A Randomized, Double-blinded Trial of a "Rule of Threes" Algorithm *versus* Continuous Infusion of Oxytocin during Elective Cesarean Delivery

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ABSTRACT

Background: The administration of uterotonic agents during cesarean delivery is highly variable. The authors hypothesized a "rule of threes" algorithm, featuring oxytocin 3 IU, timed uterine tone evaluations, and a systematic approach to alternative uterotonic agents, would reduce the oxytocin dose required to obtain adequate uterine tone.

Methods: Sixty women undergoing elective cesarean delivery were randomized to receive a low-dose bolus or continuous infusion of oxytocin. To blind participants, the rule group simultaneously received intravenous oxytocin (3 IU/3 ml) and a "wide-open" infusion of 0.9% normal saline (500 ml); the standard care group received intravenous 0.9% normal saline (3 ml) and a "wide-open" infusion of oxytocin (30 IU in 0.9% normal saline/500 ml). Uterine tone was assessed at 3, 6, 9, and 12 min, and if inadequate, additional uterotonic agents were administered. Uterine tone, total dose and timing of uterotonic agent use, maternal hemodynamics, side effects, and blood loss were recorded.

Results: Adequate uterine tone was achieved with lower oxytocin doses in the rule *versus* standard care group (mean, 4.0 *vs.* 8.4 IU; point estimate of the difference, 4.4 ± 1.0 IU; 95% CI, 2.60 to 6.15; $P < 0.0001$). No additional oxytocin or alternative uterotonic agents were needed in either group after 6 min. No differences in the uterine tone, maternal hemodynamics, side effects, or blood loss were observed.

Conclusion: A "rule of threes" algorithm using oxytocin 3 IU results in lower oxytocin doses when compared with continuous-infusion oxytocin in women undergoing elective cesarean delivery. **(Anesthesiology 2015; 123:92-100)**

UTERINE atony can result in severe postpartum hemorrhage, gravid hysterectomy, and maternal mortality.[1] Oxytocin is the most commonly used agent for the prevention and treatment of uterine atony during cesarean delivery[2]; however, rapid administration and increasing doses can result in hemodynamic instability,[3–6] cardiovascular collapse, and death.[7] Moreover, the persistent use of oxytocin results in desensitization and down-regulation of its receptor, resulting in decreased uterine contractile response over time.[8,9] Despite the demonstration of adequate uterine tone after cesarean delivery with oxytocin in low doses (<3 IU),[10,11] the prevailing practice is the continuous infusion of doses greater than 20 to 40 IU.[6,12,13] The recommended dose, timing, and rate of administration of oxytocin, as well as alternative second-line uterotonic agents, from major obstetric texts and professional obstetric societies are vague or nonexistent.[14–16] The administration of oxytocin and additional uterotonic agents has been associated with significant maternal, fetal, and neonatal adverse effects.[17] These side effects, particularly those associated with oxytocin, can be related to the dose and rate of administration.[18,19]

Recently, improvements in perioperative patient outcomes have been demonstrated with the use of algorithms and more effective communication patterns.[20] Attention fixation on particular tasks, such as closing the uterus or responding to uterine bleeding, may lead to inattention to the dose and pattern of uterotonic agent use. The adoption of algorithms with drugs administered on a timed basis (*i.e.*, advanced cardiac life saving) has been observed to result in improved outcomes.[21] Moreover, active communication in the form of inquiry, the process by which information is elicited in the form of question,[22] expedites the cocreation of plans and responses among health team members.[20]

In response to these observations, we originated a clinical "rule of threes" oxytocin algorithm, which incorporates oxytocin and alternative uterotonic agents, for use during

What We Already Know about This Topic

- The dosage of uterotonic agents, primarily oxytocin, at cesarean delivery is highly variable and may frequently exceed that necessary to obtain adequate uterine tone

What This Article Tells Us That Is New

- In 60 women randomized to treatment at cesarean delivery, a single intravenous bolus of 3 IU at delivery was as effective as continuous, wide-open infusion of oxytocin, 30 IU/500 ml despite less total oxytocin delivered
- Groups did not differ in side effects associated with oxytocin

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cesarean delivery.[23] The algorithm was designed to limit the dose-related and rate-related side effects of oxytocin through the incorporation of doses found to produce adequate uterine tone in women with or without previous exposure to oxytocin,[10,11] in a plasma half-life (3 to 12 min) context-sensitive manner[24]; moreover, in cases where oxytocin-induced uterine tone proved inadequate, the algorithm provides for the systematic timed inclusion of alternative uterotonic agents (*i.e.*, methylergonovine, carboprost tromethamine).

