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SEVERE HYPOMAGNESEMIA INDUCED BY POSTOPERATIVE ZINC SUPPLEMENTATION: AN ILLUSTRATIVE DEMONSTRATION OF ELECTROLYTE HOMEOSTASIS

Max Slosarski[1], Christ Ordookhanian[2], Ryan F. Amidon[3], Edward Lee[2], Tedrik Markarian[4], Paul Kaloostian[5]

[1] School of Medicine, Idaho College of Osteopathic Medicine, Meridian, USA
[2] Internal Medicine, University of California, Riverside School of Medicine, Riverside, USA
[3] School of Medicine, Medical College of Wisconsin, Milwaukee, USA
[4] Human Biology, University of Southern California, Los Angeles, USA
[5] Neurosurgery, Pasadena, USA

Corresponding author's e-mail: christ.ordookhanian@medsch.ucr.edu

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ABSTRACT

Background: Managing electrolyte abnormalities is one of the cornerstones of properly caring for and managing hospitalized patients. Typically, electrolyte derangements are managed by direct repletion, volume status correction, or hemodialysis; however, the persistence of electrolyte abnormalities despite utilizing appropriate initial strategies requires further investigation.

Case Description: A 72-year-old male presented to the emergency department with weakness 2 months post-exploratory laparotomy with ileostomy for small bowel perforation complicated by intra-abdominal infection. The patient was treated for sepsis and imaging revealed intra-abdominal and abdominal wall abscesses. After drainage, recovery was complicated by treatment of refractory hypomagnesemia in the context of zinc supplementation.

Discussion: If initial electrolyte repletion measures do not provide the intended benefit, investigating secondary causes of refractory electrolyte abnormalities is necessary. While hypomagnesemia is one of the least common electrolyte derangements seen within the general acute care hospital setting, in facilities with relatively high volumes of bariatric or gastrointestinal surgical patients, keeping the phenomenon of zinc-induced hypomagnesemia in mind becomes more crucial due to its frequent use in those settings.

Conclusion: This case highlights the effects of excess high-dose zinc supplementation in a patient without zinc deficiency in the postoperative period who developed treatment-resistant hypomagnesemia due to zinc-induced impairment of magnesium absorption as well as gastrointestinal and renal losses.

KEYWORDS

Hypomagnesemia, zinc supplementation, post-operative recovery, electrolytes

LEARNING POINTS

- Zinc supplementation can cause hypomagnesemia.

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INTRODUCTION

Medical management of postoperative patients requires a fine balance between managing comorbidities and addressing new concerns, while preserving the integrity of the surgical work completed. Once the surgical site is closed at the end of an operation, the medical team's focus shifts toward rehabilitation which continues for years thereafter and during which, nutritional management is of key importance. Following surgery, wound healing begins with hemostasis, followed by inflammatory, proliferative, and maturation stages[1]. During the proliferative phase, fibroblasts invade the wound site as inflammatory cells exit as endothelial cells proliferate, facilitating neovascularization that supports transport of essential nutrients. Endothelial cell proliferation requires specific enzymes, collagenases, and plasminogen activators to degrade hemostatic clots and extracellular matrix (ECM), promoting continued proliferation, migration, and angiogenesis. Importantly, the ECM-degrading metalloproteinases depend on zinc for their activity[2].

Guidelines for postoperative care supplementation are primarily directed toward bariatric surgery patients. However, using guidance from the American Association of Clinical Endocrinologists, American College of Endocrinology, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists, it is well documented that zinc supplementation should be at least considered, particularly if there is any concern for deficiency[3]. Notably, concern for deficiency can be mitigated by a patient's preoperative nutritional status or zinc levels. We highlight the need for a multimodal approach to determining if a patient is a prime candidate for zinc supplementation or if initiating such may result in unwanted metabolic complications.

