Original Research

Intravenous Calcium to Decrease Blood Loss During Intrapartum Cesarean Delivery

A Randomized Controlled Trial

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OBJECTIVE: To evaluate whether prophylactic administration of 1 g of intravenous calcium chloride after cord clamping reduces blood loss from uterine atony during intrapartum cesarean delivery.

METHODS: This single-center, block-randomized, placebo-controlled, double-blind superiority trial compared the effects of 1 g intravenous calcium chloride with those of saline placebo control on blood loss at cesarean delivery. Parturients at 34 or more weeks of gestation requiring intrapartum cesarean delivery after oxytocin exposure in labor were enrolled. Calcium or saline placebo was infused over 10 minutes beginning 1 minute after umbilical cord clamping in addition to standard care with oxytocin. The primary outcome was quantitative blood loss, analyzed by inverse Gaussian regression. Planned subgroup analysis excluded nonatonic bleeding, such as hysterotomy extension, arterial bleeding, and occult placenta accreta. We planned to enroll 120 patients to show a 200-mL reduction in quantitative blood loss in planned subgroup analysis, assuming up to 40% incidence of nonatonic bleeding (80% power, $\alpha<0.05$).

RESULTS: From April 2022 through March 2023, 828 laboring parturients provided consent and 120 participants were enrolled. Median blood loss was 840 mL in patients allocated to calcium chloride (n=60) and 1,051 mL in patients allocated to placebo (n=60), which was not statistically different (mean reduction 211 mL, 95% CI −33 to 410). In the planned subgroup analysis (n=39 calcium and n=40 placebo), excluding cases of surgeon-documented nonatonic bleeding, calcium reduced quantitative blood loss by 356 mL (95% CI 159–515). Rates of reported side effects were similar between the two groups (38% calcium vs 42% placebo).

CONCLUSION: Prophylactic intravenous calcium chloride administered during intrapartum cesarean delivery after umbilical cord clamping did not significantly reduce blood loss in the primary analysis. However, in the planned subgroup analysis, calcium infusion significantly reduced blood loss by approximately 350 mL. These data suggest that this inexpensive and shelf-stable medication warrants future study as a novel treatment strategy to decrease postpartum hemorrhage, the leading global cause of maternal morbidity and mortality.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT 05027048.

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Postpartum hemorrhage (PPH) is the leading global cause of maternal morbidity and mortality.[1–4] Uterine atony causes 70–80% of PPH.[5–7] When

PPH occurs despite oxytocin treatment, therapeutic options are limited and incompletely effective. Misoprostol confers questionable therapeutic benefit relative to oxytocin alone.[8,9] The utility of both methylergonovine and carboprost is limited by side effects, contraindications, cost, and constrained access in low-resource settings.[10,11] Therefore, there is a critical need for effective, inexpensive, shelf-stable adjuncts to oxytocin.

Intravenous calcium chloride is an inexpensive, shelf-stable medication already used in obstetric units for treating magnesium toxicity and correcting transfusion-related hypocalcemia.[12] Increasing serum calcium may improve uterine contractility. In vitro, both spontaneous and oxytocin-induced myometrial contractility decrease in the setting of low extracellular calcium.[13–15] In observational studies, laboring patients have higher serum calcium levels than matched nonlaboring patients at the same gestational age, suggesting that higher serum calcium levels may play a role in uterine contractility.[16] Lower serum ionized calcium concentration is also associated with increased PPH severity.[17] A recent pilot trial demonstrated that a 1-g infusion of calcium chloride was well tolerated and may decrease incidence of uterine atony.[18]

In this single-center randomized controlled trial, we tested the hypothesis that a calcium infusion would decrease quantitative blood loss at delivery in an obstetric population at high risk of atonic PPH: patients who received an oxytocin infusion for labor induction or augmentation but subsequently required intrapartum cesarean delivery.[10,19]

METHODS

This was a single-center, block randomized, double-blind, placebo-controlled clinical trial testing the intervention of a 1-g prophylactic dose of intravenous calcium chloride delivered in addition to standard care. The primary aim was to determine the effect of calcium on quantitative blood loss measured at the time of intrapartum cesarean delivery. Secondary aims included assessment of other hemorrhage-related outcomes as well as the safety and tolerability of the intervention.

