia* group was noted to have lower platelets (176 [confidence interval (CI), 108–237] vs. 208 [CI, 169–272], $p = 0.003$), lower pH (7.14 [CI, 6.98–7.28] vs. 7.23 [CI, 7.14–7.33], $p = 0.019$), and higher mortality (49% vs. 24%, $p = 0.007$) than the group with an ionized calcium greater than 0.90 mmol/L. Those in the severe hypocalcemia group also received more units of blood products (34 [CI, 23–58] vs. 22 [CI, 18–30] units, $p < 0.001$). Neither group ever reached a median ionized calcium of 1.12 mmol/L.

Kyle et al.[20] came to the same conclusion in a separate research study looking at United Kingdom military casualties and their ionized calcium levels on arrival to a treatment facility after

TABLE 1. Information of Studies Included in Review

Author	Publication Year	Publication Type	Primary Outcome	No. Patients
Armand et al.[7]	2003	Review	N/A	N/A
Hästbacka and Pettilä[8]	2003	Retrospective	30-d Mortality	941
Cherry et al.[9]	2006	Retrospective	In-hospital mortality	396
Holcomb et al.[10]	2007	Special Commentary	N/A	N/A
Lier et al.[11]	2008	Review	N/A	N/A
Ho and Leonard[14]	2011	Retrospective	In-hospital mortality	352
Magnotti et al.[15]	2011	Observational	In-hospital mortality	591
Kornblith et al.[16]	2014	Prospective (blood)	Multiple lab values	34
Li and Xu[17]	2015	Retrospective	Mean citrate load	267
Bjerkvig et al.[1]	2016	Review	N/A	N/A
Giancarelli et al.[18]	2016	Retrospective	iCa lab value	156
Webster et al.[19]	2016	Retrospective	iCa lab value	55
Kyle et al.[20]	2017	Retrospective	iCa lab value	297
MacKay et al.[21]	2017	Observational	In-hospital mortality	41
Shackelford et al.[22]	2017	Retrospective	24-h/30-d Mortality	502

Lab, laboratory; N/A, not available.

receiving blood products en route. Hypocalcemia (iCa, <1.12 mmol/L) among those in the nontreatment group—those who did not receive calcium concurrently with prehospital blood products—was 70% (166 of 237 patients).

Webster et al.[19] noted that once patients began to receive blood products, the incidence and severity of hypocalcemia increased. Pretransfusion, ionized calcium levels were 1.11 (95% CI, 1.09–1.14 mmol/L), and after any amount of blood product, 89% (33 of 37 patients) were hypocalcemic, with a posttransfusion ionized calcium level of 0.98 mmol/L (95% CI, 0.93–1.02 mmol/L; $p < 0.001$).

MacKay et al.[21] looked at trauma patients admitted to an ED who were anticipating receiving a massive transfusion and noted that 85% (35 of 41 patients) experienced some level of hypocalcemia (iCa, <1.0 mmol/L), with 36.6% (15 of 41 patients) experiencing extreme hypocalcemia (iCa, <0.86 mmol/L) at some point during their treatment. Those in the *extreme hypocalcemia* group had more units transfused (median units transfused, 14 [8–20] vs. 5 [3–7]) and a higher mortality (60% vs. 4%, $p < 0.01$) compared with the *no extreme hypocalcemia* group, providing another example of a dose response of calcium level to blood products.[22] Of note, the researchers also noted that mortality increased in patients with hypercalcemia (iCa, >1.25 mmol/L) either on admission or who reached it because of overcorrection by clinicians, with mortality reaching 78% (7 of 9 patients, $p < 0.01$). The total percentage of patients who experienced hypercalcemia during some phase of their treatment was 22% (9 of 41 patients).[21]

Ho and Leonard[14] also noticed increased mortality associated with hypocalcemia from bleeding patients requiring massive transfusion (≥10 units of allogenic PRBCs or WB), showing an inverse concentration-dependent relationship between the two after initiation of massive transfusion (odds ratio, 1.25 per 0.1 mmol/L decrement; 95% CI, 1.04–1.52; $p = 0.02$).

