Administration Of Calcium Gluconate for The Reduction of Blood Loss During Elective Cesarean Delivery

INTRODUCTION

Postpartum hemorrhage (PPH) is the leading cause of death related to pregnancy, reported as 5% of all deliveries and assumed to be underestimated [1]. Known risk factors include uterine atony, genital tract trauma, retained placental tissue and more [2]. PPH can lead to blood transfusion, disseminated intravascular coagulation (DIC), hysterectomy, or death [2]The prophylactic administration of uterotonic agents as part of an active management of the third stage of labor has been proven to reduce rates of PPH [3]. However, even with these treatments, PPH rate is still relatively high, and puts women at risk of heavy bleeding and death. In addition, PPH is a risk factor for postpartum complications such as venous thromboembolic disease [4].

Calcium is a divalent cation found both intracellular and extracellular. It is a key component in the coagulation cascade and known as factor IV. It has a role in platelet activation, and it is an important co-factor for the activation of factors II and X [5]. K. M. Ho et al. had proven a concentration-dependent effect of hypocalcemia on in vitro clot strength in patients at risk of bleeding [6]. Calcium gluconate is the calcium salt of gluconic acid, and it has a relatively strong safety profile.

Hypocalcemia is a poor prognostic factor in actively bleeding patients. In trauma, the term “the trauma triad of death”, describing the combination of hypothermia, acidosis, and coagulopathy as a vicious cycle that can lead to patient death eventually, has been changed to “the diamond of death” or “the lethal diamond”, including hypocalcemia in the positive feedback loop of patient deterioration[7]–[9], emphasizing the need to monitor calcium levels when treating trauma patients with hemorrhagic shock. This mechanism doesn’t apply only to trauma patients but to every patient that suffers from significant bleeding [10], [11]

Calcium also has a positive inotropic effect both on skeletal muscle and smooth muscle. The inotropic effect doesn’t skip the myometrium, and it is well-established that hypocalcemia can impair myometrial contractility [12], [13]. As so, calcium channel blockers are prescribed as a tocolytic drug and calcium gluconate should be considered as adjuvant therapy for treating PPH duo to atony, in case of prolonged tocolytic or magnesium sulfate use prior to delivery [14]. Studies have already shown an association between low ionized calcium levels and the risk for severe bleeding. In one study, the rate of hypocalcemia was 10.6% in patients with non-severe PPH and 51.5% in patients with severe PPH [15]. Furthermore, in a pilot randomized controlled trial of patients with risk factors for uterine atony, calcium was shown to reduce uterine atony compared to placebo [16]. However, current studies have small sample size and are limited to a high-risk population. Although it is acknowledged that hypocalcemia combined with acidosis and hypothermia contribute to worsening coagulopathy and increased morbidity in PPH [2], there are no recommendations in current guidelines for monitoring calcium levels or prescribing calcium as a prophylactic measure for the third stage of labor [15], despite atony and coagulopathy being significant causes of PPH.

Co-administration of calcium and oxytocin was examined in previous study, and there were no changes in maternal hemodynamics [17].

HYPOTHESIS

Administration of Calcium Gluconate at the third stage of elective Cesarean delivery will decrease the rates of blood loss during and after the surgery by reducing the rates of uterine atony and development of coagulopathy, thus has the potential of reducing the incidence of PPH and its complications without severe side effects.

RESEARCH QUESTIONS

Primary research question

Population (P), Intervention (I), Comparison (C), Outcome (O)

P: All women undergoing elective cesarean delivery.

I: Administration of Calcium Gluconate 10% IV following umbilical cord clamping.

C: Administration of normal saline 0.9% IV following umbilical cord clamping.

O: Decreased mean hemoglobin drop after cesarean delivery.

Outcome measures

Primary outcome:

.1 Decreased mean hemoglobin drop after cesarean delivery at the Calcium gluconate arm, compared to the control arm.

Secondary outcome:

1. The rate of women with a decrease of hemoglobin levels of 2 gr/dl or more.
2. The need for additional therapy for the management of PPH
3. Receipt of blood products.
4. Patients treated with intravenous ferrous (iron).
5. The estimated blood loss during the surgery.
6. Hospitalization length of stay.
7. Duration of cesarean delivery.
8. A composite of adverse maternal outcomes including at least one of the following: admission to intensive care unit (NICU), the need for a surgical treatment for uncontrolled PPH, massive blood transfusion (defined as transfusion of ≥10 units red blood cells (RBCs) in 24 hours, disseminated intravascular coagulation (DIC), and death.
9. Endometritis or antibiotic treatment following CD.

PROPOSED TRIAL

Design: Multi Center (Rambam Health Care Campus, Soroka Medical Center), cluster-randomized, double-blind controlled trial.

Eligibility criteria for participants:

We plan to conduct a randomized control trial of all women undergoing elective cesarean delivery.

Inclusion criteria:

1. Gestational age of 35 weeks or more.

Exclusion criteria:

1. Age younger than 18 years old.
2. Patients treated with calcium channel blockers.
3. Chronic renal failure and hyperphosphatemia.
4. Sarcoidosis.
5. Hypocalcemia (ionized Ca<1 mmol/L) or hypercalcemia (ionized Ca> 1.3 mmol/L) before the surgery.
6. Any QT abnormalities as evident by ECG before Calcium Gluconate administrations or any known conduction abnormality.

Research arms and randomization:

After signing a consent form prior to the surgery (at the pre-operative assessment), At the third stage of labor, women who gave their consent to participate in the study will get either 10 ml of Calcium Gluconate 10% solution (containing 0.94 gr of calcium gluconate) diluted in 100 ml of normal saline IV or 110 ml of normal saline IV.

The solutions will be given in addition to Carbetocin (a long acting oxytocin analogue), in both arms.

We will use calcium gluconate during even-numbered months and normal saline during odd-numbered months, or vice versa, according to randomization that will be known to the primary researcher alone.

A blood sample will be drawn at the beginning of the surgery and sent for blood gas analysis, determining ionized calcium levels and coagulation profile. Women with hypocalcemia or hypercalcemia will be excluded from the trial. Only patients with normal calcium levels between 1.0-1.3 mmol/L will be included in this trial.

An ECG strip will be done prior to the surgery, making sure that the patient doesn't suffer from a QT segment abnormality.

All patients will be monitored with a 3 lead- ECG prior, during, and 2 hours following calcium administration. Patients with QT interval abnormalities will be excluded from the trial.

After the surgery, a blood sample will be drawn and sent to blood gas analysis (determining ionized calcium levels) and for coagulation profile. A complete blood count will be routinely taken for all women the next day. The hemoglobin level will be compared to the hemoglobin level prior to CD.

ANALYSIS PLAN

Binyamin Y et al. demonstrated an average blood loss of 1.05 g/dL in 1000 women who have had a cesarean delivery for different indications[17]. Assuming a reduction in blood loss of 30% attributed to both coagulative effect and uterotonic effect of Calcium, and calculating a dropout rate of 10%, a sample size of 1180 patients (590 in each arm) is needed to achieve power of 0.8 and p-value <0.05. We will use SPSS 28 (IBM inc.) for statistical analysis. Categorical variables will be compared using the chi-square test or fisher's exact test. Continuous variables will be compared using the student's t-test or Mann-Whiteny test. After testing for collinearity, confoundment and interaction, a multivariate model will be built to assess the effect of calcium supplementation on postpartum hemorrhage. Alpha < 0.05 is considered statistically significant.

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