Calcium chloride for the prevention of uterine atony during cesarean in women at increased risk of hemorrhage

A pilot randomized controlled trial and pharmacokinetic study

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Summary

Uterine atony is the leading cause of obstetric hemorrhage. Low calcium levels diminish uterine muscle contractility and response to oxytocin. Our aim is to assess the effectiveness and pharmacokinetics of intravenous calcium chloride to prevent uterine atony. This will be a single-center, double blind, randomized controlled pilot trial. Women with at least 2 risk factors for uterine atony at the time of caesarean delivery will be randomized in 1:1 ratio to receive 1-gram dilute calcium chloride or saline placebo in addition to oxytocin after umbilical cord clamping. The primary outcome will be incidence of uterine atony, defined as second-line uterotonic requirement, uterine balloon, or estimated blood loss (EBL) >1000 mL.

Introduction:

Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide.[1] Uterine atony, defined as failure of the uterus to adequately contract after placental delivery, causes at least 70-80% of PPH.[2] Current management of uterine atony involves prophylaxis with oxytocin and treatment with second-line uterotonics including methylergonovine, carboprost, and misoprostol. However, these medications all carry significant limitations of poor efficacy, adverse side effect profiles, expense, or contraindications to use.[3] For example, methylergonovine is contraindicated in women with preeclampsia or hypertensive diseases, and carboprost, which may cost up to $1000 per dose, is contraindicated in women with asthma. As such, additional prevention or treatment modalities for uterine atony are needed.

Calcium has an important physiological role in uterine contractility. Uterine myometrial contractility is dependent upon an influx of calcium from intracellular stores in the sarcoplasmic reticulum as well as extracellular calcium.[4] A number of *in vitro* studies have established that myometrial contraction amplitude diminishes in the setting of low extracellular calcium.[4-7] Oxytocin's efficacy in inducing myometrial contraction diminishes by 60-75% in the setting of low or absent extracellular calcium levels in *in vitro* studies with human uterine strips.[7] Although the safety and lack of hemodynamic consequences of intravenous calcium infusion in parturients has been assessed in one study,[8] no clinical studies have been designed to assess the potential role for intravenous calcium in preventing or treating uterine atony or PPH as a primary outcome.

. This pilot study was designed to assess whether intravenous calcium chloride warrants future study as an agent for prevention of uterine atony and maternal hemorrhage. Our primary aim is to assess whether calcium, administered in addition to standard oxytocin to women with risk factors for developing uterine atony during caesarean delivery, warrants a large study for efficacy in the prevention of uterine atony. We hypothesize that providing calcium will augment uterine contraction and decrease the incidence of atony. Secondary aims include assessment of atony and hemorrhage-associated outcomes including estimated blood loss, fluid requirement, obstetrician assessment of tone. Other secondary aims assessed include potential side effects of calcium infusion including hemodynamic changes, discomfort at the site of the intravenous catheter, nausea, and vomiting. Finally, population pharmacokinetics will be assessed as a secondary aim to guide dosing in future studies.

Methods:

Inclusion criteria: Cesarean delivery with at least two of the following established risk factors for uterine atony: intrapartum delivery, oxytocin infusion for 4 hours or longer, magnesium infusion, chorioamnionitis, multiple gestation, polyhydramnios, premature preterm rupture of membranes (PPROM), preterm at <34 weeks gestation, and prior history of postpartum hemorrhage.

Exclusion criteria: renal dysfunction with serum creatinine >1.0 mg dL^{-1}, maternal treatment with digoxin, maternal treatment with a calcium channel blocker, and maternal history of cardiac condition including arrhythmia, congenital cardiac disease, or coronary disease.

Patients admitted to the labor and delivery ward will be provided a brief informational sheet regarding the study. Women who meet inclusion criteria for the study will be subsequently approached by the clinical staff for written informed consent as long as the obstetrician agrees that this discussion will not interfere with case urgency. Not all women who meet study inclusion criteria will be approached; the patients included in this pilot study will be a convenience sample approached when the clinical service allows.

