Maintenance of Ionized Calcium During Prolonged Extreme Massive Transfusion During Liver Transplantation

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ABSTRACT

Introduction: Massive transfusion may cause ionized hypocalcemia, a complication that, when severe, causes hemodynamic instability. Extant literature fails to provide effective guidance on replacement strategies to avoid severe ionized hypocalcemia in the most extreme situations.

Case Presentation: We discuss a liver transplant in which our empiric calcium replacement strategy resulted in no critically low ionized calcium values during the pre-reperfusion phase of a liver transplant with over 140 000 mL of bank blood transfusion, with an average of 10 000 mL per hour for 14 hours.

Discussion: Few comparable reports exist. Most rely upon monitoring with subsequent replacement, but these have not been effective at avoiding severely low ionized calcium values.

Conclusions: Our empiric calcium replacement strategy of 1 gram of calcium chloride per liter of citrated bank blood transfused, in 200 mg/200 mL increments, resulted in successful maintenance of ionized calcium during the anhepatic phase of liver transplantation while on continuous veno-venous hemofiltration.

INTRODUCTION

Massive transfusion is associated with ionized hypocalcemia due to citrate intoxication, a complication in which the anticoagulant citrate, added to banked blood products, chelates ionized calcium in the circulation with hemodynamic and potentially coagulopathic consequences. Citrate intoxication can be severe during liver transplantation because citrate metabolism is impaired by liver failure and is potentially nonexistent during the anhepatic phase of liver transplantation in patients with renal failure. Extant studies, opinions, and case reports suggest calcium administration paradigms that vary widely, with no effective guidance on replacement strategies.[1] As a result, a combination of empiric calcium salt administration plus reactive correction in response to measured ionized calcium values has been reported with variable success. Critically low ionized calcium values are associated with severe and life-threatening cardiovascular complications during massive transfusions.

In liver transplantation, our institution has published data on supplemental calcium requirements and resultant ionized calcium values during massive transfusion. Although no mandatory protocol exists at our institution, the results of our study[2] have become a de facto calcium replacement paradigm in the pre-reperfusion time frame amongst our small team of liver transplant anesthesiologists. Although QT interval has been shown to correlate with ionized calcium in massive transfusion,[3] this parameter would be difficult to monitor continuously with the necessary precision at our institution with our equipment.

We report the efficacy of a nominal 1 gram calcium chloride per liter of citrated blood, when given in 200 mg $CaCl_2$/200 mL citrated blood boluses, in a single patient who received the largest transfusion during liver transplantation performed to date at our institution. This was also the largest transfusion in a patient who survived that is available for comparison in peer-reviewed medical literature.[3] This transfusion consisted of approximately 140 liters of blood products, with 50 liters of transfusion during the anhepatic/pre-reperfusion phase of the operation when citrate metabolism was minimal.

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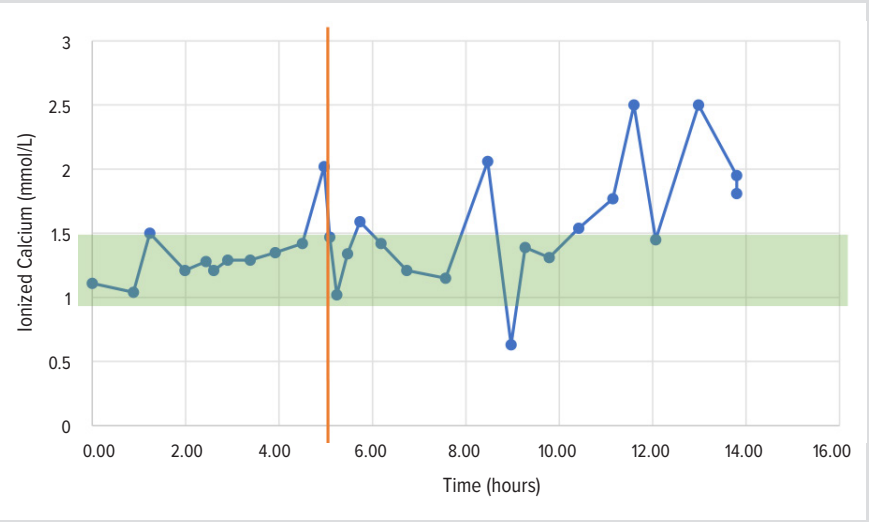
CASE PRESENTATION

The patient is an approximate 40-year-old 75 kg male with a history of sclerosing cholangitis receiving his third liver transplant for cirrhosis and end-stage liver failure, with a total bilirubin of 27 mg/dL and a direct bilirubin of 19 mg/dL at the time of transplant. Each of his prior transplants lasted approximately 10 to 15 years with good function before the recurrence of cirrhosis and liver failure. He has no significant history of alcohol or illicit drug use. He was transferred to our center because of anticipated difficulty with transplantation, substantial abdominal scarring, portal vein thrombosis, and adhesions. These predisposing factors, the projected inability to decompress the portal venous system during transplantation, and technical issues related to vascular anastomoses suggested massive blood loss would ensue during transplantation.