The aim of the current study was to determine the dose of oxytocin administered with a "rule" *versus* standard care protocols to obtain adequate uterine tone in women undergoing elective cesarean delivery with spinal anesthesia.

Materials and Methods

After obtaining approval from the Partners' Human Research Committee/Institutional Review Board (Boston, Massachusetts) and registration with ClinicalTrials.gov (NCT01549223), we obtained written informed consent from 60 healthy term patients undergoing elective cesarean delivery to participate in this prospective, randomized, double-blinded, controlled trial (fig. 1). The study was conducted at the Brigham and Women's Hospital (Boston, Massachusetts) with patients enrolled during an 8-month period (May 2011 to January 2012).

Inclusion criteria were parturients with American Society of Anesthesiologists physical status I or II, between 18 and 40 yr of age, with singleton pregnancies, and undergoing an elective cesarean delivery with a Pfannenstiel incision and a spinal anesthetic technique. Exclusion criteria were parturients with the presence of labor, ruptured membranes, maternal or fetal risk factors for uterine atony (*i.e.*, macrosomia, multiple gestations, chorioamnionitis, diabetes mellitus, and uterine fibroids), previous uterine surgery (except for one previous cesarean delivery with a low-transverse uterine incision), maternal risks for hemorrhage (*i.e.*, abnormal placentation, previous abdominal surgeries, history of previous peripartum hemorrhage, coagulation abnormalities, and thrombocytopenia $<100 \times 10^9$), contraindications to spinal anesthesia or any of the uterotonic agents, and maternal or obstetrician refusal.

Patients were randomized to receive oxytocin in accordance with the "rule of threes" algorithm (rule group)[23] or a continuous-infusion protocol (standard care group); N = 30 per group. Randomization occurred in a block size of 30 with the use of a computer-generated random numbers table, with resulting group assignments placed into sealed, opaque envelopes that were opened sequentially by a study investigator on patient enrollment; this investigator also prepared the study drugs but otherwise did not participate in the study. Oxytocin (3 IU/3 ml) for syringe administration was prepared by diluting a single, 1-ml vial of oxytocin 10 IU/ml (JHP Pharmaceuticals, LLC, USA) to 10 ml with 0.9% saline; a 3-ml syringe was then filled with the solution. Oxytocin (30 IU/500 ml) for infusion administration was prepared by administering three 1-ml vials of oxytocin 10 IU/ml to a 500-ml infusion bag of 0.9% saline. Placebo oxytocin syringes (3 ml) and infusion bags (500 ml) contained 0.9% saline only. The alternative uterotonic agents, methylergonovine maleate (0.2 mg/ml; Novartis Pharmaceuticals, USA) and carboprost tromethamine (0.25 mg/ml; Pharmacia & Upjohn, USA), were prepared (1 ml) and marked for administration at 9 and 12 min, respectively. Placebo methylergonovine maleate and carboprost tromethamine syringes (1 ml) contained 0.9% saline and were marked for possible time of administration at less than 9 min and less than 12 min, respectively; these agents were administered only upon request for an alternative uterotonic agent. Thus, all syringes were labeled with the "drug" and possible time of administration (*e.g.*, "oxytocin 0 min," "oxytocin 3 min," and "oxytocin 6 min" [either active agent or placebo]; "methylergonovine <9 min" [placebo]; "methylergonovine 9 min" [active agent]; "carboprost" <12 min" [placebo]; and carboprost 12 min" [active agent]). Oxytocin and placebo infusion bags were labeled "oxytocin study drug." Individual misoprostol 200 μg tablets (G.D. Searle, USA) were available; no placebo tablets were used. The patient, anesthesiologist, obstetrician, and a second study investigator collecting data were all blinded to group assignment; all groups were aware that 3-min timed inquiries would occur and that oxytocin and alternative uterotonic agents would be available at the timed intervals. No interim analyses were planned.