Because intrapartum cesarean delivery is an urgent procedure, we approached all laboring patients to consent to participate in the trial. Parturients were provided with an IRB-approved informational handout on admission to the labor and delivery ward. Patients were screened electronically by clinical research staff for eligibility, and research staff then visited eligible patients to obtain informed consent.

Laboring patients at 34 or more weeks of gestation, aged 18–55 years, who received an oxytocin infusion for labor induction or augmentation and subsequently required cesarean delivery were eligible for study inclusion. Exclusion criteria included: 1) blood pressure higher than 160 mm Hg systolic or higher than 110 mm Hg diastolic requiring intravenous antihypertensive therapy within 24 hours; 2) digoxin therapy within 14 days (because hypercalcemia may exacerbate digoxin toxicity); 3) serum creatinine greater than 1 mg/dL (because calcium is renally cleared); 4) calcium channel blockade within 24 hours (to avoid reversing therapeutic effect); or 5) known history of maternal cardiac disease, including arrhythmia, ischemic, and congenital cardiac disease (to avoid potential misattribution of cardiac symptoms from underlying disease to study drug side effects). To assess interval changes in clinical status or patient preferences, exclusions and ongoing assent to participate were confirmed on entry to the operating room. If case urgency did not allow sufficient time for this review, the patient was excluded from study participation.

The U.S. Food and Drug Administration's Division of Urology, Obstetrics, and Gynecology reviewed the trial protocol and granted investigational new drug exemption (PIND # 158398, September 2021). Stanford's IRB approved the protocol in September 2021, and the trial was registered with ClinicalTrials.gov (NCT 05027048, August 30, 2021). A data safety monitoring board of two physicians otherwise uninvolved in the study reviewed enrollments and all potential reported side effects monthly and ad hoc to determine whether unblinding, investigation, or pausing were required.

Participants were sequentially assigned to the calcium chloride or placebo arms using computer-generated random groups in a 1:1 ratio blocked at 10 patients (R code blockrand package),[20] prepared by a biostatistician with no further involvement in the trial and using a sealed, opaque envelope system. An anesthesiologist with no involvement in a study participant's care prepared the study solution using the assignment found in the envelope in a different operating room. All clinicians and investigators, including the obstetrician, anesthesiologists, and study investigator collecting data, and patients were blinded. Patients received either 1-g intravenous calcium chloride diluted to a total volume of 60 mL with normal saline or 60 mL normal saline placebo. The calcium and placebo solutions were visually indistinguishable clear solutions contained in a syringe labeled with, "Study Drug", participant ID, and preparation date and time,

but not the syringe contents. The 60-mL solution was delivered intravenously over 10 minutes using a programmable syringe–based infusion pump beginning 1 minute after umbilical cord clamping.

The primary outcome, quantitative blood loss (mL), was determined by measuring suction cannister contents–minus amniotic fluid and irrigation volume–and weighing soiled surgical sponges, drapes, and pads as previously described, using the Triton QBL system.[21,22] Secondary outcome hemorrhage metrics included incidence of PPH with quantitative blood loss greater than 1,000 mL, incidence of second-line uterotonic administration, blood transfusion, and change in hematocrit from preoperative to postoperative day 1 values.

The obstetric attending assessed the uterine tone on a validated 10-point numeric rating scale at 2, 7, and 12 minutes after fetal delivery.[23] To assess for hemodynamic effects of calcium, which may theoretically increase vascular tone, hemodynamics (mean arterial blood pressure and heart rate) were recorded at preoperative baseline and every 5 minutes for the 30 minutes after study drug administration. Total phenylephrine and intravenous fluid requirements were also recorded.

Potential side effects of heart rate change, arrhythmia, or blood pressure change requiring treatment were assessed continuously throughout the surgery and documented at surgery conclusion. Patients were also asked at surgery conclusion whether they experienced any of the following subjective adverse side effects: burning or irritation at the intravenous line site, new or worsened nausea or emesis, flushing, or abnormal sensations or tastes. The anesthesiologist assessing and recording side effects remained blinded to study group assignment.

