Original Research

Second-Line Uterotonics for Uterine Atony

A Randomized Controlled Trial

Naida M. Cole, MD, Jimin J. Kim, MD, Mario I. Lumbreras-Marquez, MD, Kara G. Fields, MS, Laura Mendez-Pino, MD, Michaela K. Farber, MD, Daniela A. Carusi, MD, Paloma Toledo, MD, and Brian T. Bateman, MD

OBJECTIVE: To evaluate the comparative efficacy of two of the most commonly used second-line uterotonics—methylergonovine maleate and carboprost tromethamine.

METHODS: We conducted a double-blind randomized trial at two large academic perinatal centers in patients undergoing nonemergency cesarean delivery with uterine atony refractory to oxytocin, as diagnosed by the operating obstetrician. The intervention included administration of a single dose of intramuscular methylergonovine or carboprost intraoperatively at diagnosis. The primary outcome, uterine tone on a 0–10 numeric rating scale 10 minutes after study drug administration, was rated by operating obstetricians blinded to the drug administered. Secondary outcomes included uterine tone score at 5 minutes, administration of additional uterotonic agents, other interventions for uterine atony or hemorrhage, quantitative blood loss, urine output, postpartum change in serum hematocrit, transfusion, length of hospital stay, adverse drug or transfusion reactions, and postpartum hemorrhage complications. A sample size of 50 participants per group was planned to detect a 1-point difference (with estimated within-group SD of 1.5) in the mean primary outcome with 80% power at a two-sided α level of 0.05 while accounting for potential protocol violations.

RESULTS: A total of 1,040 participants were enrolled, with 100 randomized to receive one of the study interventions. Mean±SD 10-minute uterine tone scores were 7.3±1.7 after methylergonovine and 7.6±2.1 after carboprost, with an adjusted difference in means of −0.1 (95% CI, −0.8 to 0.6, *P*=.76). Additional second-line uterotonics were required in 30.0% of the methylergonovine arm and 34.0% in the carboprost arm (adjusted odds ratio 0.72, 95% CI, 0.27–1.89, *P*=.505), and geometric mean quantitative blood loss was 756 mL (95% CI, 636–898) and 708 mL (95% CI, 619–810) (adjusted ratio of geometric means 1.06, 95% CI, 0.86–1.31, *P*=.588), respectively. No differences were detected in the occurrence of other interventions for uterine atony or postpartum hemorrhage.

CONCLUSION: No difference was detected in uterine tone scores 10 minutes after administration of either methylergonovine or carboprost for refractory uterine atony, indicating that either agent is acceptable.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT03584854.

(Obstet Gynecol 2024;144:832–41)

DOI: 10.1097/AOG.0000000000005744

Postpartum hemorrhage is the leading cause of maternal morbidity and mortality worldwide, with uterine atony accounting for approximately 80% of

From the Department of Anesthesia and Critical Care, University of Chicago Medicine, Chicago, Illinois; the Department of Anesthesiology, Perioperative and Pain Medicine and the Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Massachusetts; the Epidemiology and Public Health Division, Universidad Panamericana School of Medicine, Mexico City, Mexico; the Department of Anesthesiology, Pain Management and Perioperative Medicine, Henry Ford Hospital, Detroit, Michigan; the Department of Anesthesiology, Perioperative Medicine and Pain Management, University of Miami Miller School of Medicine, Miami, Florida; and the Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California.

Funding by the 2018 Eleanor and Miles Shore Faculty Development Award, Brigham and Women's Hospital.

Presented at the 55th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, May 3–7, 2023, New Orleans, Louisiana.

Each author has confirmed compliance with the journal's requirements for authorship.

The authors thank Somayeh Mohammadi, who contributed to subject enrollment, data collection, and data management.

Corresponding author: Naida M Cole, MD, University of Chicago Medicine, Department of Anesthesia & Critical Care, Chicago, IL; nmcole@bsd.uchicago.edu.

Financial Disclosure:

Naida M. Cole reports money was paid to her institution from the Foundation for Anesthesia Education Research through a Mentored Research Training grant. She received UpToDate royalties. Daniela A. Carusi received payment from Wolters Kluwer. Michaela K. Farber served on the advisory boards for Octapharma, HemoSonics, and Flat Medical. Paloma Toledo received speaker fees from Pacira for a SOAP-sponsored talk on a TAP blocks, unrelated to this article. The other authors did not report any potential conflicts of interest.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0029-7844/24

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

cases.[1,2] Cesarean delivery further contributes to an increased risk of postpartum hemorrhage.[3] Rates of both atonic hemorrhage and cesarean delivery have increased over the past two decades, with hemorrhage-related morbidity such as transfusion and hysterectomy following a similar trend.[4–7]

Oxytocin is recommended as the first-line pharmacologic therapy for prophylaxis and treatment of uterine atony, but up to 25% of postpartum hemorrhage cases may require a second-line uterotonic agent.[7–10] Methylergonovine maleate, a semisynthetic ergot alkaloid, and carboprost tromethamine, a synthetic prostaglandin F2α analog, are two of the most commonly used second-line drugs for the treatment of refractory uterine atony.[7] Despite the frequent use of these drugs, their pharmacology and comparative efficacy are incompletely understood.[11] As a result, there is limited guidance on their usage for clinical practice, and practice patterns vary widely according to patient and hospital-level characteristics.[9,10,12] The objective of this study was to compare the efficacy of methylergonovine and carboprost for treatment of uterine atony during cesarean delivery.

METHODS

This dual-center, prospective, double-blind, randomized controlled trial was conducted at two large academic obstetric tertiary referral centers between March 2019 and April 2022. Institutional research ethics board approval was obtained at each institution before the start of the study, and the trial was registered at ClinicalTrials.gov (Appendix 1, available online at http://links.lww.com/AOG/D851).