A standardized protocol for anesthesia was followed for all patients. In brief, an 18-gauge intravenous catheter was established in the lower forearm and connected to a liter of lactated Ringer's solution; baseline standard monitors were applied, with blood pressure measured at 3-min intervals, which was changed to 1-min intervals at the time of delivery until the uterus was closed. Spinal anesthesia was administered through a 25-gauge Whitacre needle using 1.6 ml hyperbaric 0.75% bupivacaine (12 mg) with 0.2 ml fentanyl (10 μg) and 0.2 ml preservative-free morphine (200 μg). The patient was placed in a supine position with left lateral tilt created by a uniform wedge placed under the right hip. A T4 sensory level was achieved before surgery commenced. Administration of vasopressors was guided by responding to a precalculated 20% decrease in mean arterial pressure or a systolic blood pressure less than 100 mmHg. Intravenous phenylephrine 40 μg was the vasopressor of first choice, with ephedrine 5 mg administered when hypotension was accompanied with bradycardia.

Immediately after delivery, the attending obstetrician performed manual uterine massage. The study interventions (fig. 2) are based on our "rule of threes" algorithm[23] that suggests the use of oxytocin 3 IU upon delivery, timed inquiry of uterine tone every 3 min, the systematic addition of three alternative uterotonic agents if necessary, and the use of oxytocin 3 IU/h maintenance dose upon achievement of adequate uterine tone. Upon fetal delivery (time 0 min),

