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Citrate & Hypocalcemia in Massive Transfusion

Noah Mehr, MD [1], Erik Fong [2], Timothy Carll, MD [1]

[1] Department of Pathology, University of Chicago, Chicago, IL
[2] University of California – Berkeley, Berkeley, CA

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ABSTRACT

This brief review provides an overview of the role of citrate-containing preservatives in the processing and storage of blood components for transfusion, as well as the physiologic impact of citrate ion on transfusion recipients. Correction of hypocalcemia and other toxicities arising from citrate infusion is being increasingly appreciated in trauma and damage control resuscitation; a review of current practice guidelines regarding the identification and correction of hypocalcemia and citrate toxicity in emergency scenarios is provided. Lack of awareness about the citrate content in any given blood product likely impairs prompt and accurate reversal of hypocalcemia; however, such data is limited in literature and is generally unavailable to the transfusing provider. We offer calculated citrate levels in common blood products, and emphasize that plasma-rich product such as fresh frozen plasma and apheresis platelets contains relatively greater amounts of citrate than packed red blood cells, meriting more nuanced calcium repletion.

Introduction

Citrate is an organic anion widely used in blood banking as an anticoagulant and preservative due to its ability to chelate ionized calcium, a critical cofactor in the coagulation cascade. While citrate is essential for safe blood storage and transfusion, generally in the forms of trisodium citrate and citric acid, large volume infusion such as during massive transfusion can lead to citrate accumulation and toxicity, particularly in patients with impaired hepatic function. Citrate toxicity may result in significant physiologic disturbances including hypocalcemia, hypomagnesemia, metabolic alkalosis, and coagulopathy, all of which contribute to increased morbidity and mortality in traumatic resuscitation.

Recent literature underscores the complex role of citrate in massive transfusion, and the contribution of hypocalcemia to mortality is becoming recognized. Although calcium repletion is increasingly emphasized in trauma resuscitation guidelines, current practices are often based on limited or inaccurate estimates of citrate content within blood products. Blood products are frequently regarded as interchangeable with respect to their citrate content; in fact, the actual citrate concentrations vary significantly by product type, collection method, and processing technique. Red blood cells collected via whole blood phlebotomy may incorporate different anticoagulant and preservative solutions than plasma units collected via apheresis separation, and thus citrate concentrations are certain to vary. Despite these known variations, there is limited data to guide optimal calcium repletion strategies tailored to citrate exposure.

Role of citrate as an anticoagulant & preservative

Massive transfusion—commonly defined as the administration of 10 or more units of whole blood (WB) or packed red blood cells (pRBCs) within 24 hours, or transfusion to correct the loss of more than one blood volume in the same time frame—is a mainstay of modern trauma and critical care.[1–3] It is estimated that 3–5% of civilian trauma patients and up to 10% of military trauma patients require massive transfusion, which is associated with increased mortality.[3,4] Current transfusion standards emphasize the use of either group O whole blood or a balanced component strategy (typically a ratio of pRBCs, fresh frozen plasma, and platelets to reconstitute whole blood).

All blood components are collected and processed using anionic citrate which prevents coagulation by chelating ionized calcium (Ca^{2+}), an essential cofactor for platelet activation and the coagulation cascade. Chemically, citrate is a tricarboxylic acid with three negatively charged moieties that form strong ionic complexes with divalent cations including calcium and magnesium.[5] Citrate-containing anticoagulant solutions in current usage include acid-citrate-dextrose (ACD), citrate-phosphate-dextrose (CPD) or citrate-phosphate-dextrose-adenine (CPDA-1) depending on the product type and processing method. Additionally, additive solution (AS1,3,5,7) is used to extend the shelf life of pRBC.[6]

While citrate is essential for safe blood storage, it can have adverse effects during transfusion, particularly when administered in large quantities. Routine simple transfusion of blood products containing citrate is common and not associated with toxicity in healthy adults.[7] Citrate metabolism is primarily hepatic with contributions from skeletal muscle and kidneys. The metabolism of citrate via the tricarboxylic acid (TCA) cycle creates bicarbonate as a byproduct, leading to a mild metabolic alkalosis in patients receiving large transfusion volumes.[5,7,8]

