The Role of Calcium Repletion in Patients with Septic Shock

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A. Introduction

The calcium ion performs a critical role in controlling many cellular functions and the concentrations of ionized calcium in the intracellular and extracellular fluids are carefully maintained. Studies have shown an association between hypocalcernia and hypotension as well as hypocalcernia and sepsis. Approximately 70% of patients in the intensive care unit (ICU) are hypocalcernic. Fifty percent of hypocalcemic patients in the ICU have sepsis, as opposed to 25% of normocalcernic patients.[1] Hypocalcemic patients are more likely to need vasopressor support (41% of hypocalcernic patients as opposed to 14% [2] normocalcernic patients). The mortality rate of hypocalcernic critically ill patients is significantly greater than that of normocalcernic patients (44% vs. 17%).[1]

The etiology of hypocalcernia in sepsis is multifactorial and not fully understood. Causes include impaired parathyroid gland ftinction, decreased renal and liver vitamin D hydroxylation, and end organ resistance to parathyroid hormone, vitamin D, and calcitriol.[3] Hypornagnesemia and elevated circulating cytokines may be responsible for the acquired hypoparathyroidism in some septic patients.[4] Patients with sepsis also have increased influx of calcium into the tissues, possibly at a rate that exceeds the body's ability to maintain normal circulating concentrations. [5, 6]

Animal investigations into the relationship between calcium repletion in septic shock have shown mixed results. Studies have demonstrated both improvement and no change in hemodynamic variables such as cardiac output and blood pressure. Calcium repletion in hypocalcemic septic animals has not changed mortality, and calcium repletion in normocalcemic septic rats has been associated with increased mortality.[7,8,9,10,11]

The degree to which calcium repletion is beneficial in septic shock has not been well studied in humans. Most studies have been small, observational studies with no control group, although three small, randomized controlled trials have been done. The patients were generally post-surgical patients or healthy volunteers. Most patients were normocalcernic prior to infusion of calcium. Only three studies assessed calcium repletion in critically ill patients; only four patients in all studies combined had sepsis. The results of these studies have shown either improvement or no change in hemodynamic variables such as blood pressure and cardiac oufput. All studies followed patients for a few hours or less; no studies addressed longer-term outcomes. [12]

At this institution, it is standard practice to replete calcium in hypocalcemic patients. However, there is no policy on dosing for various calcium levels. As a result, the degree of calcium repletion is variable between doctors. Our clinical experience is that maintaining normocalcernia in patients with shock improves blood pressure.

B. Hypotheses

Our primary hypothesis is that setting a standard policy in the intensive care unit for calcium repletion for hypocalcemic patients with septic shock and encouraging adherence to that policy will reduce pressor requirements. Our secondary hypothesis is that this policy will reduce morbidity and mortality, as measured by time to adverse event.

C. Methods

Conceptual and Operational Definitions By selection, all subjects will initially be dependent on vasopressor drugs. The primary outcome will be statistically significant reduction in pressor requirements. The use of pressors will be assessed using the bedside vital signs record, which includes hourly

assessment of pressor rates. The total amount of pressors used over a 24-hour period will be determined every day for the entire intensive care unit (ICU) stay.

The secondary outcome will be time to next adverse event. Adverse events will include acute renal failure, acute liver failure, disseminated intravascular coagulation (DIC), and death. Renal failure will be defined as a calculated creatinine clearance of less than I Oml/min. Liver failure will be defined as a progressive and sustained increase in bilirubin or transaminases that is associated with impaired synthetic function, as demonstrated by associated coagulopathy. DIC will be defined as a fibrinogen less than 100mg/dI.

Study Design

This is a prospective interventional, case-control study assessing the effects of a policy of consistent calcium repletion in hypocalcemic patients with septic shock. The controls will consist of patients in septic shock for the 4 months prior to initiation of a policy of consistent calcium repletion. The cases will consist of patients in septic shock for the four months after initiation of the calcium repletion policy. The cases and controls will be matched by age, APACHE II score, and diagnoses.

All patients will have total calcium measured twice daily and ionized calcium measured at least once daily. The controls will have their calcium repleted as determined by their doctors. The cases will be treated under the policy in which their doctors will be encouraged to replete calcium as follows: patients with symptomatic hypocalcernia defined as having SBP<90 or requiring pressors, and having a total corrected serum calcium <7.5mg/dL or ionized serum calcium <0.8mg/dL will be started on a calcium drip. This drip will consist of 10 ampules of calcium gluconate (90mg elemental calcium/lOml ampule) in IL of 5%dextrose infused at a rate of 50ml/hr. The drip will be titrated to maintain serum calcium in the low normal range [13] (total corrected calcium 9.09.5mg/dL or ionized calcium 1. 1- 1.2mM).

Statistical Analysis

Differences in pressor use between the two groups will be analyzed using a T-test. Differences in the time to adverse event will be analyzed using Cox proportional-hazards modeling, adjusting for differences in age, diagnoses, and APACHE 11 score.

Sample Size

The study would include 100 controls and 100 cases. This size is powered to detect a 20% decrease in pressor use. This model assumes that the average norepinephrine dose is 24mg/day with a standard deviation of 12.5mg/day. Though the model is based on estimated norepinephrine use, all vasopressors used would be analyzed.

Subject Selection

Inclusion criteria would be all patients admitted to the medical intensive care unit with septic shock requiring vasopressor therapy. Septic shock is defined according to consensus guidelines [14] as sepsis with hypotension resistant to fluid resuscitation and evidence of organ hypoperfusion or dysfunction, namely hypotension, defined as systolic pressure <90mm Hg or >40mm Hg reduced from baseline, and all of the following criteria: temperature >38'C or <36'C, heart rate >90 beats/min, respiratory rate >30 breaths/min or hyperventilation with arterial PC02<32mm Hg, WBC>12x 109/1, or <4xlO9/L or >10% band cells. Exclusion criteria would include lack of requirement for vasopressor therapy and concurrent digitalis administration, as the adverse effects of digitalis are increased by hypercalcernia.

Most of the subjects in this study will not have capacity to give informed consent. However, since this study is an evaluation of the efficacy of a policy that will be applied to all patients in septic shock in the intensive care unit as part of standard treatment, and the risks are small, request will be made to waive consent.

D. Miscellaneous

Risks and benefits The risks of this study to the subject would be those associated with hypercalcemia. The symptoms of hypercalcernia include constipation, anorexia, nausea, vomiting, pancreatitis, ulcers, confusion obtundation, psychosis, depression, coma, nephrolithiasis, renal insufficiency, polyuria, nocturia, myopathy, weakness, and hypertension. The following safeguards have been implemented in the calcium repletion policy to prevent hypercalcernia: goal repletion levels are low-normal, the form of administration is in a slow continuous infusion rather than short boluses, and calcium levels are checked at least twice daily.

Expert opinion recommends repletion for severe or symptomatic hypocalcernia. Thus, the intervention of this calcium repletion policy is expected to be beneficial.

Ethics

Because calcium repletion in patients with severe or symptomatic hypocalcernia is felt to be beneficial, it would be unethical to assess the efficacy of the calcium repletion policy with a randomized, placebo-controlled trial.

E. References

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