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ORIGINAL ARTICLE

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# The effect of co-administration of intravenous calcium chloride and oxytocin on maternal hemodynamics and uterine tone following cesarean delivery: a double-blinded, randomized, placebo-controlled trial

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**ABSTRACT**
**Background:** Oxytocin administration to prevent uterine atony following cesarean delivery is associated with adverse effects including hypotension, tachycardia, and nausea. Calcium chloride increases mean arterial pressure, systemic vascular resistance, and uterine smooth muscle contractility. This study evaluated whether the co-administration of calcium chloride with oxytocin following cesarean delivery could alter maternal hemodynamics. Secondary outcomes included uterine tone and blood loss.
**Methods:** Sixty healthy parturients with singleton, term, vertex pregnancies undergoing elective cesarean delivery under spinal anesthesia were randomized to one of three study solutions given intravenously immediately after umbilical cord clamping: (1) placebo, oxytocin 5 U alone; (2) CA-200, oxytocin 5 U + calcium chloride 200 mg; or (3) CA-400, oxytocin 5 U + calcium chloride 400 mg. Blood pressure, heart rate, uterine tone, vasopressor or alternate uterotonic use and the incidence of nausea or vomiting were recorded. Baseline and intraoperative plasma concentration of ionized calcium and hematocrit were measured.
**Results:** Plasma concentration of ionized calcium was elevated in both study groups compared with placebo ($P$=0.001). Blood pressure decreased and heart rate increased in all groups ($P$ <0.0001), with no differences between groups. No differences were observed between groups in uterine tone, vasopressor use, hematocrit change, estimated blood loss, incision-to-delivery interval, delivery-to-skin closure interval, total intravenous fluid administered or incidence of nausea.
**Conclusions:** The decrease in blood pressure associated with oxytocin administration following cesarean delivery was not attenuated with co-administration of calcium chloride at the doses evaluated. Vasopressor use, uterine tone, and blood loss were also unaffected.


***Keywords***: Calcium chloride; Oxytocin; Hemodynamics; Uterine tone

## Introduction

Oxytocin is routinely administered as the agent of choice following cesarean delivery (CD) to reduce the incidence of uterine atony and postpartum hemorrhage (PPH).[1,2] While these uterotonic effects are salutary, the administration of oxytocin has been associated with significant adverse events. The 1997–1999 UK Confidential Enquiries into Maternal Deaths reported the deaths of two women from cardiovascular instability following the intravenous administration of oxytocin 10 U.[3] Subsequently, oxytocin 5 U for CD was recommended[4] and adopted in the UK;[5] however, even this dose has been associated with hypotension, tachycardia and signs of myocardial ischemia.[6–9]

The administration of intravenous calcium chloride ($CaCl_2$) has been demonstrated to elevate mean arterial pressure (MAP), systemic vascular resistance (SVR) and cardiac contractility in patients undergoing anesthesia.[10,11] In addition, although the clinical uterotonic effect of intravenous $CaCl_2$ has not been evaluated, its administration has been observed to significantly increase the frequency, tone and contractility of isolated in-vitro rat uterine muscle strips.[12]

The purpose of this study was to determine the influence of intravenous $CaCl_2$ 200 mg and 400 mg on

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maternal hemodynamics when co-administered with oxytocin 5 U in women undergoing elective CD. We also sought to determine if the administration of $CaCl_2$ would augment uterine tone, reduce the need for alternative uterotonic agents or vasopressors or decrease blood loss. We hypothesized that intravenous $CaCl_2$ would reduce the incidence of hypotension and improve the quality of uterine tone in women undergoing elective CD under spinal anesthesia.

## Methods

After obtaining Institutional Review Board approval and written informed consent, 60 healthy women at $\geqslant$37 weeks of gestation undergoing elective CD were enrolled in this randomized, double-blinded, placebo-controlled study. Inclusion criteria were American Society of Anesthesiologists (ASA) classification I or II, age 18–45 years, singleton gestation scheduled for elective CD via a Pfannenstiel incision and a preoperative plasma ionized calcium ($iCa^{2+}$) concentration within normal range. Exclusion criteria included active labor; ruptured membranes; known drug allergy to oxytocin, bupivacaine, fentanyl or morphine; significant comorbidity (cardiac disease, pregnancy-induced hypertension or preeclampsia, arrhythmia history or diabetes mellitus), or treatment with digitalis, beta-adrenergic blockers or calcium channel blockers. Women were also excluded from the study if they had known risk factors for PPH or uterine atony such as placenta previa, multiple gestation, preeclampsia, macrosomia, polyhydramnios, oligohydramnios, uterine fibroids or prior myomectomy, more than two previous CDs, coagulation disorder or thrombocytopenia (platelet count $<100 \times 10^9$/L).