Figure. Ionized Calcium Values Versus Time



The shaded region represents values near the normal range (1.18 to 1.34 mmol/L at the authors's institution) and above those identified as critically low in the literature. The vertical line at 5 hours represents the time of reperfusion of the liver.

The operation proceeded conventionally using femoral to subclavian venous bypass with a heat exchanger to maintain body temperature in the normal range. Because the patient had renal failure secondary to hepatic failure with a creatinine of about 4 mg/dL, continuous veno-venous hemofiltration (CVVH) was instituted primarily for management of transfusion-associated hyperkalemia and acidosis, although CVVH also has the potential benefits of reducing hyperphosphatemia as well as calcium-citrate complexes from bank blood. CVVH blood flow was at 250 mL/min and dialysate with a 0K+ electrolyte solution (NxStage RFP-402) was run at 4 L/min. It was not possible after several attempts to decompress the portal venous system with venous bypass due to thrombosis of major vessels. A venous conduit was created to supply portal blood flow to the transplanted liver and decompress the portal venous system but was not available for venous bypass, as reperfusion was performed as soon as the conduit was completed. Massive blood loss was encountered on entry to the abdomen as all peritoneal surfaces were involved with engorged collateral vessels. The rate and volume of blood transfused was quantitatively measured via the Belmont Rapid Infuser (Belmont Medical Technologies, Billerica, Massachusetts), which was used solely for packed red cell, fresh frozen plasma, and crystalloid products. End of case totals were obtained from summation of measurements indicated by our blood center on individual units of blood products.

Of the 142 558 mL total volume of blood transfused, approximately 50 000 mL was given in the pre-reperfusion period. The transfusion prior to reperfusion was managed by a single anesthesiologist (corresponding author) and was performed by giving a 200 mL bolus of a 1:1 ratio of packed cells and fresh frozen plasma at up to 500 mL/min through a Belmont rapid infusion device. Although the nominal flow rate of 500 mL/min could be achieved with crystalloid solution, the actual blood product flow achieved was typically around 300 mL/min due to pressure limiting at 300 mmHg because of the higher viscosity of blood products compared to crystalloid solutions. The individual initiating the bolus of bank blood products gave a simultaneous bolus of 200 mg $CaCl_2$ intravenously through a different port of a central line. Platelets and cryoprecipitate were administered through a separate intravenous (IV) infusion set, and the patient received a proportional amount of $CaCl_2$. When cell saver blood was available, fresh frozen plasma and a proportional dose of $CaCl_2$ was administered in approximate equal volumes. Therefore, 50 grams of $CaCl_2$ were administered for these 50 liters of citrated bank blood.

On average, the ionized calcium level was recorded every 26 minutes after the initial reading at the start of the surgical intervention, resulting in a total of 13 measurements during the pre-reperfusion period of the operation (lasting 5 hours, 16 minutes). The mean and standard deviation for ionized calcium values during this time frame was 1.32 mmol/L ± 0.26 mmol/L. Of note is that there were no ionized calcium values below 1.0 mmol/L during this phase of the operation, suggesting that no critically low values resulted from this infusion paradigm.

Post-reperfusion, patient care was managed by a different anesthesiologist (second author). Clinical signs indicated that hepatic function and, therefore, citrate metabolism was reestablished. For the next approximately 93,000 mL of blood transfu-

sion over the following 8.5 hours, approximately 38 grams of calcium chloride were administered. A more "reactive" paradigm of calcium administration was performed, giving less calcium when blood was administered slowly and more calcium when blood was administered more rapidly up to the ratio used pre-reperfusion. The actual amount of calcium replacement was based on the intuition of the anesthesiologist, with corrections based on measured ionized calcium values. Measurements of ionized calcium were performed on average every 32 minutes during the post-reperfusion phase, and only one critically low measurement of ionized calcium was recorded. From the standpoint of citrate metabolism, in both phases of the operation, an average of over 10 000 mL of citrated blood was given per hour until hemostasis was obtained at the end of the case.