Patients' primary race was reported as documented in the electronic health record, self-reported by the patient and confirmed on admission. The categories included were Asian (including Pacific Islander), Hispanic, non-Hispanic Black, non-Hispanic White, and none of the above or declined to state. Race and ethnicity were included given the known racial and ethnic disparities in PPH incidence and severity and to allow assessment of study generalizability.[24,25]

Detailed institutional standard practices, including anesthetic care, uterotonic management, and quantification of blood loss, are shown in Appendix 1, available online at http://links.lww.com/AOG/D471. Study participants received neuraxial anesthesia. At fetal delivery, all patients received a 2-unit intravenous oxytocin bolus and oxytocin infusion at 7.5 units/hour. The calcium or placebo infusion began 1 minute after umbilical cord clamping as detailed above. Additional oxytocin and second-line uterotonic administration was left to the discretion of the clinical team. The operating obstetrician formally assessed adequacy of uterine tone on a validated 0–10 scale (10 is optimal, and 0 is extremely atonic) at 2, 7, and 12 minutes after delivery.[21]

Power analysis based on a pilot trial revealed that a sample size of 31 patients per arm would provide 90% power to detect a difference of 200 mL in quantitative blood loss, from an anticipated mean value 866 mL with an SD of 231 mL at the $P<.05$ significance level. The sample size was increased to 60 patients per arm to allow 80% power to detect a difference of 200 mL in a subgroup analysis excluding patients with nonatonic bleeding described below, assuming up to 40% of participants experienced nonatonic bleeding.

Analyses were conducted using the SAS 9.04.01 and R statistical programming languages (R 4.2.2). We anticipated that the primary outcome, quantitative blood loss, would be substantially right-skewed. Quantitative blood loss was presented as median with interquartile range as well as the between-group difference with 95% CI calculated by regression. Our statistical analysis plan prespecified using the inverse Gaussian distribution and log link fit to untransformed quantitative blood loss to estimate the effect size and 95% CIs if simple transformation (such as log-transformation) failed to fit the data. We assessed the effect of the statistical model choice on estimations of effect size and significance using various transformations and parametric and nonparametric tests; effect size, 95% CI, and *P*-values for the primary outcome are shown in Appendix 2, available online at http://links.lww.com/AOG/D471.

The primary analysis was unadjusted and included all study participants. Given the relatively small sample size and potential for chance imbalance in baseline patient characteristics with low counts, we planned a sensitivity analysis, adjusting the regression model for any baseline patient characteristics with a between-group absolute standardized difference greater than 0.2.

Because the proposed mechanism of calcium action–improving uterine contractility–was not expected to improve bleeding from causes such as hysterotomy extension or arterial bleeding, the trial was powered for a prespecified subgroup analysis excluding patients with nonatonic blood loss documented in the surgeon's operative report. *Documented nonatonic bleeding* was defined as presence in

the surgeon's operative report narrative of any of the following: hysterotomy extension, hysterotomy types other than low transverse (eg classical, T- or J-shaped), invasive or abnormally adherent placenta, placental abruption, uterine rupture, bleeding from leiomyomas, grade 3 or 4 vaginal lacerations, or cervical lacerations. Statistical analyses of secondary outcomes and side effects are discussed in Appendix 3, available online at http://links.lww.com/AOG/D471.

RESULTS

From April 2022 to March 2023, a total of 120 parturients underwent randomization, 60 to the study group and 60 to the placebo group (Fig. 1). All patients received the study infusion containing calcium or placebo with no discontinuations. Study groups were balanced with regard to patient characteristics including gestational age, indication for cesarean delivery, and labor oxytocin dose and duration (Table 1).