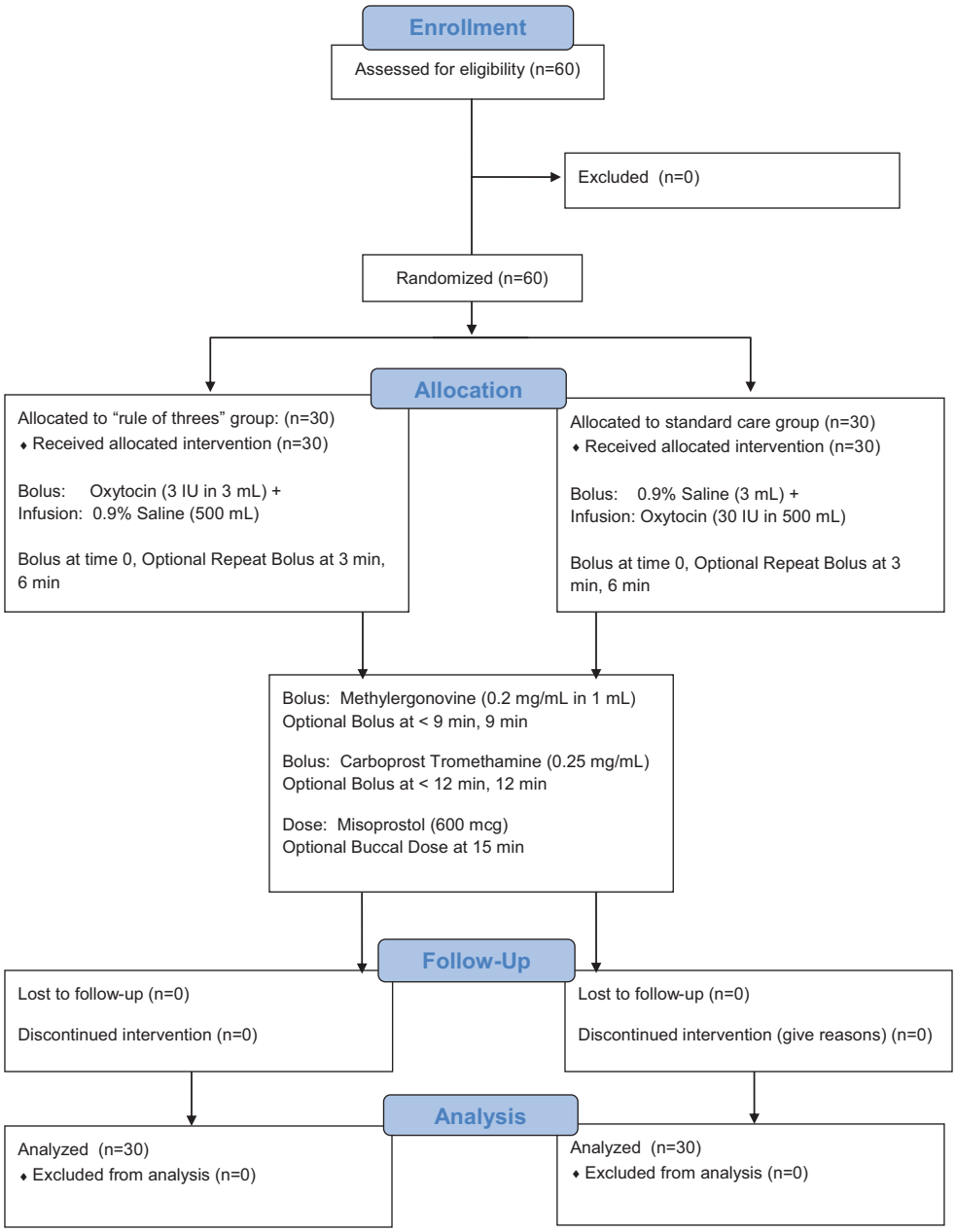

Fig. 1. CONSORT flow diagram (www.consort-statement.org) for patient participation.

all subjects received an intravenous "oxytocin" infusion at a wide-open flow rate, and the contents of an "oxytocin" syringe administered over 15 s. The rule group received an infusion of 0.9% saline 500 ml and a syringe with oxytocin 3 IU in 0.9% saline to a total of 3 ml. The standard care group received an infusion of oxytocin 30 IU in 0.9% saline 500 ml and a syringe with 0.9% saline 3 ml. Using manual palpation, the attending obstetrician provided subjective uterine tone assessment (adequate/inadequate) and verbal assessment score (VAS; 0 to 10 linear analog scale, with 0 complete atony and 10 excellent uterine tone) every 3 min for total of 12 min. For both groups, at 3 and 6 min, an "inadequate" uterine tone assessment resulted in continued "oxytocin" infusion and an additional "oxytocin" syringe. At 9 and 12 min, an "inadequate" uterine tone assessment resulted in the administration of intramuscular methylergonovine 0.2 mg and intramuscular carboprost tromethamine 0.25 mg, respectively. An obstetrician's request for methylergonovine and carboprost tromethamine before 9 and 12 min, respectively, resulted in administration of intramuscular 0.9% saline 1 ml. At 15 min, an "inadequate" uterine tone assessment resulted in the administration of misoprostol 600 μg buccally, with patient instructions to allow the tablets to dissolve. An "adequate" uterine tone rating for either group at any time point resulted in the continuous infusion being halted and converted to a maintenance infusion by pump

