Clinical Reports

Management of prolonged QT interval during a massive transfusion: calcium, magnesium or both?

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Purpose: This case report describes the intra-operative management of a prolonged QT interval in the setting of massive transfusion.

Clinical Features: A previously healthy, 45-yr-old man presented for repair of a class IV thoraco-abdominal aneurysm. The initial stages of the operation were relatively uneventful, with the exception of an estimated blood loss of 5.0 L. At this point the patient's QT interval became markedly prolonged, and subsequently narrowed in response to supplemental calcium and magnesium. A blood sample taken just before QT prolongation revealed an ionized calcium of 0.98 mmol·L^{-1} and an ionized magnesium of 0.37 mmol·L^{-1}, indicating, that low magnesium may have contributed to the QT interval prolongation.

Conclusion: This case illustrates the importance of following both ionized calcium and magnesium in the setting of a massive transfusion.

Objectif : L'observation suivante décrit le traitement peropératoire d'un intervalle QT prolongé dans le cadre d'une transfusion massive.

Éléments cliniques : Un homme de 45 ans, auparavant en bonne santé, a été admis pour la réparation d'un anévrisme thoraco-abdominal de classe IV. L'opération se déroulait sans incident, sauf pour une perte sanguine d'environ 5,0 L. Puis, l'intervalle QT s'est allongé de façon marquée pour ensuite se rétrécir, en réponse au calcium et au magnésium thérapeutiques. L'analyse de sang prélevé juste avant la prolongation QT a révélé la présence de calcium ionisé à 0,98 mmol·L^{-1} et de magnésium ionisé à 0,37 mmol·L^{-1}, ce qui pouvait indiquer que le bas taux de magnésium avait contribué à la prolongation de l'intervalle QT.

Conclusion : Ce cas illustre l'importance de tester le calcium et le magnésium ionisé au cours du traitement d'une transfusion massive.

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HYPOCALCEMIA is a well recognized cause of prolonged QT interval during massive transfusion. However, hypomagnesemia may also cause prolongation of the QT interval[1] and should also be considered in the differential diagnosis as the QT interval lengthens. This case illustrates the potential contribution of hypomagnesemia in intraoperative QT prolongation.

Case report

A 45-yr-old, 80 kg previously active and healthy man was taken to the operating room for repair of a Type IV thoraco-abdominal aneurysm. The patient's history included uneventful general anesthetics, no known drug allergies, and only a single medication, Tylenol#3 for chronic back pain. Review of systems revealed excellent exercise tolerance with no cardiovascular symptoms. He smoked a pack of cigarettes per day without any overt respiratory complications and had an epidural corticosteroid injection four weeks previously for chronic back pain. The physical examination, preoperative laboratory work, and ECG were unremarkable. The CT scan showed a large thoraco-abdominal aneurysm beginning at the level of the domes of the diaphragm, and extending caudally to involve the entire abdominal aorta and a portion of the left common iliac artery.

After a joint discussion with the surgeon, CSF drainage but not femoral/femoral bypass or spinal cooling was utilized. Anesthesia was induced with 140 mg propofol, 50 μg sufentanil, and 100 mg succinylcholine *iv*. Maintenance was achieved with intermittent sufentanil boluses, nitrous oxide/oxygen, isoflurane, and muscle relaxation with doxacurium. The airway was secured using a #41 French left-sided double lumen tube with the aid of a fibreoptic bronchoscope. Intravenous access consisted of two peripheral 14 gauge intravenous catheters, a #7 French double lumen right internal jugular catheter, and a 20 gauge right radial arterial line. Attempts to keep the patient warm included the use of two forced air warmers, a level 1® normothermic intravenous administration set, and a Fenwal® blood warmer. Prior to aortic cross clamp, 35 g mannitol *iv* were given and an epidural catheter, previously placed in the intrathecal space, was set to drain at 12 cm H_2O. The aorta was cross-clamped at 12:30, five hours after induction of anesthesia.

Throughout the morning the surgery provided a steady blood loss, and by 13:30 the estimated blood loss was 5.0 L. Replacement to that point consisted of 2.0 L pentaspan, 6.0 L normal saline, and six units packed red blood cells and the patient's temperature was 36.8°C. In addition, the patient had received 4 g magnesium, and 1 g calcium chloride in response to low ionized values we had received from our point of care testing facility, a Nova Biomedical stat profile M over the course of the morning.