Parturients with American Society of Anesthesiologists classification I, II, or III who were between 18 and 50 years of age and undergoing nonemergency cesarean delivery were enrolled. Self-reported race and ethnicity (recognized risk factors for uterine atony) were recorded to evaluate for balance between the treatment arms. Patients requiring an interpreter for urgent delivery and those with known or suspected hypersensitivity to either study drug, cardiovascular or active respiratory diseases such as hypertension or asthma, which are contraindications to one of the drugs, known or suspected delayed postpartum hemorrhage, and coagulopathy were excluded. Patients unwilling to accept blood transfusions were also excluded. All participants gave written informed consent before surgery.

Participant informed consent and enrollment took place before cesarean delivery. Randomization was performed at the time of intraoperative uterine atony diagnosed by the obstetrician despite intravenous oxytocin administration. Uterine atony was defined by the operating clinicians' subjective assessment of uterine firmness. Participants were randomized 1:1 through computer-generated site-stratified randomization schedules containing permuted blocks of four. Allocation was concealed in sequentially numbered, opaque sealed envelopes prepared by a research assistant not directly involved in the research.[13] Participants were randomized to receive an initial dose of either methylergonovine or carboprost, depending on their group allocation. The participant and all members of the clinical team except the anesthesiology team were blinded to study drug allocation.

In the operating room, standard monitors were attached. Surgical anesthesia was provided by neuraxial anesthesia or with general anesthesia when necessary. Cesarean delivery was performed per standard institutional practice. Immediately after delivery of the fetus and umbilical cord clamping (delayed up to 60 seconds at the discretion of the obstetric and neonatal teams), prophylactic intravenous oxytocin infusion was administered following the standard dosing protocols of each institution. At Brigham and Women's Hospital, an initial bolus of approximately 3 international units was typically given over approximately 3–5 minutes, followed by continuous infusion of about 3 international units/hour at the discretion of the attending anesthesiologist. In cases of suspected atony, the rate of infusion was increased at the discretion of the anesthesiologist. At Northwestern, an infusion of 300 milliunits/min was administered for participants at low risk of uterine atony, and 600 milliunits/min was administered for participants at high risk or with suspected atony.

If uterine tone was deemed inadequate by the obstetrician on the basis of their manual intraoperative assessment and a second-line uterotonic was requested by the obstetrician (regardless of concurrent blood loss), participants were then randomized by the anesthesiologist to receive either 0.2 mg methylergonovine or 0.25 mg carboprost intramuscularly. Uterine tone was determined by the blinded operating attending obstetrician at 0-, 5-, and 10-minute intervals after study drug administration using a validated numeric rating scale of 0–10.[14] The only instruction given to the obstetricians for using the tone score was that 0 should correspond with "no tone" and 10 with "excellent tone" according to their manual assessment.[14] If the surgeon requested additional uterotonic drugs at any time, the participant received the alternative study drug (eg,

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

carboprost if the patient has randomized to methylergonovine and vice versa), and the timing of this administration was documented. Any further uterotonic drug was administered in an unblinded fashion as needed.

Transfusion needs were determined jointly by the anesthetic and obstetric teams following standard institutional practices. The circulating nurse in the operating room was responsible for measuring quantitative blood loss, with the total amount calculated at the conclusion of surgery. A combined system of gravimetric, colorimetric, and volumetric measurements was used for quantitative blood loss calculation. Treatment with other hemostatic agents such as misoprostol or tranexamic acid and surgical measures (ie, compression sutures, balloon placement, or hysterectomy) were performed freely at the discretion of the obstetric clinicians. Prophylactic administration of antiemetic and antidiarrheal medications was permitted at the discretion of unblinded postpartum nurses and obstetric clinicians. *Significant complications* were predefined as systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 110 mm Hg or higher up to 2 hours postpartum, chest pain up to 24 hours postpartum, intraoperative ischemic electrocardiogram changes, acute renal dysfunction, transfusion-related reactions, intubation, hypovolemic shock, or intensive care unit admission at any time postoperatively during the admission. A blinded investigator assessed each participant between 2–4 hours and 18–24 hours postpartum for self-reported side effects of the study drugs.

The primary outcome was uterine tone score on a 0–10 numeric rating scale 10 minutes after study drug administration. Secondary outcomes included an earlier assessment of change in uterine tone score at 5 minutes after study drug administration; need for additional uterotonic agent(s), including misoprostol; quantitative blood loss measurement per routine clinical practice; intraoperative crystalloid and vasopressor administration; urine output; change in postoperative serum hematocrit from admission; blood product administration; surgical or radiologic intervention(s) for postpartum hemorrhage; length of hospital stay; adverse reaction to study drugs (eg, headache, chest pain, arrhythmia, bronchospasm, nausea, vomiting, diarrhea, flushing, change in blood pressure requiring medical treatment); and medical complications related to postpartum hemorrhage (eg, vasopressor requirement, transfusion-related reactions, intensive care unit admission, myocardial injury).

Investigators defined 1 point as the minimum difference between groups in mean uterine tone at 10 minutes after study drug administration that would be clinically meaningful. This definition is consistent with our estimate of the uterine tone scale standard error of measurement as 1 point at 3 minutes after delivery (corresponding approximately to baseline/time of study drug administration in this trial) in our previous study of 85 cesarean deliveries.[14,15] Our estimate of within-group SD in mean uterine tone at 10 minutes after study drug administration was taken to be 1.5 points, slightly larger than the observed SD of 1.2 at 10 minutes after delivery in our prior study. An a priori power analysis determined that enrollment of 37 participants per group would provide 80% power at a two-sided α level of 0.05 to detect a 1-point difference, with an estimated within-group SD of 1.5 in mean uterine tone at 10 minutes after study drug administration using a two-sample *t* test. Randomization of 100 participants was planned to account for anticipated protocol violations.