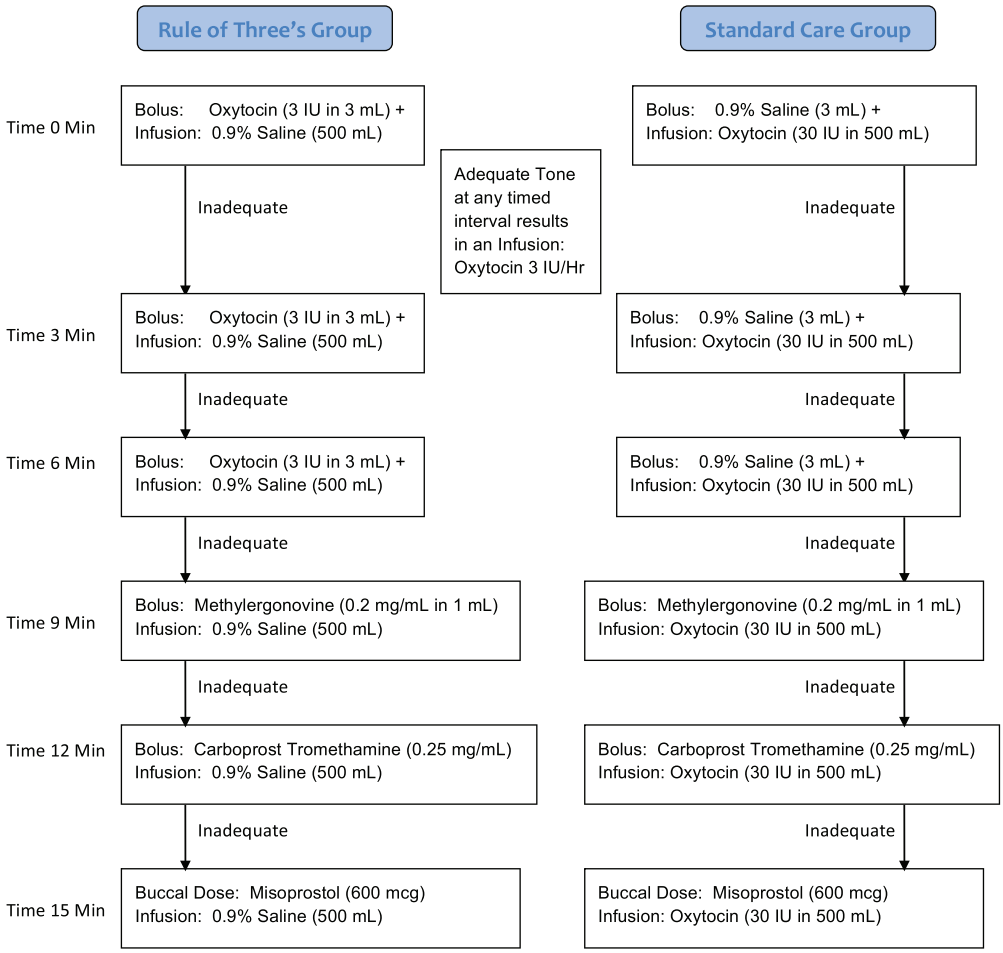

Fig. 2. Study flow diagram for rule of threes and standard care groups.

(Alaris® System; CareFusion Corp., USA) of oxytocin (30 IU in 0.9% 500 ml saline) at 3 IU/h for total of 6 h.

We collected demographic data (*i.e.*, age, race, body mass index [calculated by using weight at delivery]), weeks of gestation, medical, surgical, and obstetric history, and laboratory data (preoperative and postoperative hematocrit if drawn for clinical purposes). Blood pressure and heart rate were recorded preoperatively at the time of delivery and then at the noted intervals until the end of the case. Electrocardiography and pulse oximetry were monitored continuously. At delivery, 3, 6, 9, and 12 min postpartum, the patients were asked if they had nausea, flushing, headache, chest pain, or other complaints, and the electrocardiography was assessed for rhythm, ST-T wave changes.

All patients received intravenous ondansetron 4 mg after the delivery for nausea prophylaxis, and additional antiemetic agents were administered only if indicated. Postpartum, the patients were followed hourly for 6 h for any signs of uterine atony or bleeding, and if diagnosed, the choice of additional uterotonic agents and/or additional laboratory tests was at the discretion of the obstetrician. After discharge, the medical record of each patient was reviewed and any medications and adverse events were recorded.

The primary study outcome was the total amount of oxytocin required to establish adequate uterine tone. Secondary outcomes included the timing of oxytocin doses and uterine tone adequacy, VAS of uterine tone, use of additional uterotonic agents, maternal blood pressure, heart rate, side effects (*i.e.*, flushing, nausea, headache, chest pain, and electrocardiography changes), vasopressor use, blood loss (as measured by estimating blood collected in suction canisters and by calculating the weight of blood on surgical lap sponges), and change in hematocrit (*i.e.*, difference in preoperative and postoperative values). Moreover, we wanted to examine whether the practice of timed inquiry of uterine tone, inserted into both the rule and standard care infusion protocols, would be useful in limiting the administration of additional uterotonic agents.

Statistical Analysis

The statistical analysis was conducted with the use of STATA version 12.1 (StataCorp, USA). We calculated 0.80 power to detect differences in the uterine tone between both groups with 30 patients per group by using $P = 0.05$ and mean uterine tone of 8.0 at 3 min in an oxytocin 3 IU group *versus* mean uterine tone of 7.5 in an oxytocin 5 IU group.[25] The

differences between both groups were analyzed by using *t* test for continuous variables and Fisher exact test for binary variables; the primary outcome was analyzed by using *t* test. The temporal relation between the two groups was analyzed by using mixed-effects linear model for the systolic and diastolic blood pressure, heart rate, and uterine tone. For all models, the fixed effects were the respective variable, time and interaction between the aforementioned, and the random effects were for patient. All patients enrolled in the clinical trial were analyzed on an intent-to-treat basis. Statistical significance was defined as *P* value less than 0.05.