As part of consent, women will be asked if they will permit the team to draw 3 blood specimens for ionized calcium assessment and nested pharmacokinetic analysis; however, women who declined phlebotomy are still allowed study participation.

Patients will be informed about possible side effects including intravenous line discomfort during the consent process and asked to inform the anesthesiologist if they experience this at any point during the delivery course. The anesthesiologist is

instructed to assume all patients are receiving a 1 gram bolus of calcium chloride, and to immediately discontinue the infusion if any concerns for medication extravasation, arrhythmia, hemodynamic disturbance, or for severe nausea or vomiting.

Patients will be sequentially assigned to one of two computer-generated random groups (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA) using in a sealed, opaque envelope system. Patients will either receive 1 gram of intravenous calcium chloride or saline placebo diluted to a total volume of 60mL with normal saline in addition to our institution's standard oxytocin regimen (2 U bolus and 7.5 U hr^{-1} infusion for 4 hours). All participants including the obstetrician, supervising and resident anesthesiologists, patient, and study investigator collecting data will be blinded to the study solution received. An anesthesiologist with no further involvement in patient care will prepare the study solution in a different operating theater.

Upon entering the operating room, standard noninvasive monitors will be applied: pulse oximetry, electrocardiography (ECG), heart rate (HR), and baseline non-invasive blood pressure (NIBP). Mean arterial blood pressure (MAP) will be measured with an automated, non-invasive sphygmomanometer (Dinamap, Critikon Inc., Tampa, FL, USA) at 1 minute intervals until fetal delivery and hysterotomy closure and then at 2.5 minute intervals at the discretion of the clinical anesthesiologist.

All patients will have an 18-gauge peripheral intravenous cannula in place at the time of cesarean delivery per standard protocol. Lactated Ringers solution will be administered at the discretion of the clinical anesthesiologist with general guidelines not to exceed 3 L during the caesarean delivery. Total administered fluid volume will be recorded. Colloid infusion with 6% hydroxyethyl starch in 0.9% sodium chloride or 5%

albumin is also recorded. Patients receive prophylactic phenylephrine infusion (starting at 0.5 mcg kg^{-1} min^{-1}) and phenylephrine (50-100 mcg) or ephedrine (5-10 mg) bolus doses as needed at the discretion of the clinical anesthesiologist to maintain MAP within 20% of baseline. The total phenylephrine infusion dose received as well as total bolus doses of vasopressors will likewise be left to the discretion of the clinical anesthesiologist and recorded.

Following fetal delivery and umbilical cord clamping, patients will receive 2 U oxytocin bolus, and oxytocin infusion will be initiated at a rate of 7.5 U hr^{-1}. At this same time point, the 60 mL study drug infusion will be administered over 10 minutes using an Alaris syringe infusion pump (BD Alaris syringe module, Beckton, Dickinson and Company, Franklin Lakes, NJ, USA) through microbore infusion tubing connected to the intravenous injection port most proximal to the patient. Adequacy of uterine tone (yes or no) will be formally assessed at 3, 6, and 10 minutes after delivery by the operating obstetrician. If tone is deemed inadequate at 3 minutes or 6 minutes, a 2 U bolus of oxytocin will be administered, and the oxytocin infusion rate doubled. If at 10 minutes, tone is still deemed inadequate, a second-line uterotonic agent of intramuscular methylergonovine 200 mcg, intramuscular 250 mcg, or buccal misoprostol 600 mcg will be chosen at the discretion of the obstetrician and clinical anesthesiologist and recorded. After leaving the operating theater, all patients receive our institution's standard protocol of oxytocin 7.5 U hr^{-1} for 4 hours.

Primary outcome:

The primary outcome will be incidence of uterine atony, a binary composite outcome defined as any of the following: second-line uterotonic requirement, EBL >1000 mL, placement of a Bakri balloon, B-lynch suture, or O'Leary sutures by the obstetrician, uterine artery embolization or hysterectomy. For this pilot study, any *P* value less than 0.2 is defined a priori as indicating potential for efficacy, and thus warranting a future, larger study.