Uterine tone scores at 10 minutes (primary outcome) and 5 minutes (secondary outcome) after study drug administration were compared between groups with adjustment for baseline tone and trial site using the generalized estimating equations method with an identity link to account for the correlation between repeated measurements on the same participant. The main primary outcome analysis used a complete-case approach whereby 3 participants with incomplete uterine tone follow-up did not contribute a uterine tone score at 10 minutes after study drug administration to the analysis. Counts and percentages of missing data for each variable are shown by randomized group in Appendix 2, available online at http://links.lww.com/AOG/D851. The magnitude and direction of the difference in percentage missing were quantified for each variable as the standardized difference. With a sample size of 50 patients per group, a standardized difference with magnitude greater than $1.96\times(2/n)^{(1/2)}=0.392$ was taken to indicate an imbalance in percentage missing between groups.[16] A multiple imputation sensitivity analysis for the primary outcome also was performed that used the multivariate imputation by chained equations approach to impute missing uterine tone values using observed tone measurements (baseline, 5, and 10 minutes), parturient characteristics (age, race, body mass index [BMI, calculated as weight in kilograms divided by height in meters squared], parity), pregnancy characteristics (number of

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

fetuses, neonatal birth weight), trial site, interventions (randomized study drug, administration of second study drug, intraoperative transfusion), and outcomes (intraoperative blood loss, change in hematocrit from baseline to 24 hours after delivery) to create 10 complete data sets. The primary outcome was compared between groups in each of the 10 imputed data sets, and the resulting 10 sets of estimates were combined using the Rubin rules.

All continuous secondary outcomes were initially assessed for the normality of residuals from a multivariable linear regression model with trial site and baseline uterine tone as covariates. Outcomes displaying normally distributed model residuals were analyzed with multivariable linear regression, with effect size presented as an adjusted difference in means with a 95% CI. Outcomes with all nonzero values that displayed skewed linear regression model residuals were natural log-transformed and analyzed with multivariable linear regression, with effect size presented as an adjusted ratio of geometric means with 95% CI. Outcomes containing at least one zero value that presented skewed linear regression model residuals were compared between groups with multivariable quantile regression, with effect size presented as the adjusted difference in medians with 95% CI.

All binary outcomes were initially considered for comparison using multivariable logistic regression (for single measurements) or generalized estimating equations with a logit link (for repeated measurements) with trial site and baseline uterine tone as covariates. If the multivariable regression model converged, effect size was presented as an adjusted odds ratio (aOR) with 95% CI. If the model did not converge because of low incidence, groups were compared with a Fisher exact test, and effect size was presented as risk difference with exact 95% CI.

Time to administration of a second study drug was compared between groups with multivariable

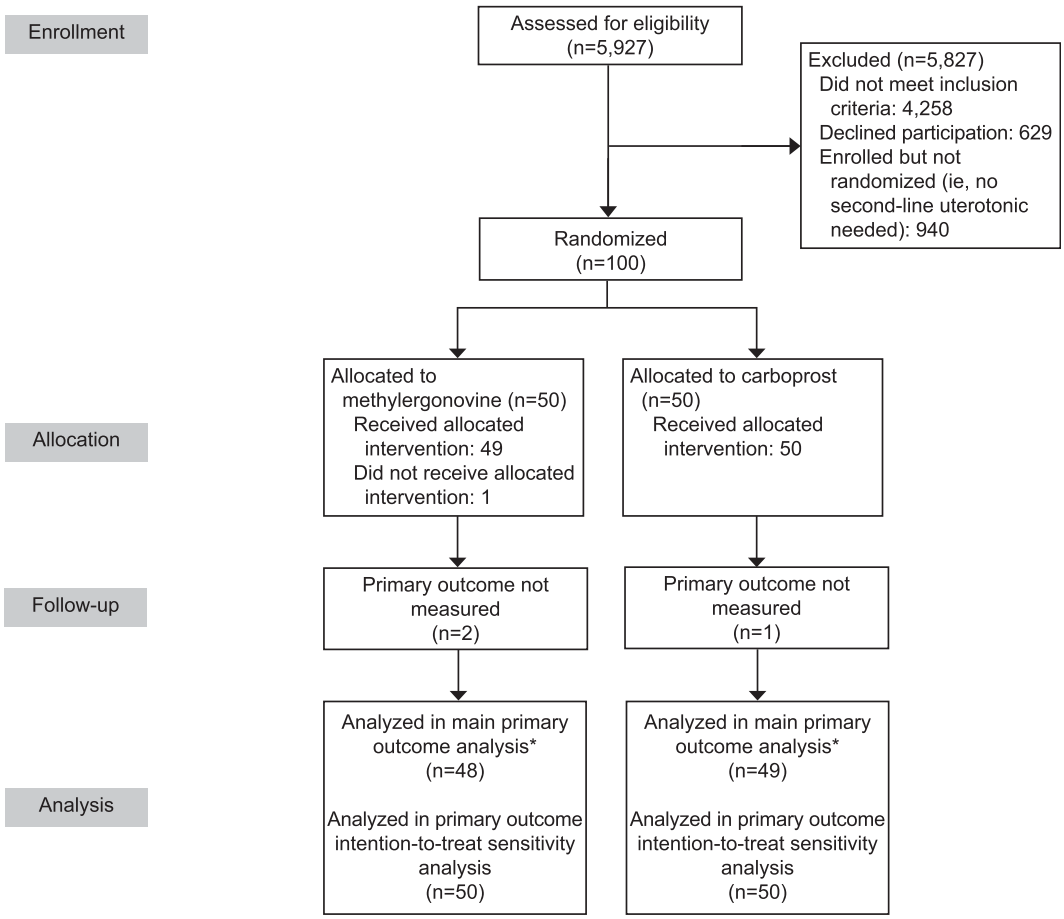

Fig. 1. Flow diagram of enrollment. *Primary outcome recorded.
Cole. Second-Line Uterotonics RCT. Obstet Gynecol 2024.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Cox proportional hazards regression with trial site and baseline uterine tone as covariates, with effect size presented as an adjusted hazard ratio (HR) with 95% CI. Complete-case analysis was performed for all secondary outcomes. All analyses were performed with SAS 9.4. This trial is reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[17]