Results

A total of 60 patients were enrolled and randomized; all completed the study. There were no significant differences between the rule and standard care groups in demographic characteristics, preoperative hemodynamic variables, or initial hematocrit (table 1). In the rule and standard care groups, adequate uterine tone was achieved within 3 min (90 *vs.* 87%, $P = 1.0$), 6 min (100 *vs.* 90%, $P = 0.2$), or 9 min (100% both groups), with no patients exhibiting inadequate uterine tone after 9 min. With the exception of the oxytocin maintenance infusion, no uterotonic agents (*i.e.*, additional oxytocin bolus or infusion doses, methylergonovine, carboprost tromethamine, or misoprostol) were requested or used after this time, including in the postpartum period. There were no differences in the VASs for uterine tone at any time (table 2 and fig. 3). The uterus was closed and returned into the abdomen in one patient at 9 min and seven patients at 12 min in the rule group and four patients in the standard of care group at 12 min, after which VASs were no longer collected. Overall, the rule group, when compared with the standard care group, received less oxytocin (mean, 4.0 *vs.* 8.4 IU; point estimate of the difference, 4.4 ± 1.0 IU; 95% CI, 2.60 to 6.15; $P < 0.0001$) to produce adequate uterine tone.

Table 1. Patient Characteristics

	Rule Group	Standard Care Group	*P* Value
Age (yr)	32.7 ± 5.0	32.8 ± 4.0	0.89
BMI, kg/m^2	29.5 ± 3.9	28.7 ± 4.0	0.44
Preoperative Hct	35.8 ± 3.4	35.8 ± 2.8	0.99
Race			
African American	4 (13.3)	6 (20.0)	0.73
Asian	4 (13.3)	4 (13.3)	1.00
Caucasian	21 (70.0)	17 (56.7)	0.30
Hispanic	1 (3.3)	3 (10.0)	0.61
Hemodynamic variables			
Baseline SBP, mmHg	120 ± 13	122 ± 13	0.75
Baseline DBP, mmHg	72 ± 10	74 ± 11	0.58
Baseline HR, beats/min	86 ± 14	83 ± 11	0.50
Intravenous fluids (ml)	1,525 ± 205	1,620 ± 379	0.24
Neonatal weight (g)	3,582 ± 423	3,532 ± 446	0.70

Values are mean (SD) ± SD or N (%).

BMI = body mass index; DBP = diastolic blood pressure; Hct = hematocrit; HR = heart rate; SBP = systolic blood pressure.

There were no differences in systolic and diastolic blood pressures or heart rate between the groups as determined by mixed-effects linear model ($P > 0.5$). A linear decrease in systolic and diastolic blood pressures was observed in both groups with no differences between groups (figs. 4 and 5). Eight and six patients in the rule and standard care groups received intravenous phenylephrine 40 μg, respectively; no differences in vasopressor agent use were observed ($P = 0.76$). No differences in heart rate were observed between the two groups.

There were no significant differences in the incidence of side effects such as flushing, nausea, and electrocardiography changes (table 2) although one patient from the standard care group developed a new-onset atrial fibrillation after receiving oxytocin 6.3 IU over 6 min. She remained hemodynamically stable, underwent cardiology consultation, and had an echocardiography investigation in the recovery room that revealed no cardiac abnormalities. The patient was administered intravenous β-adrenergic blocking agents, with conversion to sinus rhythm within 24 h and no further consequences.

There were no differences in the amount of blood loss or in the preoperative *versus* postoperative hematocrit (table 2) although only 50% of our patients in both groups had both of the hematocrit values drawn.

Discussion

The key findings of this study of healthy parturients at low risk of postpartum hemorrhage undergoing elective cesarean delivery with spinal anesthesia were (1) a "rule of threes" uterotonic agent algorithm[23] using low-dose oxytocin bolus (3 IU) achieves adequate uterine tone after elective cesarean delivery at lower oxytocin doses when compared with a continuous-infusion oxytocin protocol; (2) a "timed inquiry" method of assessing adequate uterine tone can be used to limit additional doses of oxytocin in both groups; and (3) a systematic approach to the administration of additional uterotonic agents may diminish their use.