DISCUSSION

Today, the concepts of damage control resuscitation (DCR)[10] and remote damage control resuscitation are well documented and supported. It is suggested that the resuscitative fluid of choice for DCR and remote damage control resuscitation is WB as shown by Kornblith et al.[16] This study compared the hemostatic potential of WB to that of reconstituted WB (1:1:1 or 2:1:1 PRBC–fresh frozen plasma–platelets) and crystalloids, showing that WB was superior to both component therapy and crystalloid therapy for hemostatic potential. Similar results were seen in a retrospective study of combat casualties in Afghanistan who received blood transfusions conducted by Shackelford et al.,[22] including a threefold decrease in 30-day mortality compared with the not-transfused group. This data is included in Table 2.

In addition to the bleeding itself causing patients to suffer from hypocalcemia, the treatment for hemorrhagic shock, that is, blood products, is further exacerbating the problem. This is due to the citrate present in blood products.

Both WB and red blood cells are stored using citrate as the anticoagulant, where 3 g of citrate is used per 1 unit of red blood cell and 1.66 g of citrate is used per unit of WB stored with citrate phosphate dextrose adenine.[17,23] Citrate works by chelating calcium in the blood.[17] During the clotting cascade, the release of calcium occurs after platelet adhesion, where it binds to phospholipids that appear after the activation of platelets and functions as a binding point for other coagulation factors.[17] Figure 1 details the different points in the coagulation cascade where ionized calcium is used.[11]

Once in the body, citrate is metabolized in the liver, where it is converted into bicarbonate. A healthy adult can metabolize 3 g of citrate in 5 minutes. However, in instances of decreased liver function (e.g., following trauma) or during a transfusion rate greater than 1 unit over 5 minutes, ionized calcium levels in the patient begin to decrease because of the ionized calcium in the blood being chelated by the free-floating citrate.[17] This condition is exacerbated more quickly when transfusing components (over WB) because of the increased amount of citrate in component therapy.[7]

As serum calcium levels drop, coagulopathy occurs, which can lead to continued hemorrhage and possible death.[17] The Kyle et al.[20] study suggested that "there was a dose response of calcium level to blood products with a significant decrease

TABLE 2. MEDEVAC Study Population Posttreatment Characteristics and Outcomes

Unadjusted Posttreatment Between-Groups Difference	Transfused Prehospital	Not Transfused Prehospital	*p**
KIA* (%)	2 (3.8)	58 (20.3)	0.003*
Died (KIA + DOW) within 24 h of MEDEVAC take-off from POI* (%)	2 (3.8)	64 (22.4)	0.001*
Died (KIA + DOW) within 30 d*	5 (9.4)	77 (26.9)	0.005*
TXA* (%)	48 (90.6)	144 (50.3)	<0.001*
Documented shock (SBP <90, HR >120, or shock index >0.09) upon ED arrival (%)	n = 52, 39 (75)	n = 233, 137 (63)	0.11
Massive transfusion (>10 units/24 h)* (%)	40 (75)	119 (42)	<0.001*
ISS, median (IQR)	29 (17–36)	24 (17–36)	0.179
AIS score indication torso hemorrhage (%)	22 (41.5)	108 (37.8)	0.646

*Statistically significant at <0.05 level by Fisher exact test.

KIA, killed in action; DOW, died of wounds; MEDEVAC, medical evacuation; POI, point-of-injury; SBP, systolic blood pressure; HR, heart rate; ISS, injury severity score; IQR interquartile range; AIS, abbreviated injury scale; TXA, tranexamic acid.

in calcium levels as the volume of blood products increased."[20] Again, as similar to the Kyle et al.[20] study, Webster et al.[19] showed that the more units of blood that were given, the lower the ionized calcium levels that were seen in patients.