Physiologic impact of citrate infusion

Citrate toxicity in the setting of massive transfusion has been associated adverse effects on the cardiovascular, coagulation, and metabolic systems.[5,9,10] The major consequence is hypocalcemia, a direct result of citrate binding to ionized calcium (Ca^{2+}), rendering it unavailable for physiologic use. Hypocalcemia in trauma is commonly defined as an ionized calcium level <1.1mmol/L.[11] While it is estimated that the liver can metabolize 3g of citrate in 5 minutes, decreased citrate clearance has been demonstrated in circumstances of hepatic hypoperfusion, hypothermia and liver dysfunction.[9,10,12–14] Additionally, patients who receive proportionally large blood volume transfusions such as newborns undergoing exchange transfusion or trauma patients undergoing massive transfusion protocols are at increased risk for citrate toxicity.[10] Importantly, the risk of citrate toxicity is not just proportional to the dose administered but also to the rate and context of administration—particularly in massive transfusion protocols involving component therapy. In trauma patients, hypocalcemia has been identified in up to 55% in patients not receiving transfusion, possibly reflecting intracellular calcium shift during tissue ischemia or necrosis, and in up to 97% for those undergoing massive transfusion protocol.[9] Subsequently it has been shown that trauma patients with hypocalcemia have a marked increase in morbidity and mortality irrespective of injury severity.[9,15–19] Authors Ditzel et al have proposed that hypocalcemia be included in the so-called “diamond of death” in trauma patients in which the common trauma findings of acidosis, hypothermia and coagulopathy are all exacerbated by hypocalcemia.[9,10,16,20] A recent comprehensive review article by authors Schriner et al has further demonstrated the likely detrimental effects of citrate independent of hypocalcemia.[10]

Hypocalcemia has significant cardiovascular implications, as calcium homeostasis impacts myocardial contractility, vascular smooth muscle tone, and cardiac conduction.[5,21–23] Low ionized calcium levels due to citrate toxicity blunt the inotropic response of the myocardium, reducing cardiac output.[5] Additionally, hypocalcemia has been shown to prolong the QT interval, increasing the risk of ventricular arrhythmias and sudden cardiac events.[5,24,25]

The effect of citrate on acid-base balance is complex and influenced by both the metabolism of citrate and the underlying physiology of trauma. When metabolized, citrate is converted into bicarbonate, which can contribute to a metabolic alkalosis with respiratory acidosis.[7] This has been demonstrated in orthotopic heart and liver

transplant patients, as well as in pediatric patients.[7,8] However, this alkalinizing effect is often delayed or diminished in trauma patients, who commonly have hepatic hypoperfusion due to shock, leading to slower citrate clearance.[14] Conversely, stored blood products are very mildly acidic, with a pH ranging from 7.0 initially to 6.3 at the end of shelf life, contributing to a transient metabolic acidosis upon transfusion.[20,26,27] This acidosis can be further worsened in hemorrhagic shock due to systemic switches to anaerobic metabolism by hypoperfused tissues and lactic acid accumulation. In trauma, acidemia itself has been identified as an independent predictor of mortality, with worsening outcomes observed as pH drops below 7.2.[15,20,28,29]

Calcium is a vital component of the coagulation cascade and is required for the formation of the tenase and prothrombinase complexes. Calcium is essential for optimal platelet activation and aggregation, including calcium-dependent shape change, granule release, and binding of fibrinogen to GPIIb/IIIa receptors.[30,31] As such not only is hypocalcemia in trauma associated with acute traumatic coagulopathy, but circulating citrate has been shown to decrease thrombin generation and platelet aggregation independent of calcium levels.[32–34]

Magnesium, which binds to citrate even more strongly than calcium, also plays a fundamental role in coagulation, platelet function and ventricular function.[35–38] It acts as a cofactor in the activation of clotting factors and supports platelet aggregation and membrane stability. It also contributes to cardiac repolarization and contractility, with deficiency linked to arrhythmias, prolonged QT intervals, torsade de points and reduced cardiac output.[35,39–44] In addition to direct binding of citrate to magnesium in massive transfusion, hypomagnesemia can also contribute to refractory hypocalcemia by disrupting parathyroid hormone (PTH) physiology.[45–47] Low serum magnesium impairs the secretion of PTH and induces target tissue resistance to PTH, resulting in hypocalcemia that fails to correct even with calcium repletion until magnesium levels are restored[48,49].