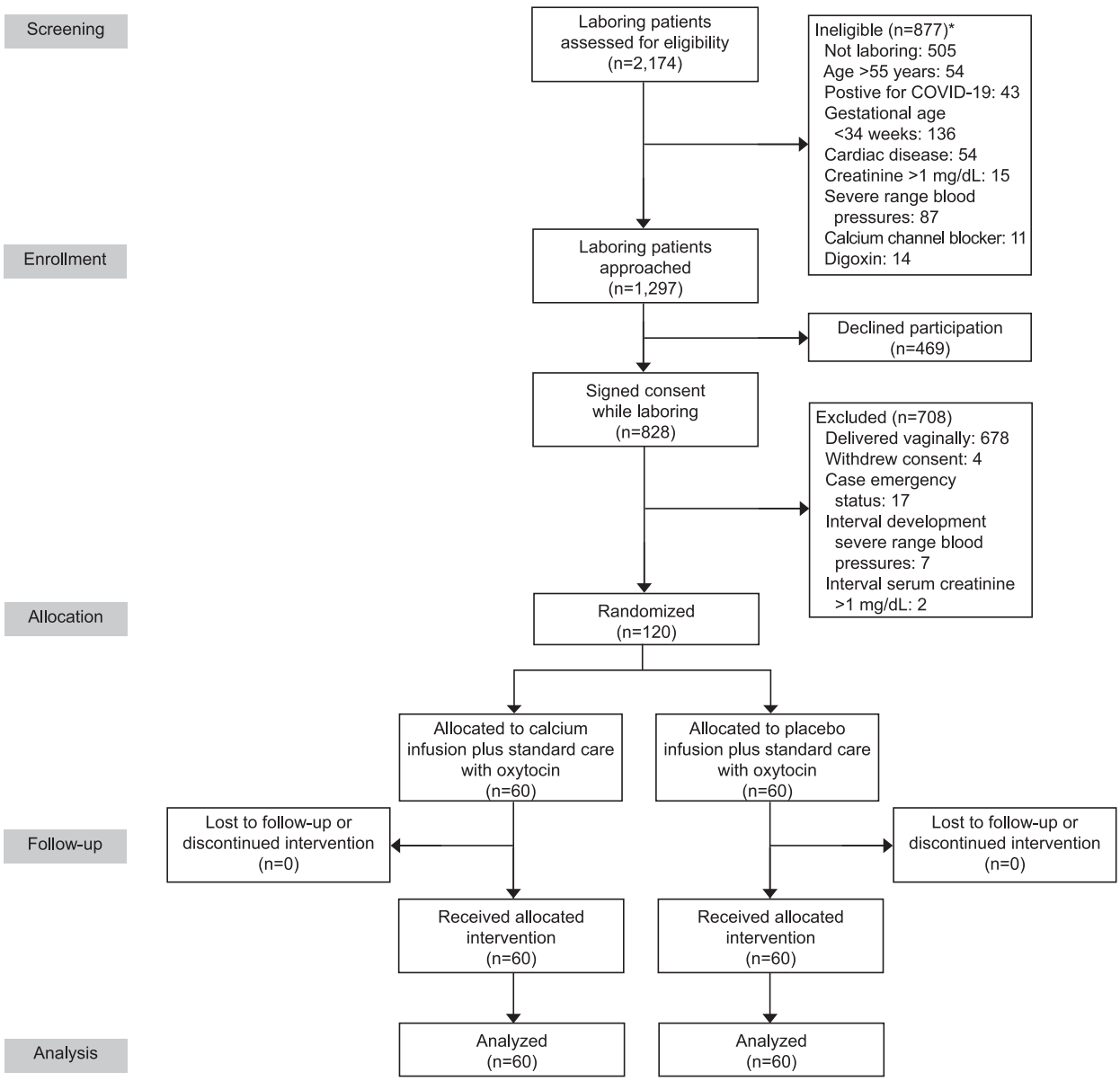

Fig. 1. CONSORT (Consolidated Standards of Reporting Trails) enrollment diagram. *Not mutually exclusive. COVID-19, coronavirus disease 2019.