Both trauma itself and transfusion of blood are associated with worsening hypocalcemia. What is the significance of this? As stated above, Giancarelli et al.[18] noted that patients in the severe hypocalcemia group had a higher mortality than those with an ionized calcium above 0.90 mmol/L on admission. Magnotti et al.[15] noticed higher mortality with ionized calcium levels of less than 1.0 mmol/L. Hästbacka and Pettilä[8] also concluded that a low ionized calcium level on admission of critically ill patients to an intensive care unit was associated with increased mortality, showing hazard ratios of 5.1 (95% CI, 2.9–9.0) for severe (<0.90 mmol/L) and 1.8 (95% CI, 1.3–2.4) for mild ionized hypocalcemia (0.90–1.15 mmol/L). In addition, Cherry et al.[9] noted that mortality was significantly increased in trauma patients with an ionized calcium of less than or equal to 1.0 mmol/L regardless of age or injury severity (26.4% vs. 16.7%, $p < 0.05$; odds ratio, 1.92) upon admission. While none of these studies prove causation, the evidence for correlation, at least, is overwhelming. This evidence suggests that the importance of early management of hypocalcemia in trauma patients may be of more significance than previously believed.

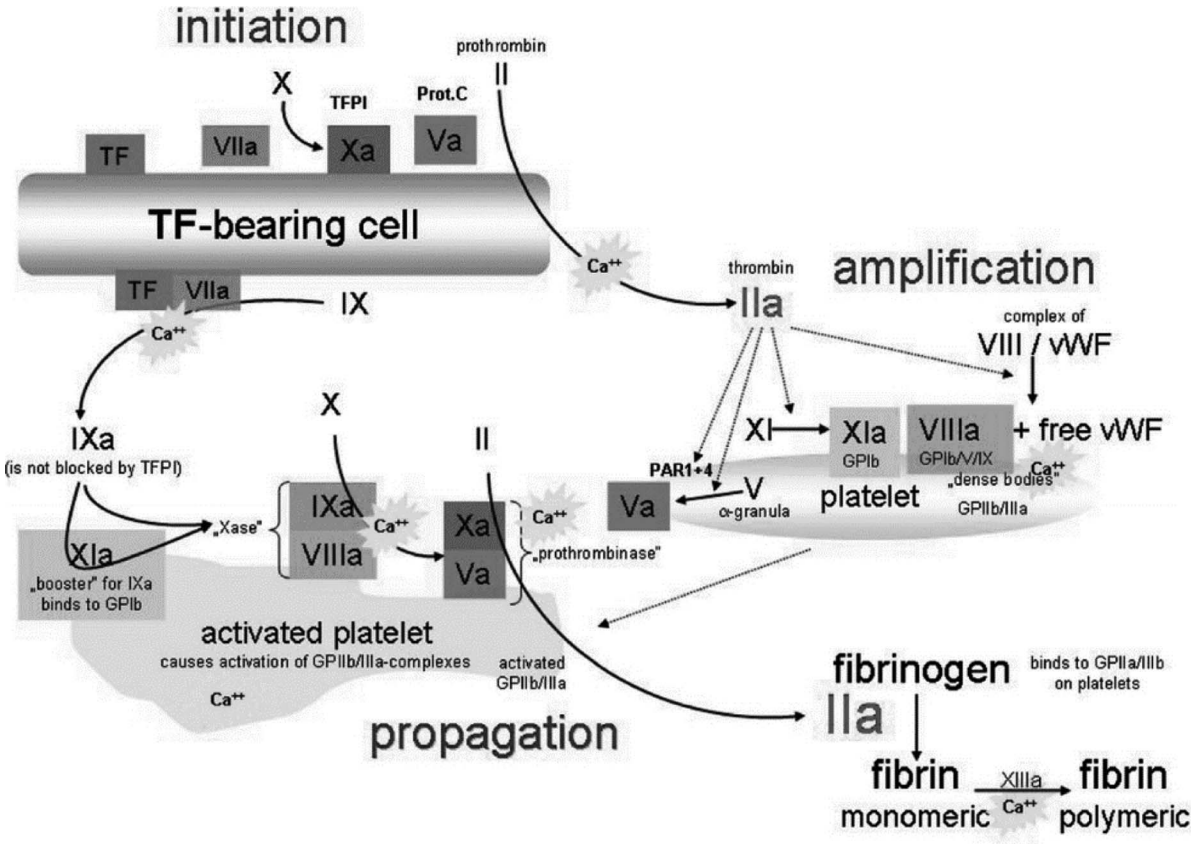

Figure 1. Present model of cell-based coagulation according to Hoffman and the target location of ionized calcium.[11–13]

