



## Letter to the Editor

## Calcium management in massive hemorrhage protocols



We read with great interest the article by Chin et al. [1], which provides compelling information about the heterogeneity in Massive hemorrhage protocols (MHP) among all hospitals in Ontario with a transfusion service.

However being engaging, these different MHP propose few solutions regarding calcium management. First of all, the article reported that testing for ionized calcium (iCa) was routinely performed in 42% (41/97) hospitals only (more likely in large and medium hospitals). Then, there is no information about whether this testing lead to attempts at maintaining iCa concentration to normal levels or not.

Ionized calcium is a divalent cation essential for many biological functions ranging from coagulation to cardiovascular tonus. Thus, calcium homeostasis is tightly regulated, and disorders in calcium levels can lead to life threatening situations. Severe hemorrhages challenge this homeostatic balance, likely through calcium chelation by phosphate from tissue injury and citrate accumulation during blood product transfusion resuscitation. In both severely injured patients and mixed populations of patients requiring massive transfusion, disturbed calcium levels are associated with poor outcomes. However, there is still a lack of evidence about the causal role of these derangements, and whether maintaining or correcting calcium to normal levels is associated with better outcomes.

Magnotti et al. [2] hypothesized that admission iCa levels could potentially predict the need for multiple transfusions in critically ill trauma patients. Data were collected retrospectively over nine months on 591 trauma activations. 332 patients (56%) presented at admission with hypocalcemia (iCa < 1.00 mmol/L). Furthermore, as compared to those with iCa > 1.00 mmol/L, mortality was significantly increased in low iCa group (15.5% vs. 8.7%,  $p=0.036$ ). Finally, multivariable logistic regression revealed ionized hypocalcemia as an independent predictor for multiple transfusions (OR = 2.94 [95% CI, 1.053–4.996]).

In 2016, Giancarelli et al. [3] completed a detailed study describing the incidence and severity of hypocalcemia in trauma patients receiving massive transfusion. This retrospective study reported iCa monitoring and replacement, and blood products administration in 156 trauma patients receiving massive transfusion (>10 units pRBC/24 h) over a 4-year period. In this study, calcium levels were repeated, up to 24 h after massive transfusion protocol discontinuation. The overall incidence of severe hypocalcemia (iCa < 0.90 mmol/L) in this population was 71% ( $n=111$ ). Severe hypocalcemia was then associated with higher mortality (49% vs 24%;  $P < .01$ ) and higher transfusion volumes.

A recent study by MacKay et al. [4] analyzed iCa management data from 41 patients admitted to the Hospital of the University of

Pennsylvania with massive transfusion protocol activation from January 2013 through December 2014. Data about admission demographics, injury severity and mechanism, mortality and details of the electrolyte trends and timing of transfusions over the first 24 h of admission were retrospectively collected. The authors found that laboratory-defined hypocalcemia was likely not a clinically useful marker of deranged calcium homeostasis. Receiver operator curve analysis identified inflection points in mortality outside a Ca<sup>2+</sup> range of 0.84 to 1.30 mmol/L. Using these extreme values, 15 (37%) patients had hypocalcemia with a 60% mortality (vs 4%;  $P < .01$ ). More unexpectedly, hypercalcemia on presentation or from overcorrection by even the laboratory-defined limit is associated with increased mortality (78% vs 9%;  $P < .01$ ). Patients with extreme hypocalcemia and hypercalcemia received more red blood cells, plasma, platelets, and calcium repletion. Finally, mortality was highest in those patients who received large volumes of blood products, a resuscitation ratio closer to 1:1:2 (FFP:PLT:pRBC) and whose calcium concentration significantly deviated from normal. However, if calcium levels remained within normal limits, even during massive resuscitation, associated mortality was lower.

These results highlight the importance of monitoring and maintaining iCa concentration to normal ranges in injured patients requiring blood transfusion. As a body of proof, the 2016 European guideline on management of major bleeding and coagulopathy following trauma recommended that iCa levels be monitored and maintained within the normal range during massive transfusion. (Grade 1C) [5]. We believe that further investigations in massive hemorrhage protocols could give more details regarding monitoring and targets of iCa, and the best way to maintain calcium homeostasis: Ca<sup>2+</sup> molecule, route of administration, dose. To conclude, we would like to know if the authors could provide their opinion regarding the management of Ca<sup>2+</sup> in MHPs.

## Conflict of interest

All authors declare no conflict interest.

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