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Table 1. Demographic and Obstetric Characteristics by Study Group

Characteristic	Calcium (n=60)	Placebo (n=60)	Std Diff
Age (y)	33.8±5.2	32.8±5.2	0.18
BMI (kg/m^2)	31.6±4.6	32.2±6.1	0.12
Race and ethnicity			
Asian	24 (40.0)	19 (31.7)	0.17
Hispanic or Latina	17 (28.3)	23 (38.3)	0.21
Non-Hispanic Black	0 (0)	2 (3.3)	0.26
Non-Hispanic White	16 (26.7)	12 (20.0)	0.16
None of the above or declined to state	3 (5.0)	4 (6.7)	0.07
Gravida	1 (1–2)	1 (1–2)	0.05
Para	0 (0–1)	0 (0–1)	0.04
Gestational age (completed wk)	39 (39–40)	39 (39–40)	0.17
Maternal comorbidities			
Advanced maternal age	28 (46.7)	18 (30.0)	0.35
Hypertension (all cause)	7 (11.7)	17 (28.3)	0.28
Preeclampsia	4 (6.7)	7 (11.6)	0.18
Diabetes (all cause)	7 (11.7)	11 (18.3)	0.26
Asthma	3 (5.0)	7 (11.7)	0.24
Multiple gestation	1 (1.7)	1 (1.7)	0.00
Chorioamnionitis	9 (15.0)	8 (13.3)	0.05
TOLAC	5 (8.3)	3 (5.0)	0.13
Indication for cesarean*			
1st-stage arrest	31 (51.7)	30 (50.0)	0.03
2nd-stage arrest	20 (33.3)	18 (30.0)	0.08
Fetal intolerance of labor	16 (26.7)	18 (30.0)	0.07
Failed operative delivery	1 (1.7)	3 (5.0)	0.18
Maternal request	1 (1.7)	3 (5.0)	0.18
Other	3 (5.0)	2 (3.3)	0.08
Maximum oxytocin dose in labor	11.7±8.5	12.4±9.1	0.08
Total hours oxytocin in labor	16.3±12.0	18.5±12.1	0.18

Std Diff, standardized difference; BMI, body mass index; TOLAC, trial of labor after cesarean.
Data are mean±SD, n (%), or median (interquartile range) unless otherwise specified. For nonnormally distributed continuous characteristics such as gestational age, a standardized difference in ranks was calculated.
* Some participants had more than one indication.

In the primary analysis of all study participants (n=120), median (interquartile range) quantitative blood loss was 840 mL (650–1,434) in patients allocated to calcium and 1,051 mL (796–1,395) in patients allocated to placebo (Fig. 2A). Quantitative blood loss was not significantly different in the calcium group (mean reduction 211 mL, 95% CI −33 to 410 mL; *P*=.086). The distribution of quantitative blood loss remained right-skewed after log transformation. All estimates for the primary outcome were obtained using an inverse Gaussian generalized linear model with a log link following our prespecified analysis plan. Results from several statistical techniques did not vary from the prespecified approach (Appendix 2, http://links.lww.com/AOG/D471).

In planned sensitivity analyses, we analyzed the primary outcome with adjustment for imbalanced baseline patient characteristics that could occur by chance, despite randomization, due to low counts and a small sample size. Advanced maternal age, Black and Hispanic race and ethnicity, hypertension, diabetes, and asthma were adjusted in sensitivity analyses given an absolute standardized difference greater than 0.2. Adjusted quantitative blood loss was 250 mL lower in the calcium group (95% CI 37–425) mL (*P*=.024).

When cases of nonatonic bleeding were removed for the prespecified subgroup analysis, calcium significantly reduced quantitative blood loss by calculated mean effect of 356 mL (95% CI 159–515) mL (*P*=.001) (n=79, Fig. 2B). Among the excluded patients who experienced nonatonic bleeding (n=21 in patients allocated to calcium and n=20 in patients allocated to placebo), there was no difference in quantitative blood loss between groups (2 mL, 95% CI −449 to 453 mL.)