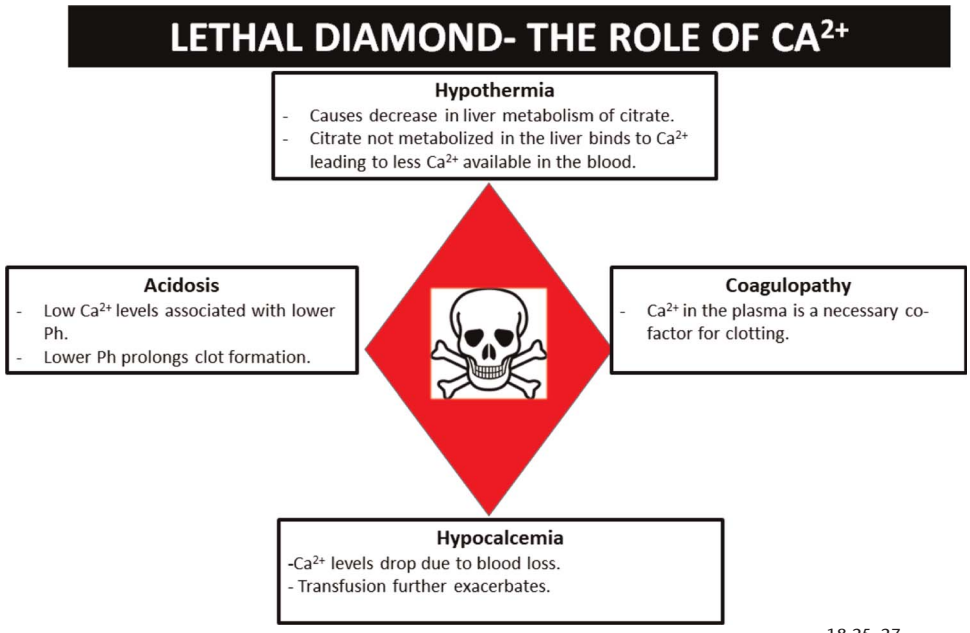

Figure 2. Demonstration of the interaction of calcium with the other aspects of the lethal diamond.[18,25–27]

Knowing that low ionized calcium levels on admission to an ED are associated with higher mortality, Kyle et al.[20] assessed whether early intravenous administration of calcium in the prehospital environment given concurrently with blood products had any impact on ionized calcium levels upon admission to the military treatment facility. Hypocalcemia in the treatment group, which received 10 mL of calcium chloride intravenously, was 28.3% (17 of 60 patients) compared with 70% (166 of 237 patients) of those in the nontreatment group who received blood products without calcium. Only 26.6% (63 of 237 patients) of those in the nontreatment group had ionized calcium levels within normal limits compared with 41.7% (25 of 60 patients) of those in the treatment group. Of note, patient mortality information was not included in this study.

Current US Military Protocols

The Joint Trauma System released an updated Clinical Practice Guideline (CPG) for DCR during the review process for this article that states a gram of calcium should be administered to patients "in hemorrhagic shock during or immediately after transfusion of the first unit of blood product and with ongoing resuscitation after every 4 units of blood products."[24] This CPG then recommends that ionized calcium should be monitored and treated if it drops below 1.20 mmol/L.[24]