RESULTS

A total of 5,927 parturients were assessed for eligibility; 1,040 met inclusion criteria and were enrolled between March 2019 and April 2022. Enrollment at Brigham and Women's Hospital was suspended between March 2020 and June 2020 as a result of institutional restrictions on clinical research during the coronavirus disease 2019 (COVID-19) pandemic.

Table 1. Baseline Characteristics of Study Group Participants

Characteristic	Methylergonovine	Carboprost	All
Age (y)	34.4±4.4	32.7±5.6	33.6±5.1
Non–English-speaking			
Yes	2 (4.0)	6 (12.0)	8 (8.0)
No	41 (82.0)	36 (72.0)	77 (77.0)
Unknown	7 (14.0)	8 (16.0)	15 (15.0)
Self-reported race and ethnicity, by institution			
Asian	9 (18.0)	5 (10.0)	14 (14.0)
African American	5 (10.0)	10 (20.0)	15 (15.0)
Hispanic	6 (12.0)	3 (6.0)	9 (9.0)
White	26 (52.0)	25 (50.0)	51 (51.0)
None of the above*	4 (8.0)	6 (12.0)	10 (10.0)
Unknown	0 (0)	1 (2.0)	1 (1.0)
Delivery BMI (kg/m^2)	31.5±5.8	30.8±5.8	31.2±5.7
Gestational age (wk)	38.7±1.5	38.8±1.6	38.8±1.5
Parity			
0	29 (58.0)	23 (46.0)	52 (52.0)
1	13 (26.0)	19 (38.0)	32 (32.0)
2	6 (12.0)	6 (12.0)	12 (12.0)
3	1 (2.0)	2 (4.0)	3 (3.0)
5	1 (2.0)	0 (0)	1 (1.0)
No. of fetuses			
1	48 (96.0)	48 (96.0)	96 (96.0)
2	2 (4.0)	2 (4.0)	4 (4.0)
Elective cesarean delivery	25 (50.0)	25 (50.0)	50 (50.0)
Fetus 1			
Male sex	32 (64.0)	32 (64.0)	64 (64.0)
1-min Apgar score	8 (8, 8)	8 (8, 8)	8 (8, 8)
5-min Apgar score	9 (9, 9)	9 (8, 9)	9 (9, 9)
Birth weight (g)†	3,375 (3,155, 3,840)	3,510 (3,020, 3,840)	3,420 (3,020, 3,840)
Fetus 2			
Male sex†	2 (100)	2 (100)	4 (100)
1-min Apgar score‡	8 (8, 8)	7.5 (7, 8)	8 (7.5, 8)
5-min Apgar score‡	9 (9, 9)	8.5 (8, 9)	9 (8.5, 9)
Birth weight (g)‡	2,545 (2,490, 2,600)	2,524 (2,098, 2,950)	2,545 (2,294, 2,775)
Anesthesia type			
CSE	5 (10.0)	6 (12.0)	11 (11.0)
Spinal	26 (52.0)	25 (50.0)	51 (51.0)
Epidural	18 (36.0)	19 (38.0)	37 (37.0)
General	1 (2.0)	0 (0)	1 (1.0)
Preoperative hematocrit (%)	35.0±4.8	35.3±3.9	35.1±4.4
Baseline uterine tone§	4.4±1.8	4.7±1.9	4.6±1.9

BMI, body mass index; CSE, combined spinal–epidural.
Data are mean±SD, n (%), or median (quartile 1, quartile 3).
* Includes those of American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander descent and those of two or more races.
† n=49 in the carboprost arm.
‡ n=2 and 2 in the methylergonovine and carboprost arms, respectively.
§ n=49 in the methylergonovine arm.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

One hundred participants undergoing nonurgent cesarean delivery were randomized because of inadequate uterine tone despite prophylactic oxytocin administration. One participant did not receive the allocated intervention as a result of improvement in uterine tone after randomization. A total of 48 participants who received methylergonovine and 49 participants who received carboprost contributed 10-minute uterine tone scores to the primary analysis (Fig. 1). The counts and percentages of missing values for each baseline and outcome variable alone and combined are reported by group and overall in Appendix 2 (http://links.lww.com/AOG/D851). No imbalance was detected between groups in percentage missing for any variable alone or combined.

Baseline characteristics were similar between the two groups (Table 1). Twenty-nine of those who received methylergonovine (58.0%) and 23 of those who received carboprost (46.0%) were nulliparous. Mean±SD uterine tone scores at the time of intervention were 4.4±1.8 in the methylergonovine and 4.7±1.9 in the carboprost groups. No differences were detected between those who received methylergonovine and those who received carboprost with respect to uterine tone score 10 minutes later, with mean±SD scores of 7.3±1.7 and 7.6±2.1, respectively, and the difference in means after adjustment for baseline tone and study site was −0.1 (95% CI, −0.8 to 0.6, *P*=.76) (complete-case analysis) (Fig. 2). The multiple imputation sensitivity analysis produced similar results (−0.1, 95% CI, −0.8 to 0.6, *P*=.73).