Secondary hemorrhage outcomes are displayed in Table 2. In a subgroup analysis excluding patients

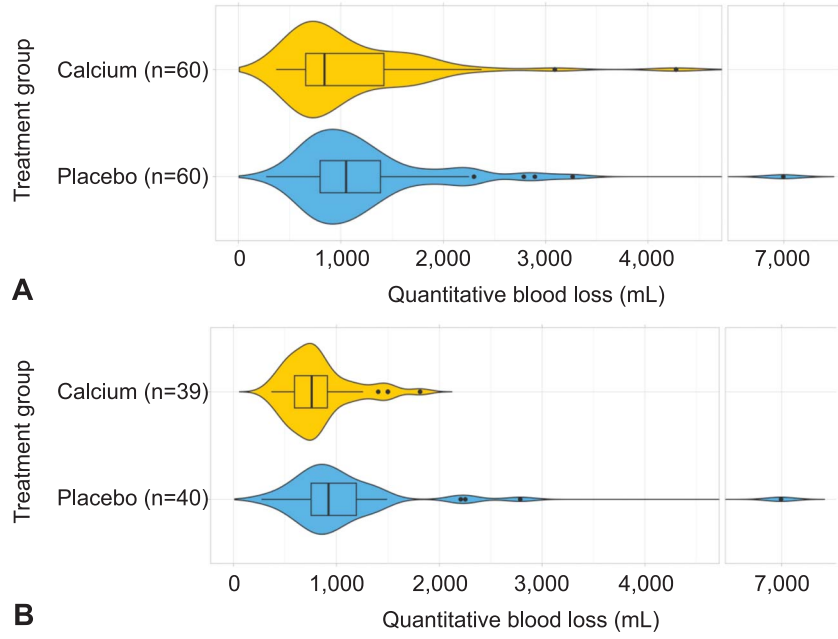

Fig. 2. Primary outcome analysis. Violin plots with superimposed box plots of the primary outcome are displayed by study group for all patients **(A)** and for the prespecified subgroup of patients* (excluding patients with documented nonatonic blood loss) **(B)**. Violin plots display the density of the overall data, and boxplot boxes display the median and interquartile range. **Documented nonatonic bleeding* was defined as surgeon's operative report description including any of the following: hysterotomy types other than low transverse (eg, classical, T- or J-shaped), invasive or abnormally adherent placenta, placental abruption, uterine rupture, bleeding from leiomyomas, grade 3–4 vaginal lacerations, or cervical lacerations. Nonatonic bleeding was evenly distributed between study groups, with 21 patients (35%) in the calcium group and 20 patients (33%) in the placebo group (P=.847).

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with nonatonic bleeding, PPH incidence (21% vs 43%) and change in hematocrit (6.2 vs 9.5) were lower among patients allocated to calcium.

Uterine tone scores reported by the obstetrician did not differ significantly between groups at the timepoints assessed. Five minutes after starting the infusion, median (interquartile range) tone scores were 7.0 (6.0–8.0) in patients allocated to calcium compared with 6.5 (6.0–7.0) in patients allocated to placebo (P=.415). At completion of study drug infusion, median (interquartile range) tone scores were 7.0 (6.0–8.0) in patients allocated to both groups (P=.566).

Two participants required hysterectomy and massive transfusion due to severity of PPH. One

Table 2. Secondary Hemorrhage Outcomes Among All Study Participants and the Prespecified Subgroup of Study Participants, Excluding Patients With Nonatonic Bleeding*

Cohort and Secondary Outcome	Calcium	Placebo	RR or Absolute Difference (95% CI)†
All study participants	(n=60)	(n=60)	
PPH incidence‡	24 (40.0)	34 (56.7)	0.71 (0.48 to 1.03)
2nd-line uterotonic	18 (30.0)	24 (40.0)	0.75 (0.46 to 1.23)
Blood transfusion	5 (8.3)	9 (15.0)	0.56 (0.20 to 1.56)
Absolute change in hematocrit§	7.8 (6.6–9.2)	9.7 (8.1–11.7)	−2.0 (-3.6 to 0.2)
Prespecified subgroup of study participants	(n=39)	(n=40)	
PPH incidence‡	8 (20.5)	17 (42.5)	0.48 (0.24 to 0.99)
2nd-line uterotonic	10 (25.6)	17 (42.5)	0.60 (0.32 to 1.15)
Blood transfusion	1 (2.6)	3 (7.5)	0.34 (0.04 to 3.15)
Absolute change in hematocrit§	6.2 (5.2–7.6)	9.5 (7.5–11.9)	−3.2 (−4.9 to 1.1)