Patients were randomized using computer-generated random number allocations (Microsoft Excel, Microsoft Corporation, Redmond, WA, USA) to receive one of two different doses of $CaCl_2$ or placebo in addition to 5 U oxytocin: placebo group (saline 7.5 mL + oxytocin 5 U), CA-200 group ($CaCl_2$ 200 mg + oxytocin 5 U) or CA-400 group ($CaCl_2$ 400 mg + oxytocin 5 U). The study drugs were diluted to a total volume of 8 mL with normal saline and marked "study solution". All participants, including the obstetrician, supervising and resident anesthesiologists, patient and study investigator collecting the data, were blinded to the study solution received. An anesthesiologist who had no further involvement in the study prepared the study solutions.

An 18-gauge peripheral intravenous cannula was inserted into an antecubital vein. Lactated Ringer's solution was administered at the discretion of the clinical anesthesiologist with general guidelines to not exceed 3 L. At cannula insertion and 20 min following the injection of the study solution, a blood sample was withdrawn from a three-way stopcock attached to the catheter hub for determination of $iCa^{2+}$ and hematocrit (Hct) levels. The sample collection at 20 min involved stopping the intravenous fluid for 10 min, applying a tourniquet and withdrawing blood (10 mL discard + 1 mL study sample into a non-heparinized syringe). The $iCa^{2+}$ and Hct were immediately determined with an i-STAT 1 system (i-STAT Corp., Princeton, NJ, USA).[13] Patients were premedicated with oral sodium citrate 30 mL and intravenous metoclopramide 10 mg. Upon entering the operating room, pulse oximetry, electrocardiography (ECG), heart rate (HR) and baseline right arm non-invasive blood pressure (NIBP) were measured.

Spinal anesthesia was administered via a 25-gauge Whitacre needle at the L3–4 or L4–5 vertebral interspace in the sitting position using 0.75% hyperbaric bupivacaine 1.6 mL (12 mg), fentanyl 10 μg and morphine 200 μg. Patients were repositioned to the supine position with left lateral uterine displacement and surgery commenced after a T4 sensory level to pinprick was achieved. Supplemental oxygen was administered by mask (6 L/min) until fetal delivery.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with an automated, non-invasive sphygmomanometer (Dinamap, Critikon Inc., Tampa, FL, USA) at 3-min intervals before and after uterine exteriorization and at 1-min intervals during uterine exteriorization. Values for MAP were calculated from SBP and DBP. Hypotension was defined as SBP <20% of baseline or <100 mmHg and was treated with intravenous bolus doses of ephedrine or phenylephrine at the discretion of the anesthesiologist. Vasopressor choice, dose, and time of administration (before or after umbilical cord clamping) were recorded. Phenylephrine equivalents were calculated based on the conversion factor of 12.5 μg phenylephrine for each 1 mg ephedrine.[14]

Following fetal delivery and umbilical cord clamping (designated as time 0), the assigned study solution was infused at a rate of 2 mL/min for 4 min (oxytocin 1.25 U/min plus study solution) using a Bard/Parker Infusion Pump (InfusOR Pump Syringe Pump, Baxter International, Deerfield, IL, USA) through infusion tubing connected to the intravenous injection port most proximal to the patient. Upon study solution completion, a 10 mL bolus of saline was administered through the infusion tubing.

The uterus was exteriorized and massaged before hysterotomy closure. The attending obstetrician assessed the uterine tone based on a verbal numerical scale score (0–10; 0=completely atonic; 10=fully contracted).[7] Scores were obtained immediately upon clamping of the umbilical cord and at 5-min intervals up to 20 min or until the uterus was returned to the pelvis. If uterine tone was inadequate, additional uterotonic agents (intravenous oxytocin 3 U, intramuscular methylergonovine maleate 200 μg, or intramuscular