Generally, no meaningful differences were detected between groups in the secondary endpoints (Appendix 3, available online at http://links.lww.com/AOG/D851, and Table 2). Uterine tone at 5 minutes after study drug administration was (mean±SD) 6.4±1.9 and 6.8±1.9 in the methylergonovine and carboprost groups, respectively. A second study drug was given in 30.0% of participants who initially received methylergonovine and 34.0% of participants who initially received carboprost (aOR 0.72, 95% CI, 0.27–1.89, *P*=.505). Among those who needed a second study drug, time to second study drug administration was somewhat shorter in the methylergonovine than in the carboprost group: median 9 minutes (interquartile range 6–15) compared with 6 minutes (interquartile range 3–8), respectively (adjusted HR 0.47, 95% CI, 0.22–1.01, *P*=.053) (Fig. 3). Misoprostol was administered for atony in 6.0% of participants who received methylergonovine and 4.0% who received carboprost. The geometric mean intraoperative quantitative blood loss was 756 mL (95% CI, 636–898) in the methylergonovine group and 708 mL (95% CI, 619–810) (adjusted ratio of geometric means 1.06, 95% CI, 0.86–1.31, *P*=.588) in the carboprost group. Only 10.0% and 8.0% of participants required an intraoperative surgical intervention for atony in the methylergonovine and carboprost groups, respectively, with an aOR of 1.31 (95% CI, 0.32–5.34, *P*=.71) for methylergonovine compared with carboprost. No difference was detected in odds of tranexamic acid administration between groups (aOR 2.93, 95% CI, 0.81–10.58, *P*=.10). Geometric mean hospital length of stay was 4.4 days (95% CI, 4.1–4.7) for the methylergonovine group and 4.1 days (3.7–4.6) for the carboprost group. Three participants in the methylergonovine group required packed red blood cell transfusion in the operating room compared with one participant in the carboprost group. One participant received intraoperative fresh frozen plasma; one received intraoperative albumin; and one received intraoperative cryoprecipitate, all in the methylergonovine group. No participants received platelets, salvaged autologous red blood cells, or fibrinogen concentrate at any time. No participants required arterial embolization or occlusion, and none were admitted to the intensive care unit postoperatively. Adverse drug effects were rare and

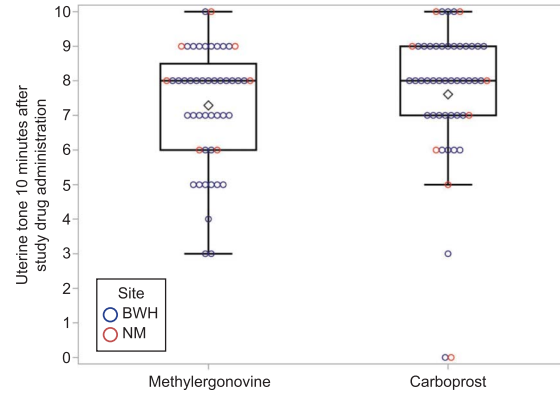

Fig. 2. Boxplot of uterine tone 10 minutes after methylergonovine and carboprost tromethamine administration. *Circles* show individual patient values (recorded for 48 and 49 patients in the methylergonovine and carboprost groups, respectively). *Diamonds* show the means; *boxes* show the first quartiles, medians, and third quartiles. *Whiskers* extend from the lowest value within 1.5 times the interquartile range below the first quartiles to the highest value within 1.5 times the interquartile range above the third quartile. The difference between groups in mean uterine tone score 10 minutes after study drug administration with adjustment for baseline tone and study site was −0.1 (95% CI, −0.8 to 0.6) as estimated with generalized estimating equations with an identity link. BWH, Brigham and Women's Hospital; NM, Northwestern Medicine.

Cole. Second-Line Uterotonics RCT. Obstet Gynecol 2024.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 2. Secondary Outcomes

Outcome	Methylergonovine	Carboprost	Effect Size (95% CI)
Uterine tone score at 5 min*	6.4±1.9	6.8±1.9	−0.2 (−0.8 to 0.4)
2nd study drug given†	15 (30.0)	17 (34.0)	0.72 (0.27–1.89)
Time to 2nd study drug administration after 1st study drug (min)‡	9 (6, 15)	6 (3, 8)	0.47 (0.22–1.01)
Intraoperative QBL (mL)§	756 (636–898)	708 (619–810)	1.06 (0.86–1.31)
Intraoperative products (albumin, RBCs, FFP, platelets, cryoprecipitate, fibrinogen concentrate)‖	3 (6.0)	1 (2.0)	4.0 (−5.4 to 14.6)
Intraoperative TXA†	10 (20.0)	4 (8.0)	2.93 (0.81–10.58)
Intraoperative cell saver	0 (0)	0 (0)	—
Surgical intervention (Bakri, compression suture, packing, hysterectomy, arterial occlusion or embolization)†	5 (10.0)	4 (8.0)	1.31 (0.32–5.34)
Total intraoperative crystalloid (mL)§	1,635 (1,474–1,812)	1,612 (1,475–1,762)	1.01 (0.89–1.15)
Intraoperative UOP (mL)§	144 (112–185)	175 (146–209)	0.85 (0.63–1.16)
Intraoperative RiaSTAP	0 (0)	0 (0)	—
Total intraoperative phenylephrine (micrograms)¶	2,540 (560, 3,930)	1,945 (200, 3,340)	740 (−351 to 1,831)
Any intraoperative ephedrine†	17 (34.0)	16 (32.0)	1.16 (0.50–2.70)
Average hourly UOP, in 1st 2 h postpartum#	100 (60, 130)	94 (58, 188)	—
Postpartum 6-h Hct (%)#	33.2 (25.0, 35.0)	29.4 (27.5, 32.3)	—
Postpartum 24-h Hct (%)**	27.7±5.0	28.3±3.7	−0.6 (−2.5 to 1.2)
Change from most recent preoperative to 24-h Hct (%)**	−7.4±5.1	−6.7±3.1	−0.4 (−2.1 to 1.4)
24-h QBL, including intraoperative (mL)§	758 (636–903)	713 (621–820)	1.05 (0.85–1.30)
24-h products, including intraoperative (albumin, RBCs, FFP, platelets, cryoprecipitate, fibrinogen concentrate)†	5 (10.0)	2 (4.0)	2.74 (0.50–15.12)
Length of hospital stay (d)§	4.4 (4.1–4.7)	4.1 (3.7–4.6)	1.05 (0.93–1.19)
Intraoperative misoprostol†	3 (6.0)	2 (4.0)	1.49 (0.22–9.98)
Postoperative misoprostol‖	1 (2.0)	0 (0)	2.0 (−5.4 to 10.6)