RR, rate ratio; PPH, postpartum hemorrhage.
Data are n (%) or median (interquartile range).
* *Nonatonic bleeding* was defined as operative report description of any of the following: hysterotomy extension to the uterine artery, hysterotomy types other than low transverse (eg, classical, T- or J-shaped), invasive or abnormally adherent placenta, placental abruption, uterine rupture, bleeding from leiomyomas, grade 3 or 4 vaginal lacerations, or cervical lacerations.
† RR and 95% CI were estimated by Poisson regression with robust standard errors.
‡ Quantitative blood loss greater than 1,000 mL.
§ Hematocrit was analyzed with linear regression after log transformation to approximate a normal distribution.

Table 3. Incidence of Potential Medication Side Effects by Study Group

	Calcium (n=60)	Placebo (n=60)	Risk Difference (95% CI) (%)
Any possible side effect	23 (38.3)	25 (41.7)	−3.3 (−20.9 to 14.2)
New or worsened nausea	18 (30.0)	18 (30.0)	0.0 (−16.4 to 16.4)
New or increased vomiting	12 (20.0)	11 (18.3)	1.7 (−12.4 to 15.7)
Burning or discomfort in the arm at or near IV line	1 (1.7)	3 (5.0)	−3.3 (−9.7 to 3.1)
Flushing	0 (0.0)	6 (10.0)	−10.0 (−17.6 to −2.4)
Clinically significant heart rate changes from baseline warranting treatment*	1 (1.7)	6 (10.0)	−8.3 (−16.6 to 0.0)
Hypertension necessitating treatment†	0 (0.0)	1 (1.7)	−1.7 (−4.9 to 1.6)
Abnormal taste or sensations	0 (0.0)	2 (3.3)	−3.3 (−7.9 to 1.2)

IV, intravenous.
Data are n (%) unless otherwise specified.
* Treatment included medications to increase an abnormally low heart rate (epinephrine, glycopyrrolate, atropine) or decrease an abnormally high heart rate (IV fluid bolus, phenylephrine, beta blocker, calcium channel blocker).
† Treatment included medications to reduce blood pressure, including IV beta blocker, hydralazine, clevidipine, or other antihypertensive agent.

patient allocated to calcium had an unanticipated intraoperative diagnosis of placenta accreta (quantitative blood loss=4,274 mL), and one patient allocated to placebo experienced unremitting uterine atony refractory to uterotonic agents, intrauterine balloon tamponade, and extrauterine compression sutures (quantitative blood loss=6,993 mL).

Patients allocated to calcium had less increase in heart rate after delivery compared with their preoperative baseline (Appendix 4, available online at http://links.lww.com/AOG/D471). Percent change in mean arterial blood pressure from the patient's preoperative baseline did not differ significantly between groups (Appendix 4, http://links.lww.com/AOG/D471). Median [interquartile range] phenylephrine dose did not differ between groups (1.02 [0–2.26] mg and 1.09 [0.08–2.72] mg for participants allocated to calcium and placebo, respectively). Mean±SD intravenous fluids also did not differ (1,594±762 mL and 1,502±892 mL, respectively).

There were no study-related or possibly study-related severe adverse events and no patient deaths. The data safety monitoring board did not require any unblinding or pausing during the 12-month trial period. Incidence of any overall potential side effects did not differ between groups (Table 3), with the exception of flushing and clinically significant heart rate changes, which occurred more frequently in placebo recipients.

DISCUSSION

In this trial, calcium infusion during intrapartum cesarean delivery did not achieve statistical significance for reduction in blood loss in the primary analysis. However, the trial was designed and powered for a subgroup analysis excluding cases of bleeding due to etiologies no uterotonic medication could prevent (eg, hysterotomy extension, arterial injury, or placenta accreta). In the subgroup analysis, calcium reduced blood loss by more than 350 mL, an effect that achieved statistical significance and was supported by secondary hemorrhage outcome analysis. Calcium was well tolerated, with no observed adverse hemodynamic effects or untoward sequelae compared with placebo, though this study was not powered to detect differences in these parameters.