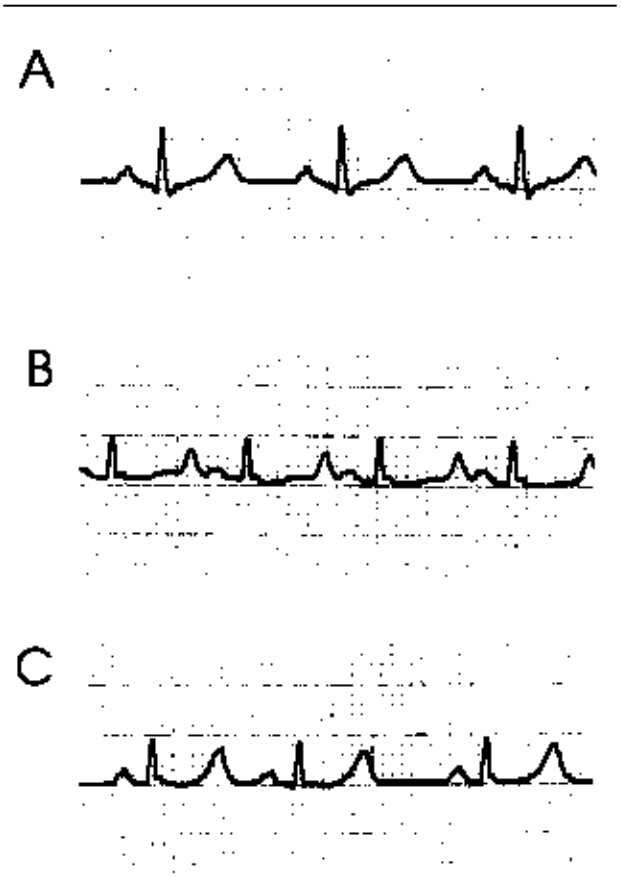

FIGURE Lead II ECG illustrating variation in the QT interval at various times
A) 08:45, pre-induction
B) 13:33, after 5.0 L blood loss
C) 13:37, after 1 g $CaCl_2$ and 2 g Mg *iv*

At this time (13:33) the patient's QT interval became markedly prolonged (Figure). This was treated with 1 g calcium chloride, and 2 g magnesium with prompt effect and the QT interval returned to baseline. The blood sample from 12:52 revealed ionized calcium of 0.98 $mmol \cdot L^{-1}$ (normal, 1.13-1.32 $mmol \cdot L^{-1}$), and ionized magnesium of 0.37 $mmol \cdot L^{-1}$ (normal, 0.41-0.61 $mmol \cdot L^{-1}$). The blood sample at 13:50 revealed ionized calcium of 1.38 $mmol \cdot L^{-1}$ and ionized magnesium of 0.35 $mmol \cdot L^{-1}$.

Unfortunately, this patient continued to bleed due to ongoing surgical difficulty and by the end of the case had required 13 L normal saline, 2.0 L pentaspan, 25 units platelets, 52 units packed red cells, 2.0 L cell sal-

TABLE Causes of Prolonged QT interval[14,15]

- Congenital (often associated with deafness)
- Drug Induced (an ever increasing number of medications, notably)
  - Antiarhythmic Class Ia (procainamide, quinidine)
  - Antiarhytmic Class III (amiodarone, sotalol)
  - Anti-histamine (Terfenadine, Astemizole)
  - Anti-microbial, anti-malarial, anti-protozoal
  - GI prokinetic (cisapride)
  - Psychoactive (chloral hydrate, phenothiazines, haloperidol)
- Electrolyte Abnormalities
  - Hypocalcemia, hypokalemia, hypomagnesemia
- Right radical neck dissection
- Increased sympathetic nervous system activity

vage blood, 27 units FFP, and 10 units cryoprecipitate. He received 8 g magnesium, and 9 g calcium using point of care ionized determinations. Despite this aggressive supplementation the last recorded values for ionized calcium and magnesium were 1.38 and 0.35 $mmol \cdot L^{-1}$ respectively, thus leaving a low ionized magnesium despite receiving 8 g magnesium *iv* in supplementation. The remainder of the blood chemistry was: sodium 146 $mmol \cdot L^{-1}$, potassium 4.7 $mmol \cdot L^{-1}$, hydrogen ions 55.2 $nmol \cdot L^{-1}$, bicarbonate 18.4 $mmol \cdot L^{-1}$, PCO_2 45.9 mmHg, and a pH of 7.26.

The patient remained in the ICU for eight days. The postoperative course was complicated by ongoing bleeding requiring blood products and hypotension requiring inotropic support. On day three, a left hemicolectomy was performed for a gangrenous left hemicolon. By day six, the patient required dialysis secondary to acute renal failure. Care was then withdrawn on day eight after seizure activity, a CT scan of the brain, and EEG consistent with severe cerebral anoxia were observed.

Discussion

Hypocalcemia is a well-recognized complication of massive blood transfusion. As such, several influential bodies have made statements regarding monitoring ionized calcium in the setting of transfusion medicine. The American Association of Blood Banks[2] states "low ionized calcium concentration can induce severe cardiac arrhythmias . . . Extra precaution must be taken in patients who are unable to communicate or who may metabolize citrate poorly." This includes patients under general anesthesia who may have several risk factors for poor metabolism of citrate: namely, they are frequently hypothermic, may have decreased cardiac output with a corresponding decrease in liver perfusion, and may be hyperventilated. In terms of specific recommendations for calcium monitoring, the American Association of Blood Banks[2] mention the possibility of observing the QT interval on the ECG, and measurement of ionized calcium without indicating which is the preferred option. A final statement of "massively transfused patients or those with severe liver disease may benefit from measurement of ionized calcium levels as a guide to replacement therapy" seems to indicate that measurement of ionized calcium may be preferable.