QBL, quantitative blood loss; RBCs, red blood cells; FFP, fresh frozen plasma; TXA, tranexamic acid; Hct, hematocrit; UOP, urine output.
Data are mean±SD, n (%), median (quartile 1, quartile 3), or geometric mean (95% CI) unless otherwise specified.

* n=49 in methylergonovine arm. Effect size is baseline tone and site-adjusted difference in means. Effect size, CI, and *P* value were estimated by generalized estimating equations with identity link (allowing for simultaneous modeling of longitudinally measured outcomes, which include patients with partially missing outcome data). The covariate-adjusted comparison included 99 patients because of missing uterine tone at 5 minutes after study drug administration and baseline tone for n=1 patient in the methylergonovine arm.

† Effect sizes are baseline tone and site-adjusted odds ratios. Effect sizes, CIs, and *P* values were estimated by multivariable logistic regression. The covariate-adjusted comparisons included 99 patients because of missing baseline tone for n=1 patient in the methylergonovine arm.

‡ n=15 and 17 in the methylergonovine and carboprost arms, respectively, for medians and quartiles. Effect size is baseline tone and site-adjusted hazard ratio. Effect size, CI, and *P* value were estimated by Cox proportional hazards regression. The covariate-adjusted comparison included 99 patients because of missing baseline tone for n=1 patient in the methylergonovine arm.

§ n=49 in the methylergonovine arm for intraoperative UOP and n=49 in the carboprost arm for 24-hour QBL. Effect sizes are baseline tone and site-adjusted ratios of geometric means. Effect sizes, CIs, and *P* values were estimated by multivariable linear regression with natural log-transformed outcomes. Because of missing baseline tone for n=1 patient in the methylergonovine arm, the intraoperative blood loss, crystalloid, and hospital length of stay covariate-adjusted comparisons included 99 patients and the intraoperative UOP and 24-hour QBL covariate-adjusted comparisons included 98 patients.

‖ Effect sizes are crude risk differences. Effect sizes, CIs, and *P* values were estimated by the Fisher exact test. Comparisons were not adjusted for baseline uterine tone and site because multivariable logistic regression models did not converge as a result of low outcome incidences.

¶ Effect size is baseline tone and site-adjusted difference in medians. Effect size, CI, and *P* value were estimated by multivariable quantile regression. The covariate-adjusted comparison included 99 patients because of missing baseline tone for n=1 patient in the methylergonovine arm.

Analyses were not performed because average hourly UOP in first 2 hours postpartum was recorded for only n=9 and 8 patients in the methylergonovine and carboprost arms, respectively, and postpartum 6-hour Hct only was recorded for n=9 and 9 patients in the methylergonovine and carboprost arms, respectively.

** n=47 and 45 in the methylergonovine and carboprost arms, respectively. Effect sizes are baseline tone and site-adjusted differences in means. Effect sizes, CIs, and *P* values were estimated by multivariable linear regression. The covariate-adjusted comparisons included 91 patients because of missing baseline tone for n=1 patient in the methylergonovine arm.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

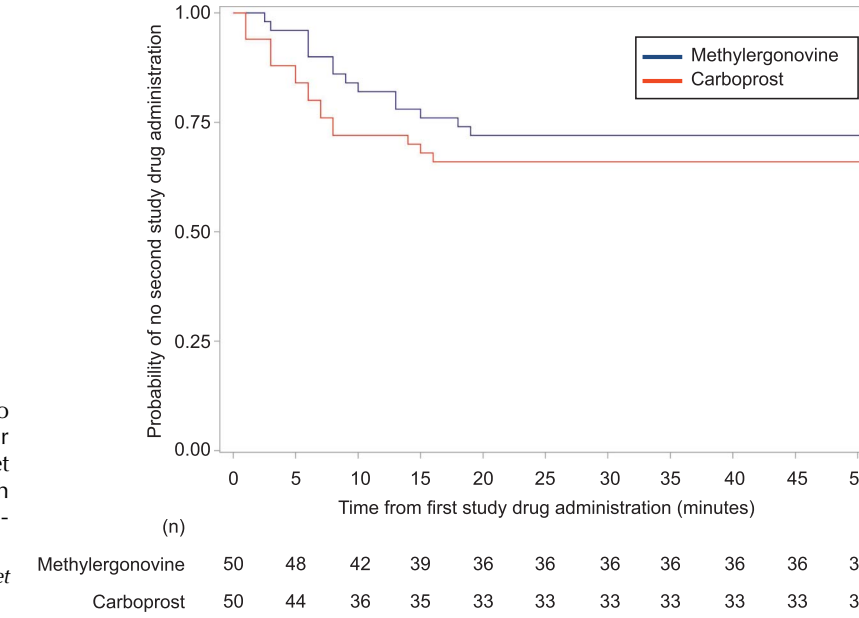

Fig. 3. Kaplan–Meier curve of time to second drug administration. Number of patients at risk (ie, who did not yet receive a second study drug) in each randomized group is shown at 5-minute intervals below the x-axis.
Cole. Second-Line Uterotonics RCT. Obstet Gynecol 2024.

similar between groups. No significant complications were noted.