Calcium has strong biological plausibility as a uterotonic agent. We hypothesize that augmenting serum calcium concentrations increases uterine contractility. In uterine smooth muscle cells, oxytocin induces contractility by causing influx of extracellular calcium; without sufficient extracellular calcium, the uterus cannot contract.[13–15,26] Observational clinical studies suggest that higher serum calcium levels may trigger physiologic onset of uterine contractility with labor and that serum calcium correlates inversely with PPH severity.[16,17] The present findings are consistent with a pilot study suggesting benefit from 1 g of calcium chloride.[18]

Calcium chloride is an attractive uterotonic agent. It is a familiar medication that anesthesiologists routinely administer in a variety of clinical contexts. In direct contrast to second-line uterotonic agents methylergonovine and carboprost, calcium is also inexpensive and shelf-stable.[27] These features make calcium accessible in low-resource settings where patients suffer disproportionate morbidity and mortality from PPH.[28]

Calcium was well tolerated with our protocol and potentially reduced oxytocin-mediated tachycardia

and flushing, likely through vasoconstrictive effects. However, we administered a dilute solution through slow, controlled infusion in awake patients who could report symptoms. Rapid administration of concentrated calcium chloride may cause unpleasant or even dangerous side effects, including hot flushes, bradycardia, and hypotension. In addition, extravasation from an infiltrated intravenous line may cause local tissue injury.[12]

A strength of this study lies in its double-blind, randomized controlled trial design. Our study occurred in a generalizable clinical setting, and second-line uterotonic administration and blood transfusion rates in our placebo arm were concordant with prior reports.[10,19] The conclusions regarding effect size and statistical significance thresholds were also consistent across multiple statistical techniques, including nonparametric tests, as shown in Appendix 2, http://links.lww.com/AOG/D471.

This study has several limitations. First, the primary analysis failed to demonstrate statistical significance at a $P<.05$ threshold, owing, most likely, to a lack of statistical power rather than a lack of treatment effect. The 350-mL reduction in blood loss demonstrated in the prespecified subgroup analysis excluding patients with nonatonic bleeding points strongly to efficacy. For comparison, in the TRAAP2 trial (Tranexamic Acid for Preventing Postpartum Hemorrhage Following a Cesarean Delivery), investigating prophylactic tranexamic acid in more than 4,000 patients undergoing cesarean delivery, investigators found no difference in quantitative blood loss (between-group difference −30.6 mL, 95% CI −90.2 to 29.0 mL).[29]

Second, the trial medication was administered by 10-minute infusion beginning after umbilical cord clamping. This design was chosen to comply with the package insert maximum infusion rate and to avoid any potential neonatal effects from transplacental transfer of calcium. As such, second-line uterotonic administration often occurred before the completion of the 10-minute study drug infusion. We expect that delayed uterine tissue penetration of the calcium infused after umbilical cord clamping may have exerted a uterotonic effect not captured in the assessment of uterine tone by the obstetrician during the infusion. A different protocol likely would be needed to demonstrate a significant reduction in second-line uterotonic use or uterine tone scores.

Third, enrollment in this trial was limited to laboring, oxytocin-exposed parturients to increase the baseline prevalence of PPH. Follow-up treatment studies in lower-risk populations should follow.

Finally, few non-Hispanic Black parturients were enrolled, a limitation reflective of the demographics of parturients delivering at our institution. Black patients suffer disproportionate PPH morbidity and mortality[25,28,30,31] as well as higher prevalence of asthma and hypertensive conditions that contraindicate treatment with second-line uterotonics,[32,33] making it imperative to prioritize including Black patients in future studies.

In conclusion, calcium chloride is a well-tolerated medication that warrants additional investigation as a novel uterotonic agent. Given the limitations of current therapies and the high prevalence of maternal morbidity and mortality due to PPH, the present trial should motivate urgent, well-powered, multicenter studies. We believe that the marked efficacy found in our subgroup analysis, combined with the tolerability of our infusion protocol, meets the definition of a low-risk, high-reward intervention to potentially address PPH, the leading global cause of maternal morbidity and mortality.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? No.

What data in particular will be shared? Not available.

What other documents will be available? Not available. When will data be available (start and end dates)? Not applicable.

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