The Lethal Diamond

Early, systematic management of these factors may lead to better outcomes for trauma patients. It is the belief of these authors that the lethal triad may be leaving out one other crucial factor that interacts with these other three conditions to the detriment of the trauma patient: hypocalcemia. We propose a new leg to the lethal triad, making a "lethal diamond," in which the four arms are coagulopathy, hypothermia, acidosis, and hypocalcemia. Hypocalcemia works as a functional piece in this diamond by interacting with the other three conditions as they do each other in the lethal triad. Coagulopathy occurs as calcium levels drop because the extrinsic, intrinsic, and central clotting cascade pathways rely on proper levels of ionized calcium in the blood.[18] Furthermore, these same receptors necessary for clotting that require ionized calcium can also be blocked by hydrogen ions because it is a competitive receptor antagonist.[25] Lower levels of ionized calcium in the blood are also associated with lower pH, increasing acidosis. Hypothermia decreases liver metabolism, which is important to metabolize citrate, as it is introduced to the patient through transfusion.[26] Lastly, proper ionized calcium levels are necessary for the cardiac myocytes to properly function. Because they rely on a calcium-induced calcium release, low levels of ionized calcium reduce the heart's ability to properly contract. This problem also adds to the other three factors of the current lethal triad.[27] This information is depicted below in Figure 2.

By including hypocalcemia in the lethal diamond, it is the hope of these authors that this will emphasize the need for early management of ionized calcium levels in trauma patients, to prevent or minimize the presence and severity of hypocalcemia. Although MacKay et al.[21] did notice increased mortality associated with hypercalcemia, because of either natural or iatrogenic causes, the conclusions ascertained previously stress the importance of hypocalcemia management, while being cognizant of overtreating to the point of hypercalcemia. These authors propose the Joint Trauma System DCR CPG to become the current standard for treating patients suffering from hemorrhagic shock, with the addition of ensuring that ionized calcium levels do not exceed 1.25 mmol/L, as a result of the data from the MacKay et al. study.[21,24] However, currently there is a knowledge gap on whether early administration of calcium products to serious trauma patients expecting to receive a transfusion has any impact on patient mortality. The inverse relationship between ionized calcium level on admission to an ED and patient mortality does not necessarily guarantee that early administration of calcium will correct this problem. While low ionized calcium levels have been

associated with increased mortality, it is not clear whether the low ionized calcium is a cause of this outcome or just a predictor of it.

As seen in Table 1, to these authors' knowledge, there are currently zero prospective randomized, controlled trials focused on patient-centered outcomes concerning early calcium administration to bleeding trauma patients requiring transfusion. Therefore, targeted research is needed to determine if the early management of hypocalcemia in trauma can have a positive impact on patient mortality.

CONCLUSIONS

Thus far, the following has been established: over half of trauma patients are hypocalcemic before receiving any blood products on arrival to an ED;[15,19] transfusions further increase the severity of hypocalcemia, with more units transfused correlating to worsening ionized calcium levels;[14,15,18–21] lower ionized calcium levels on admission to an ED are associated with increased mortality;[8,9,15,18] and early administration of calcium products concurrently with blood product administration has been associated with a higher ionized calcium level on admission to an ED.[20] A double-blinded placebo-controlled randomized trial is needed to determine whether this is correlation or causation. It is the hope of these researchers that this review will promote interest in conducting this study and result in better outcomes for trauma patients using the lethal diamond as a reference, focusing on early administration of calcium products to trauma patients expected to receive transfusion. The authors also believe that existing research networks in the military and civilian prehospital and trauma systems will be instrumental in generating this study.

Limitations

Because of the time-sensitive nature of trying to initiate a prospective trial looking toward patient-centered outcomes of early calcium administration to trauma patients, the authors elected to not perform a full systematic review, so we could publish our search of the available data. The concept of the lethal diamond cannot be proven until a prospective, double-blind, placebo-controlled randomized control study has been completed and published. As such, there are concerns about study limitations of the available literature.

AUTHORSHIP

R.M.D. conceived of the presented idea and first developed the theory. J.L.A. conducted the literature search and wrote the article with the help of the other authors. All authors discussed the results and contributed to the final article.

DISCLOSURE

The authors declare no conflicts of interest.

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