Study Synopsis

Title: Ionized hypocalcemia during post out-of-hospital cardiac arrest (OHCA) treatment in the intensive care units: incidence and management practices

Rationale and hypothesis: Ionized hypocalcemia is frequently observed among critically ill patients admitted to intensive care units (ICUs), with reported incidence rates of 55-85%. [1] Hypocalcemia is associated with increased morbidity and mortality, although it remains unclear whether this association is causal or merely indicative of severe underlying illness. [2] Current ICU practices for managing hypocalcemia through parenteral calcium supplementation vary considerably due to limited evidence regarding optimal calcium thresholds and clinical benefits. Some retrospective analyses suggest harm from calcium supplementation in mild hypocalcemia. [3]

To date, there is no randomized controlled trial (RCT) evidence supporting routine calcium supplementation in critically ill patients. Furthermore, a recent double-blind, placebo-controlled RCT among OHCA patients suggested potential harm associated with calcium supplementation during resuscitation, despite its suggested inotropic effects. [4]

Given these uncertainties, we aim to investigate the incidence of hypocalcemia among OHCA patients during the post-OHCA treatment in ICU and examine current ICU practices for managing hypocalcemia.

Methods:

Population: OHCA patients enrolled in the STEPCARE trial.

We will define hypocalcemia as ionized calcium level below 1.15 mmol/L any time during the ICU admission. We will calculate the prevalence of hypocalcemia and assess the severity of hypocalcemia. For assessing severity, we will categorize ionized calcium levels according to following: Ca-ion <0.7mmol/L, 0.7-0.79 mmol/L, 0.8-0.89mmol/L, 0.9-0.99 mmol/L, and 1-1.15mmol/L, 1.15-1.3 mmol/L, above 1.3 mmol/L.

Due to a retrospective data collection, we will not record symptoms of hypocalcemia.

We will calculate the frequency, amount, and type of calcium supplementation in the population, and assess the level of hypocalcemia triggering supplementation.

As exploratory analyses, we will compare mortality between patients with any hypocalcemia with no calcium supplementation, patients with any hypocalcemia with calcium supplementation and patients without hypocalcemia.

Our primary study question is the frequency of ionized hypocalcemia during the first 48 hours of ICU admission.

Data requirements (to study eCRF):

Daily data (during the first 48 hours)

- All Ionized calcium levels from blood-gas analyses

  On this day (hours 0-24), was the patient

  - In shock requiring vasopressors/inotropes (YES / NO)
  - Bleeding requiring RBC transfusion (YES / NO)
  - On RRT with regional citrate anticoagulation (YES / NO)

- Documentation of parenteral calcium supplementation

  Was i.v. calcium supplementation administered on that day? **If yes,**

  - How many times was calcium administered on that day?
  - Time of 1st calcium administration
  - Type administered (calcium gluconate or calcium chloride).
  - Amount administered (mg)
  - Last Ca-ion value before supplementation (mmol/L)
  - Was the patient receiving vasopressors before calcium supplementation
  - Which vasopressor? (Norepinephrine, epinephrine, vasopressin, angiotensin 2, dopamine, other)
  - Last vasopressor dose before supplementation ug/kg/minute
  - Vasopressor dose 1 hour after supplementation ug/kg/minute
  - Was the patient receiving inotropes before supplementation?
  - Which inotrope? (Dobutamin, Levosimendan, Adrenalin, Milrinone, other)
  - Inotrope dose 1 hour after supplementation?

Sample Size and Power Estimation:

- The sample size is calculated considering the primary study question, the incidence of hypocalcemia. With an estimated incidence of 70%, we need 1291 patients to show the incidence with a 2.5% margin of error.

Statistical Analysis Plan:

- Descriptive statistics for patient demographics, hypocalcemia prevalence, and calcium supplementation practices.

- Group comparisons using chi-square tests, t-tests or Mann-Whitney U tests as appropriate.
- Multivariate logistic regression analyses to identify independent predictors of hypocalcemia and associated clinical outcomes. Additionally, multiple regression analyses will evaluate the adjusted effects of calcium supplementation on relevant clinical outcomes.

Lead Investigators:

- Markus Tujunen, Heikki Kiiski, Joonas Tirkkonen, Matti Reinikainen, Markus Skrifvars, Johanna Hästbacka

Co-Investigators:

- All site PIs interested in participating

Participating Sites:

- Open to all sites involved in the STEPCARE trial.

Funding:

The eCRF expenses will be covered by Markus Skrifvars ´s funding from the Academy of Finland and Sigrid Juselius Foundation. Other expenses will be covered by J.Hästbacka ´s Government funding for University-level research.

How to join?

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References:

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