DISCUSSION

In this study, no difference in uterine tone score was detected 10 minutes after methylergonovine or carboprost administration for uterine atony. Five-minute uterine tone scores, blood loss, and the need for additional second-line uterotonic drugs also did not differ meaningfully between groups. Adverse event rates were similar between groups, with no severe morbidity or mortality.

Methylergonovine and carboprost are two of the most commonly used second-line uterotonics in the United States. National and international guidelines do not recommend a preferred second-line agent, and randomized trials on their comparative efficacy have been lacking.[9,10] Observational comparative data are mixed. Isolated studies demonstrate less blood loss after prophylactic carboprost compared with methylergonovine in the third stage of labor. However, a secondary analysis of data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network Cesarean Registry found lower hemorrhage-related morbidity risk after therapeutic methylergonovine.[18–22] Therefore, U.S. administration patterns vary widely, in the absence of contraindications, according to individual clinician and institutional factors, with methylergonovine administered more frequently.[7,23]

Uterine tone score using a validated scale was chosen for the primary outcome as the most direct assessment of uterotonic drug efficacy. Quantitative blood loss was assessed as a secondary outcome because it can reflect a combination of surgical factors that contribute to postpartum hemorrhage besides uterine atony; quantitative blood loss was not meaningfully different between groups. Various qualitative scales have assessed uterine tone in clinical trials.[24–26] A strength of the study is the use of the 0–10 uterine tone score, which is the most common score and the only score with very good interrater reliability and agreement.[15,27,28] Randomization allowed direct comparison of methylergonovine and carboprost for second-line treatment of uterine atony.

Some limitations must be noted. Oxytocin dosing differed between institutions, although results were adjusted for site to account for this. Nausea, vomiting, and diarrhea rates were low, potentially because of prophylactic postoperative administration of medications to avoid undesired effects of uterotonic drugs. This trial was powered to detect superiority of one of the treatments in the primary outcome; a test of equivalence would have required a larger sample size. The 95% confidence limits of the observed adjusted difference in means were −0.8 to 0.6. However, this excludes the a priori defined 1-point minimum clinically meaningful difference between groups. It is therefore unlikely that inadequate sample size resulted in failure to detect superiority. We did not detect a difference in minor drug effects, quantitative blood loss, or need for additional uterotonics between

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

groups, but some differences were imprecisely estimated; these outcomes need to be further evaluated in larger studies.

A second study drug was administered in 30.0% and 34.0% of participants after methylergonovine or carboprost administration at median of 9 minutes (interquartile range 6–15) compared with 6 minutes (interquartile range 3–8) after initial drug administration, respectively. Second study drug administration before the 10-minute outcome could arguably complicate result interpretation. Although the intention-to-treat approach has limitations, exclusion of participants receiving a second study before the 10-minute mark would produce biased results in that participants who required a second study drug may have had systematically different characteristics from those who did not. The intention of the trial was not to determine which drug should be used but instead whether one drug could be recommended first. The adjusted HR point estimate for second study drug administration of 0.47 (95% CI, 0.22–1.01) suggests later second study drug administration in participants receiving methylergonovine compared with carboprost. However, this large effect size may reflect mainly a faster onset time for methylergonovine with early perception of inadequate uterine tone after carboprost because of its slower onset time, and the CI for this estimate was wide. The risk of receiving a second study drug at any point during the trial was also slightly lower for methylergonovine compared with carboprost, but the odds ratio estimate had a wide CI that intersects the null (aOR 0.72, 95% CI, 0.27–1.89, P=.505).

In summary, this study did not detect a difference in efficacy between methylergonovine and carboprost for the treatment of refractory uterine atony during cesarean delivery. Clinicians may confidently use either agent according to patient comorbidities and drug contraindications, given that one was not found to be superior to the other. Likewise, in cases of clinical equipoise, drug choice may be determined by clinician preference, side effects, cost, or availability.