The Figure graphically shows ionized calcium versus time, with the shaded region representing values close to the normal range (1.18-1.34 mmol/L) at our institution. The vertical line at 5 hours represents the time of reperfusion of the liver. Prior literature suggests that critically low ionized calcium values that impact hemodynamic function and outcome begin at a lower limit around 1.0 - 0.9 mmol/L;[2] hence, the shaded region representing optimal values has a lower limit in the Figure of 1.0 mmol/L. The upper limit of the shaded region represents the mid normal range ± 1 SD of the pre-reperfusion values (1.24 mmol/L ± 0.26 mmol/L), giving 1-1.5 mmol/L as optimal ionized calcium values. There were no critically low values pre-reperfusion and only one post-reperfusion. Although several high values existed, the value immediately pre-reperfusion was an intentional prophylactic $CaCl_2$ bolus for hyperkalemia on reperfusion. Elevated ionized calcium values post reperfusion are common during liver transplantation. At the end of surgery, the ionized calcium was approximately 1.8 mEq/L, although the total calcium was 19.8 mg/dL (normal range 8.5-10.2 mg/dL). Most blood gas electrolyte values were in the normal range intraoperatively, with potassium values of 4.5-5.5 mEq/L, and only a few intraoperative potassium values were elevated by blood gas.

DISCUSSION

The ability to perform massive transfusion has evolved to extreme levels for prolonged durations, and for those managing the transfusions and metabolic consequences, this creates the emerging problem of proper calcium management to avoid citrate toxicity. Critically low ionized calcium concentrations are associated with worse outcomes during massive transfusion, although the literature involves diverse surgical populations of trauma, transplant, and vascular surgery. In trauma patients, critically low ionized calcium concentrations are associated with larger transfusions and also with more severe injuries; therefore, multiple confounders exist in this relationship, making the study of individual factors more difficult. However, in the liver transplant population, very large transfusions are possible, and proper management of ionized calcium concentrations can be more readily associated with protocols of transfusion management without concurrent pathology as a confounding factor in the size of the transfusion. In liver transplantation, it is common to progress from low citrate metabolism compared to normal, to no citrate metabolism in the anhepatic phase, to normal or high citrate metabolism post-reperfusion in a functioning hepatic graft. This gives distinct phases to this operation in terms of how calcium replacement is managed for citrated blood products.

The size of the bolus delivered through the rapid infusion device is partially based on the practical consideration of 200 mL representing approximately 2-3 mL citrated blood/kg for a 70-100 kg adult. Similarly, we chose a 200 mg bolus of calcium chloride to match calcium to citrate using our previously published data prior to reperfusion of the liver. Because we routinely place central lines in liver transplant recipients, the calcium chloride is given through the central line to reduce the risk of peripheral vein sclerosis. Adverse events occasionally have been observed or reported with larger boluses of calcium chloride through central lines or when calcium administration causes transient extreme hypercalcemia. Cardiovascular collapse has been described with excessive calcium administration, possibly related to hypercalcemia-mediated mast cell degranulation.[4] Acute hypercalcemia also has been associated with tachyarrhythmias[5] and bradyarrhythmias.[6,7] The package insert for calcium chloride[8] recommends a maximum rate of 100 mg $CaCl_2$ per minute through a central vein, although the clinical scenario of massive transfusion and citrate intoxication is not mentioned in this recommendation. Clearly, the rate we required in this transfusion of 10 000 mL/hour would require a continuous infusion rate of 167 mg/min if the transfusion had been uniform and continuous; but in reality, the transfusion was neither continuous nor uniform. Rates of 300 mL/min blood with calcium chloride replacement at 300 mg/minute were required at times, as that was the maximal achievable blood flow rate with our equipment and extant vascular access.

CVVH undoubtedly helped with some electrolyte abnormalities during this massive transfusion. Our prior study indicated that ionized calcium was kept in a narrower range closer to normal when CVVH was used.[2] The solution used during most of the procedure, which incorporated all of the massive transfusion, was NxStage RFP-402, with 140mEq/L Na^+, 0 mEq/L K+, 1.35 mEq/L Ca^{++}, 109 mEq/L Cl-, 1 mEq/L Mg^{++}, 100 mg/dL glucose, and 35 mEq/L bicarbonate. This may explain why we were able to use less calcium than the prior study[2] indicated in the average of patients who had lower usage of CVVH. Only 850 mEq of bicarbonate were used during this 14-hour operation, so the bicarbonate content of CVVH may have reduced the propensity to develop a metabolic acidosis, as blood products have substantial loads of lactic acid from the anaerobic metabolism of red cells in storage.[9]

CONCLUSIONS

This case demonstrates that in the absence of citrate metabolism, matching 200 mg of calcium chloride with each 200 ml of citrated bank blood bolus provides good results in massive transfusions prior to reperfusion by keeping ionized calcium levels near the normal range and preventing critically low values. After reperfusion, an average of 40% of this ratio of $CaCl_2$ to banked blood was required due to metabolism of citrate.

Financial Disclosures: None declared.

Funding/Support: None declared.

Acknowledgements: The patient gave written authorization for publication of this case report.

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