Secondary outcomes:

Several secondary outcomes related to uterine atony and hemorrhage will be assessed. At completion of study drug infusion (10 minutes after umbilical cord clamp), the operating obstetric attending will be asked to assess and grade the uterine tone based upon palpation of the fundus using a verbal numerical scale score from 0-100 (0=completely atonic, 100=fully contracted). Blood loss will be estimated by visual examination of the graduated suction jars, surgical sponges, drapes, table and floor. The difference in preoperative and postoperative day 1 hematocrit gathered as standard of care at our institution will be calculated. The total volume of intravenous fluid given from start to conclusion of the surgical procedure will be recorded.

For patients who consent to phlebotomy, blood specimens will be collected into a non-heparinized syringe at three different time intervals: once in the operating room prior to fetal delivery for a baseline value, once within 1-30 minutes of completing study drug infusion, and once 30 minutes to 3 hours after completing study drug infusion. To allow for painless sample collection for patients with a surgical lumbar neuraxial block, a

tourniquet will be placed at the patient's lower calf, and a 21-gauge winged blood collection needle was utilized to collect a 3 mL venous specimen from the foot or saphenous vein. The ionized calcium level and pH will be immediately determined with an i-STAT 1 system (i-STAT Corp., Princeton, NJ, USA).

Calcium pharmacokinetics will be analyzed with NONMEM (Nonlinear Mixed-Effects Modeling; Globomax, Ellicott City, MD) using PLT Tools (PLT Soft, San Francisco, CA). We will evaluate calcium kinetics using a 1-compartment model with administration into the central compartment. We will use an exponential model for interindividual variability on the volume of distribution and clearance and an additive model of interindividual variability on the baseline calcium concentration. The model parameters will be estimated by NONMEM using the first order conditional estimation approach. Confidence intervals for each parameter will be assessed using log likelihood profiling and bootstrap analysis.

Hemodynamic variables analyzed will include heart rate and mean arterial pressure at baseline, at fetal delivery, and at 5 minute intervals for the next 30 minutes. This will be used to calculate a maximal increase and decrease from baseline calculation for each patient. The clinical anesthesiologist will fill out a checklist prior to exiting the operating theater at case conclusion answering whether the patient experienced nausea, vomiting, intravenous line discomfort, changes in heart rate or blood pressure, any arrhythmia, or other possible side effect (with a free-text field) during or following the study drug infusion.

Statistical analysis:

A sample size of 40 parturients was selected for this pilot study as most likely feasible to perform in approximately one year or less at our institution. Internal quality improvement data at our institution revealed that in patients with more than one atony risk factor, incidence of EBL >1000 mL or second line uterotonic use was >60%. If calcium were to halve the rate of uterine atony, we estimated that a sample size of 20 subjects in the calcium and 20 subjects in the placebo group should allow sufficient data to show a difference between groups with 75% power and a two-sided type I error probability of 0.2.

For analysis of the primary outcome, the relative risk (RR), and its 95% confidence interval will be calculated according to Altman.[13] The number needed to treat (NNT) will be defined and calculated using the terminology suggested by Altman.[14] The 95% confidence interval for NNT will be calculated according to Daly,[15] and P-value calculated according to Sheskin.[16] Bootstrap analysis for sample size calculation for future studies will be performed using R programming and 10,000 replicates of the pilot dataset.

Demographic and baseline characteristics will be reported as mean ± standard deviation (SD) or median and interquartile range [IQR] as appropriate for continuous variables. Categorical variables will be presented as percent. The mean differences and their 95% confidence intervals (CI) will be presented for outcomes of interest. Univariate comparisons between groups will be performed using Chi-square analysis or the Kruskal–Wallis test, as appropriate for categorical or continuous variables, respectively.

Statistical analyses will be performed using STATA version 14.0 (StataCorp, CollegeStation, TX, USA).

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