CASE DESCRIPTION

A 72-year-old male with a past medical history significant for diabetes mellitus type 2, iron deficiency anemia secondary to chronic blood loss, hereditary hemorrhagic telangiectasia, hepatic hematomas, and portal vein thrombosis status post thrombectomy presented to the emergency department from a rehabilitation facility with a chief complaint of weakness. He recently underwent exploratory laparotomy with ileostomy two months prior for small bowel perforation complicated by intra-abdominal infection requiring antibiotic therapy at a medical facility in Mexico. The cause of the perforation was unknown to the patient and his family, and records were not made available.

At presentation to the emergency department, code sepsis was initiated due to the patient being hypotensive at 91/55 mmHg, tachycardic with a heart rate of 107 bpm, and tachypneic with a respiratory rate of 28 bpm. Oxygen saturation on room air was 96% and the patient was afebrile with a temperature of 36.3°C. Initial laboratory values were significant for an unremarkable white blood cell count and platelet count of 6.9 K/µl and 263 K/ µl respectively, a critically low hemoglobin of 4.7g/dl with a normocytic mean corpuscular volume of 86.3 fl and increased red-cell distribution width to 22.6%, an international normalized ratio of 1.2, hyponatremia of 125 mmol/l, hypochloremia of 89 mmol/l, an elevated blood urea nitrogen to 54 mg/dl, an elevated creatinine of 1.44 mg/dl with a known baseline of 0.8 mg/dl, magnesium (Mg) of 2.3 mg/dl, phosphate (PO_4) of 3.70 mg/dl, and calcium (Ca) of 8.6 mg/dl.

A computed tomography scan of the abdomen and pelvis was significant for multiple rim-enhancing fluid collections in the lower abdominal and pelvic cavity. There were collections in the left lower abdomen *(Fig. 1A)*, the left pelvis *(Fig. 1C)*, and the deep right pelvis *(Fig. 1D)*. Additionally, there was a skin wound on the midline anterior abdominal wall and a drainage catheter terminated at the superior aspect of the wound. There was a rim-enhancing fluid collection deep to the skin wound and diffuse edema of abdominal and pelvic mesenteric fat *(Fig. 1B)*.

The patient was taken to the operating room. Drainage of the abdominal wall abscess was completed with debridement of skin and subcutaneous tissue, as well as pulse lavage of the abdominal wall wound. Surgical abscess cultures grew carbapenemase-producing organism *Klebsiella oxytoca*

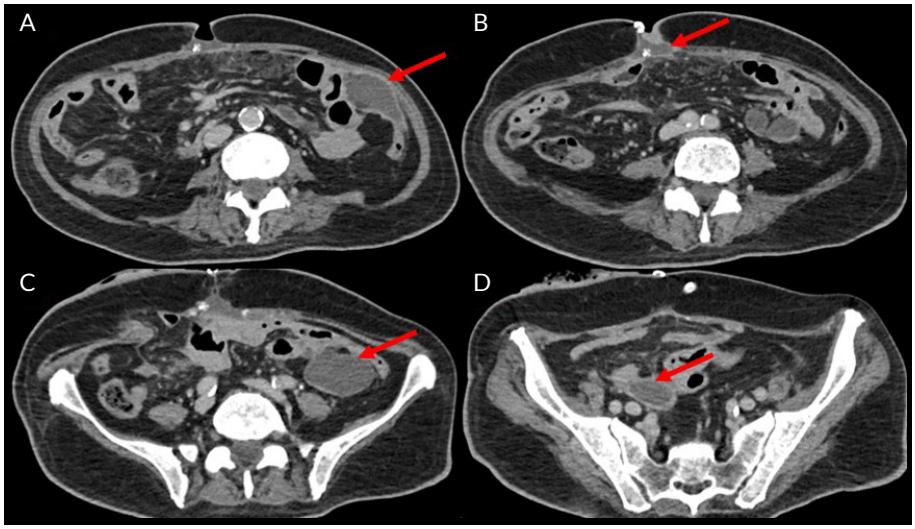

Figure 1. Axial computed tomography scan with contrast demonstrating (A) a rim-enhancing fluid collection in the left lower abdomen (red arrow), (B) a skin wound on the anterior abdominal wall along the midline with a drainage catheter terminating at the superior aspect of the wound as well as with diffuse edema of the mesenteric fat (red arrow), (C) a rim-enhancing fluid collection in the left pelvis (red arrow), and (D) a rim-enhancing fluid collection in the deep right pelvis (red arrow).

and *Escherichia coli* with both having high antimicrobial agent sensitivities to levofloxacin (minimum inhibitory concentration <0.5 for both). A 5-day course of 500 mg levofloxacin three times per day was initiated.