REFERENCES

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2:e323–33. doi: 10.1016/S2214-109X(14)70227-X
2. Bateman BT, Berman MF, Riley LE, Leffert LR. The epidemiology of postpartum hemorrhage in a large, nationwide sample of deliveries. Anesth Analg 2010;110:1368–73. doi: 10.1213/ANE.0b013e3181d74898
3. Al-Zirqi I, Vangen S, Forsen L, Stray-Pedersen B. Prevalence and risk factors of severe obstetric haemorrhage. BJOG 2008;115:1265–72. doi: 10.1111/j.1471-0528.2008.01859.x
4. Callaghan WM, Kuklina EV, Berg CJ. Trends in postpartum hemorrhage: United States, 1994-2006. Am J Obstet Gynecol 2010;202:353.e1–6. doi: 10.1016/j.ajog.2010.01.011
5. Reale SC, Easter SR, Xu X, Bateman BT, Farber MK. Trends in postpartum hemorrhage in the United States from 2010 to 2014. Anesth Analg 2020;130:e119–22. doi: 10.1213/ANE.0000000000004424
6. Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of caesarean section rates: global and regional estimates. BMJ Glob Health 2021;6:e005671. doi: 10.1136/bmjgh-2021-005671
7. Bateman BT, Tsen LC, Liu J, Butwick AJ, Huybrechts KF. Patterns of second-line uterotonic use in a large sample of hospitalizations for childbirth in the United States: 2007-2011. Anesth Analg 2014;119:1344–9. doi: 10.1213/ANE.0000000000000398
8. World Health Organization. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. WHO; 2018
9. Prevention and management of postpartum haemorrhage. Green-top guideline No. 52. BJOG 2017;124:e106–49. doi: 10.1111/1471-0528.14178
10. Postpartum hemorrhage. Practice Bulletin No. 183. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e168–86. doi: 10.1097/AOG.0000000000002351
11. Likis FE, Sathe NA, Morgans AK, Hartmann KE, Young JL, Carlson-Bremer D, et al. Management of postpartum hemorrhage. Report No. 15- EHC013-EF. Agency for Healthcare Research and Quality (US); 2015.
12. Leduc D, Senikas V, Lalonde AB. No. 235–active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can 2018;40:e841–55. doi: 10.1016/j.jogc.2018.09.024
13. Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. J Crit Care 2005;20:187–93. doi: 10.1016/j.jcrc.2005.04.005
14. Cole NM, Abushoshah I, Fields KG, Carusi DA, Robinson JN, Bateman BT, et al. The interrater reliability and agreement of a 0 to 10 uterine tone score in cesarean delivery. Am J Obstet Gynecol MFM 2021;3:100342. doi: 10.1016/j.ajogmf.2021.100342
15. Wyrwich KW, Tierney WM, Wolinsky FD. Further evidence supporting an SEM-based criterion for identifying meaningful intra-individual changes in health-related quality of life. J Clin Epidemiol 1999;52:861–73. doi: 10.1016/s0895-4356(99)00071-2
16. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107. doi: 10.1002/sim.3697
17. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869. doi: 10.1136/bmj.c869
18. Gupta A. A comparative study of methylergonovine and 15-methyl prostaglandin F2α in active management of third stage of labor. Obstet Gynecol Sci 2013;56:301–6. doi: 10.5468/ogs.2013.56.5.301
19. Lambda A, Joshi G, Purohit R. Comparison of oxytocin, Methergin and carboprost in active management of third stage of labour. Int J Med Sci 2013;6:65–8.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

20. Verma D, Thakur R, Mishra S, Verma A, Bansal P. Comparative analysis of prophylactic intramuscular 15 PGF2 α 125 μ g v/s intravascular methylergometrine for prevention of atonic post-partum haemorrhage (PPH) in high risk cases. Int J Biomed Adv Res 2016;7:265–6. doi: 10.7439/ijbar.v7i6.3344

21. Nambiar M, Suresh A, Kurian K. Comparison of methylergometrine and carboprost for prophylaxis of postpartum haemorrhage. Indian J Obstet Gynecol Res 2017;4:50–3.

22. Butwick AJ, Carvalho B, Blumenfeld YJ, El-Sayed YY, Nelson LM, Bateman BT. Second-line uterotonics and the risk of hemorrhage-related morbidity. Am J Obstet Gynecol 2015;212:642.e1–7. doi: 10.1016/j.ajog.2015.01.008

23. Seligman K, Ramachandran B, Hegde P, Riley ET, El-Sayed YY, Nelson LM, et al. Obstetric interventions and maternal morbidity among women who experience severe postpartum hemorrhage during cesarean delivery. Int J Obstet Anesth 2017;31:27–36. doi: 10.1016/j.ijoa.2017.03.009

24. Duffield A, McKenzie C, Carvalho B, Ramachandran B, Yin V, El-Sayed YY, et al. Effect of a high-rate versus a low-rate oxytocin infusion for maintaining uterine contractility during elective cesarean delivery: a prospective randomized clinical trial. Anesth Analg 2017;124:857–62. doi: 10.1213/ANE.0000000000001658

25. George RB, McKeen D, Chaplin AC, McLeod L. Up-down determination of the ED(90) of oxytocin infusions for the prevention of postpartum uterine atony in parturients undergoing cesarean delivery. Can J Anaesth 2010;57:578–82. doi: 10.1007/s12630-010-9297-1

26. Boucher M, Horbay GL, Griffin P, Deschamps Y, Desjardins C, Schulz M, et al. Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. J Perinatol 1998;18:202–7.

27. Butwick AJ, Coleman L, Cohen SE, Riley ET, Carvalho B. Minimum effective bolus dose of oxytocin during elective caesarean delivery. Br J Anaesth 2010;104:338–43. doi: 10.1093/bja/aeq004

28. Farber MK, Schultz R, Lugo L, Liu X, Huang C, Tsen LC. 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. Int J Obstet Anesth 2015;24:217–24. doi: 10.1016/j.ijoa.2015.03.007

Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *Deidentified, anonymous participant data and a data dictionary from this study will be made available to requestors in a data pack to minimize the possibility of reidentification.*

What data in particular will be shared? *In the interests of the public good, ethical transparency, and economic and scientific support of future research, the data pack will be available to all appropriate requestors.*

What other documents will be available? *Additional documents such as the study protocol, statistical analysis plan, and informed consent form may be included as needed.*

When will data be available (start and end dates)? *The data will be shared electronically in a secure fashion and encrypted to protect the privacy of participants. The data will be available on publication of the study and for 10 years thereafter.*

By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? *Data requestors will be required to provide a detailed IRB-approved study protocol, data collection tools to be used, and planned statistical analysis to the data generator. Citation of the data generator will be required if the data are used in a peer-reviewed publication.*

PEER REVIEW HISTORY

Received May 29, 2024. Received in revised form August 9, 2024. Accepted August 15, 2024. Peer reviews and author correspondence are available at http://links.lww.com/AOG/D852.

© 2024 by the American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.