The Canadian Blood Services state that citrate toxicity is very rare, but potentially serious as "symptoms can range from muscle tremors to cardiac arrhythmia, and even cardiac arrest."[3] With respect to monitoring for hypocalcemia the handbook points out that standard serum calcium estimation does not distinguish the ionized from complexed fractions. However, no specific guidelines about the use of ionized calcium measurements in the setting of transfusion exist. Monitoring of the ECG is referred to in that: "ECG monitoring can be helpful in detecting the effect of hypocalcemia."

The presence of hypocalcemia in massive transfusions has been documented in a previous review of the subject.[4] In this report, 471 massive transfusions were reviewed and the ionized calcium was less than normal (1.13 – 1.32 $mmol \cdot L^{-1}$) in 94% of patients and was very low (<0.70 $mmol \cdot L^{-1}$) in 46% of patients. When dealing intra-operatively with ionized calcium values it becomes important to realize at what level treatment is indicated. The literature[5] suggests ionized calcium <0.60 $mmol \cdot L^{-1}$ may be associated with cardiac arrest and should be treated aggressively. Conversely, an ionized calcium of >0.80 $mmol \cdot L^{-1}$ that is asymptomatic does not require treatment. However, the authors recognize that the threshold to treat may be higher than 0.8 $mmol \cdot L^{-1}$ if the patient is under anesthesia as symptoms cannot be assessed.

The problem of hypomagnesemia receives less attention than that of calcium homeostasis. Neither the Canadian Blood Services nor the American Association of Blood Banks mention the problem of hypomagnesemia in their respective manuals. However, low ionized magnesium is a problem in the setting of a massive transfusion due to both the administration of magnesium free crystalloid,[6] and binding with excess citrate.[7] Citrate toxicity leads to hypomagnesemia because citrate has an equal binding affinity for both ionized magnesium and ionized calcium.[8] That this leads to clinically relevant hypomagnesemia has been documented in liver transplantation[7] and in the setting of massive transfusion.[9]

The manifestations of hypomagnesemia mimic hypocalcemia and include central nervous system irritability, skeletal muscle spasm, and cardiac dysrhyth-

mias. Specifically, hypomagnesemia as was seen in our case, is known to cause a prolonged QT interval.[1] In addition, cardiac arrhythmias seen in association with hypomagnesemia may only respond to magnesium therapy and are often refractory to conventional antiarrythmics and defibrillation.[10] Thus, hypomagnesemia does occur in massive transfusions and its clinical and electrocardiographic features may be difficult to distinguish from hypocalcemia.

The normal range for ionized calcium is 1.13 to 1.32 $mmol \cdot L^{-1}$. In our case, the ionized calcium was 0.98 $mmol \cdot L^{-1}$ (well above 0.8 $mmol \cdot L^{-1}$) 30 min before prolongation of the QT interval. The next measurement 20 min after receiving supplemental 1 g $CaCl_2$ *iv* was 1.38 $mmol \cdot L^{-1}$, indicating that perhaps low ionized calcium was not entirely responsible for our observed QT prolongation. In contrast, the ionized magnesium was 0.37 $mmol \cdot L^{-1}$ (<0.41 $mmol \cdot L^{-1}$) a half-hour before the QT prolongation and despite receiving an additional 2 g Mg *iv*, remained low at 0.35 $mmol \cdot L^{-1}$ after the QT interval had returned to baseline. It is then difficult to implicate hypomagnesemia alone as being responsible for the observed prolongation of the QT interval. However, an ionized calcium of 0.98 $mmol \cdot L^{-1}$ would not be expected to prolong the QT interval. Therefore, we believe that low ionized magnesium may have been partly responsible for the QT prolongation we observed. In addition, by the time the case was finished the patient had received 8 g magnesium and still the ionized magnesium remained below normal. Therefore we agree with previous authors[9] who state that serum ionized magnesium should be monitored in the setting of massive transfusion.

When magnesium is to be replaced in the setting of massive transfusion the preparation of choice is magnesium chloride as the sulfate ions in magnesium sulfate can bind calcium and aggravate an associated hypocalcemia.[11] Magnesium is known to be a vasodilator. Magnesium is associated with a mild and transient decrease in blood pressure due to peripheral vasodilatation and causes a consistent increase in cardiac index.[12] However, large doses of magnesium are well tolerated. This is illustrated in a study in which magnesium was given in doses of 60 $mg \cdot kg^{-1}$ (about 4 g) over one minute *iv* as part of an induction technique and only a minor decrease in blood pressure was noted.[13] Magnesium supplementation can then be administered fairly rapidly. Although prudence may suggest avoidance of a bolus administration in the setting of massive transfusion because these patients may be cardiovascularly unstable.

In summary, both hypocalcemia and hypomagnesemia are recognized complications of massive transfusion and both may give rise to a prolonged QT interval. Therefore, if the QT interval prolongs in association with massive transfusion, both possibilities should be considered.

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