Starting on postoperative day (POD) 1, the patient was started on 220 mg zinc sulfate which contains 50 mg of elemental zinc. This was prescribed daily by the surgical team for improved wound healing. The Mg level on POD-1 was 2.1 mg/dl which was a marginal drop from initial laboratory findings. From POD-2 to POD-7, the patient's Mg levels decreased from 2 to 0.4 mg/dl despite daily 4 mg of magnesium sulfate replacement and high Mg supplementation via total parenteral nutrition (TPN). During this time, the patient's serum Ca, albumin-corrected Ca, ionized Ca, and intact parathyroid hormone remained unremarkable. An extensive search of the patients' hospital and home medications did not yield any obvious causes for the treatment-refractory hypomagnesemia. A 24-hour urinary Mg level revealed a severely elevated value of 736 mg urinary Mg loss, consistent with our theoretical understanding of zinc-induced hypomagnesemia. Zinc supplementation was discontinued on POD-8 and Mg was repleted with an additional 4 g of magnesium sulfate intravenously. On POD-9, Mg levels improved to 1.9 mg/dl and continued to normalize at 2.1±0.3 mg/dl. During the postoperative period, all other electrolytes were within reference range and no additional supplementation was required.

The patient continued TPN until POD-14, transitioning to a clear liquid diet and eventually to a normal heart-healthy and diabetic diet on POD-22 when he was discharged with a functional ileostomy. On clinic follow-up, the patient continued to improve without abdominal pain, recurrence of septic-like symptoms, or subsequent episodes of severe anemia or electrolyte derangements.

DISCUSSION

Hospitalized patients in the acute care setting, especially those in the postoperative realm, require constant monitoring of their serum electrolytes. Zinc and Mg in particular are necessary for many biochemical processes. In this case, our patient underwent an extensive intra-abdominal procedure where wound healing was of major concern. While there are no published guidelines for prophylactic zinc supplementation in patients without established hypozincemia, it is common practice to supplement zinc for at least three to five days postoperatively to optimize wound healing as zinc is a cofactor in enzymes that regulate the initial stages of healing via neovascularization[2].

The intricate relationship between zinc and Mg may often go overlooked as dysregulation of this interaction is rare in the general human population, with the prevalence of hypomagnesemia ranging from 2.5 to 15%. However, among hospitalized individuals' prevalence increases to 20%, and up to 65% in intensive care patients[4,5]. Thus, we wish to highlight this important point concerning the effects of zinc supplementation on the development of hypomagnesemia.

Importantly, the relationship between zinc and Mg homeostasis is bidirectional with regard to influence. Mg deficiency influences the distribution and storage of zinc. For instance, hypomagnesemia may elevate hepatic zinc concentrations[6]. Additionally, both intestinal absorption and renal reabsorption of Mg are altered by diet, hormones, and electrolyte balance[7]. In the case of excess zinc, both mechanisms of Mg retention are hindered, which may result in hypomagnesemia. In one study, low-dose zinc intake (under 53 mg daily) from diet and/or supplements was not significantly associated with the development of hypomagnesemia while higher zinc consumption was associated with greater gastrointestinal and renal losses, potentially resulting in hypomagnesemia[8].

Many acute care settings have electrolyte management protocols in place to ensure a standardized protocol, usually focusing on potassium, sodium, and chloride. Mg and PO_4, however, are not part of routine metabolic panels. This case presents the occurrence of a rare side-effect to zinc supplementation, which is recommended by many surgical societies and mentioned in recent medical literature. For patients receiving zinc supplementation, regularly evaluating Mg levels is crucial for ensuring proper Ca homeostasis and maintenance of adequate Mg levels to prevent complications such as cardiac arrhythmias, neuropsychiatric disturbances, and seizures.

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