Citrate content in blood products

While the adverse effects of hypocalcemia, coagulopathy, and metabolic alkalosis due to citrate toxicity in massive transfusion are well recognized,[9,10,15] the exact citrate content of specific blood components remains poorly characterized in literature. This lack of detailed, product-specific concentrations makes it difficult to develop evidence-based calcium repletion protocols, and such data is routinely unavailable to the transfusing provider. Although manufacturers and blood banking guidelines do describe the concentrations and volumes of these solutions, reported values vary by source and often contradict one another[6,50].

In reality, citrate content varies significantly depending on the collection method (whole blood vs apheresis), the type and volume of anticoagulant and additive solutions used and the degree of post-collection processing. Additionally, the use of pathogen reduction technologies and special product modification such as cell washing or volume reduction introduce additional variability in the final citrate content of the transfused product. It should be noted that component therapy using a 1:1:1 ratio of pRBCs, plasma, and platelets exposes the patient to more cumulative citrate than whole blood transfusion due to the greater combined volume of anticoagulants and preservatives used in processing each product separately.

By reviewing the reagent contents reported by manufacturers of blood product collection and processing kits, expected content of citrate in common blood product can be estimated. These are proposed in Table 1 following the methods outlined in Alghanem et al[21] and reflect a representative sampling of blood bank inventory at a large academic trauma center.

Table 1: Estimated citrate concentration in commonly transfused blood products.

Blood Product	Preservative and/or additive solution(s)	Estimated citrate content (mmol)	Estimated citrate content (mg)
Whole Blood	CPD	7.35	1390
pRBC (from whole blood)	CPD, AS-1/5/7	1.00	189
pRBC (from apheresis)	CP2D, AS-3	2.62	494
FFP (from whole blood)	CPD	6.35	1200
FFP (from apheresis)	ACD	3.69	698
Platelets (from apheresis)	ACD, PAS	4.14	783
Cryoprecipitated antihemophilic factor (5-unit pool)	CPD	1.49	282

Footnote: Common blood components are listed with their relevant citrate-containing preservative solutions. Citrate concentration and per-unit citrate mass load are calculated based on manufacturer reagent data and assuming distribution of citrate in the extracellular volume compartment without significant catabolism during processing and storage.

These expected values assume distribution of citrate in the extracellular product volume during component processing and storage. Citrate was assumed to have minimal intracellular uptake or metabolism, however a study by D'Alessandro et al showed that RBCs stored in AS-3 were able to uptake and metabolize citrate[51]. These estimates suggest plasma-rich products to have a greater citrate load than pRBC units; however, they have not been directly validated. To our knowledge, no direct measurement of product citrate concentrations has yet been published.

Current practices in emergency & massive transfusions

The importance of detecting hypocalcemia and of calcium repletion has gathered attention in recent years. The European Task Force for Advanced Bleeding Care in Trauma (TFABCT) sixth edition guidance recommends monitoring of ionized calcium following major trauma and during massive transfusion, noting ionized calcium as superior to total serum calcium for its sensitivity to acidotic conditions and wide availability on blood gas analyzers, often at the point of care.[52] The American College of Surgeons TQIP massive transfusion in trauma guidelines recommend baseline assessment of ionized calcium upon arrival in the ICU, followed by repeat assessment as needed or at least hourly.[53] Baseline assessment may allow for earlier identification and correction of hypocalcemia, which is often present even before transfusion. Indeed, a 2024 meta-analysis identified high rates of hypocalcemia in trauma patients upon admission; subgroup analysis of patients not receiving prehospital blood transfusion demonstrated mean ionized calcium levels of 1.07mM.[54]

Intravenous calcium may be administered in two commonly available formulations. Calcium chloride is relatively inexpensive and has high bioavailability; a 1g/10mL vial of 10% calcium chloride (formulated as calcium chloride dihydrate) contains approximately 272mg of elemental calcium. However, due to risk of tissue irritation or necrosis if extravasated, calcium chloride should be administered through a central line. By comparison, a 1g/10mL vial of 10% calcium gluconate contains approximately 93mg of elemental calcium but can be safely administered via peripheral intravenous line. In the emergent setting, calcium chloride is more frequently used because of the difference in elemental calcium availability—approximately threefold that of calcium gluconate.

However, the optimal dosing for calcium repletion remains elusive. Guidance on traumatic damage control resuscitation from the Joint Trauma System recommends repletion of calcium to patients in shock—in particular, one 10mL ampoule of 10% calcium chloride (or 30mL of 10% calcium gluconate) should be administered "after approximately four units of citrated blood products transfused".[55] This corresponds to approximately 70mg elemental calcium per blood product, but this guidance does not acknowledge any heterogeneity in blood product citrate content. Treatment of ionized calcium <1.2 mM is also advised. TFABCT sixth edition guidance recommends administration of calcium chloride to correct ionized calcium levels below 0.9mM or total serum calcium levels below 7.5 mg/dL.[52] No empiric recommendation for concurrent calcium repletion is provided. Alarmingly, this guidance also cites each unit of pRBC or FFP as containing approximately 3 grams of citrate, which exceeds the total input of citrate used in any FDA-approved blood collection or manufacturing process. A recent survey of United Kingdom-based helicopter services identified all respondents as carrying exogenous calcium for repletion during pre-hospital transfusion; however, repletion guidelines varied, with respondents administering calcium chloride usually after the first or second blood product but some after the fourth or greater and some having no guidance at all.[56,57]

A retrospective cohort study by Chanthima et al[58] affirmed the majority (83.2%) of trauma admissions receiving blood products to be hypocalcemic upon first measurement of ionized calcium. However, this study did not identify a relationship between either initial hypocalcemia (there defined as ionized calcium <1.18 mM) or calcium repletion on in-hospital mortality. No difference in molar ratio of repleted calcium dose to citrate load was identified. The authors were unable to recommend any specific calcium repletion regimens.

Another retrospective study by Alghanem et al[21] evaluated both the ratio of administered calcium to number of blood transfusions (all types) and the ratio of administered calcium to infused citrate based on our calculations in relation to ionized calcium. Using receiver operating characteristic curves, no calcium administration ratio was identified as meaningfully differentiating patients who would develop severe hypocalcemia (ionized calcium <0.9 mM). However, an upper limit ratio of 0.903 mmol calcium per citrated blood product was identified which differentiated patients who would develop hypercalcemia (ionized calcium >1.35mM), possibly reflecting over-repletion. This ratio would correlate to approximately 36 mg elemental calcium per citrated blood product—half that recommended by Joint Trauma System guidance. Clearly, further prospective study is required to refine calcium repletion guidance.

Conclusion

It is generally accepted that correction of hypocalcemia during emergency transfusions is of survival benefit; however, guidance on how to correct remains conflicted and based on flawed or nonexistent data regarding the citrate content in transfused blood products. Although we offer calculations suggesting that plasma-rich components likely contribute a higher citrate load than red cell products, this remains to be demonstrated with real-world testing of blood product inventories.

Further study is needed to refine evidence-based calcium supplementation protocols that account for product-specific citrate content while remaining practical in emergent settings. Further study into the role of magnesium is also merited—to our knowledge, no formal guidance exists regarding identification and correction of hypomagnesemia. Magnesium homeostasis is scarcely mentioned in traumatic resuscitation literature and is often overlooked in the acute bleeding setting. In our view, the best guidance would acknowledge the relatively greater concentration of citrate in plasma-rich products while maintaining a simple approach that is intuitive to the transfusing provider.

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