Our finding that a continuous infusion of oxytocin more than doubled the bolus dose necessary to provide adequate uterine tone during cesarean delivery[10,11,18] provides several insights relevant to clinical practice. First, the provision of a single established dose more effectively limits the dose of oxytocin when compared with the common clinical practice of a continuous infusion until adequate uterine tone is established or when a greater oxytocin dose is achieved; similar to many other institutions,[6,11–13] our conventional practice was to administer a minimum dose of oxytocin 30 IU before leaving the operating room. Second, despite the greater amount of oxytocin administered in the continuous-infusion group when compared with the rule group, there were no differences in systolic or diastolic blood pressure, heart rate, or vasopressor use. Although both groups experienced decreases in blood pressure and increases in heart rate with oxytocin administration, the similar hemodynamic variables likely emphasize an interaction between

Table 2. Primary and Secondary Outcomes

	Rule Group	Standard Care Group	*P* Value
Oxytocin dose (IU)	4.0 ± 0.9	8.4 ± 4.8	<0.0001
Flushing	3 (10)	7 (23)	0.30
Nausea/vomiting	7 (23)	6 (20)	1.00
EKG changes	2 (7)	3 (10)	1.00
All side effects	11 (37)	14 (47)	0.77
Blood loss (ml)	711 ± 124	728 ± 141	0.62
Delta hematocrit	5.0 ± 2.4	4.5 ± 2.4	0.57
Uterine tone			
Adequate at 3 min	27 (90)	26 (87)	1.00
Adequate at 6 min	30 (100)	27 (90)	0.20
Adequate at 9 min	30 (100)	30 (100)	1.00
Adequate at 12 min	30 (100)	30 (100)	1.00

	Rule Group	Standard Care Group	Difference (95% CI)	*P* Value
VAS at 3 min	7.5	7.7	0.2 ± 0.35 (–0.5 to 0.9)	0.6
VAS at 6 min	8.2	8.1	–0.1 ± 0.30 (–0.7 to 0.5)	0.8
VAS at 9 min	8.3 (n = 29)	8.1	–0.1 ± 0.29 (–0.7 to 0.4)	0.6
VAS at 12 min	8.5 (n = 23)	8.3 (n = 26)	–0.2 ± 0.28 (–0.7 to 0.4)	0.5

Values are mean ± SD or N (%).
EKG = electrocardiogram; VAS = verbal assessment score.

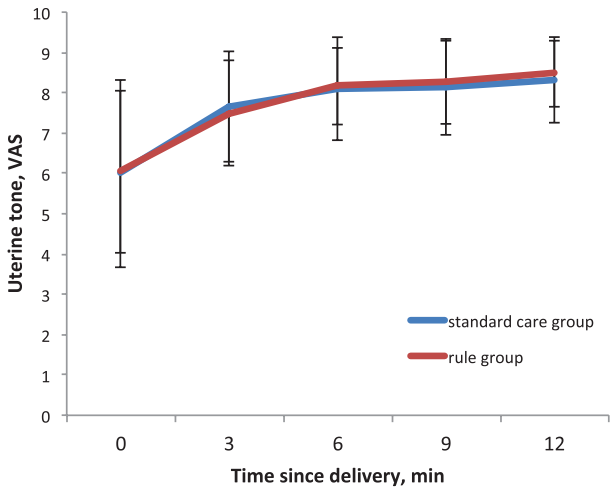

Fig. 3. Verbal assessment score (VAS) of uterine tone for rule of threes and standard care groups.

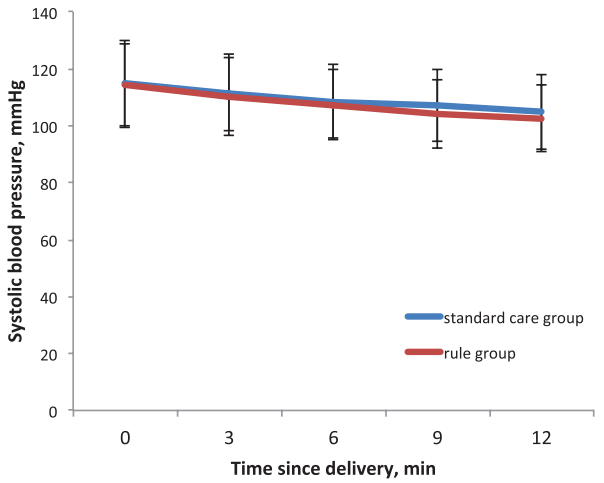

Fig. 4. Systolic blood pressure for rule of threes and standard care groups.

oxytocin dose and rate of administration. Although the British National Formulary advised a reduction in the bolus dose of intravenous oxytocin from 10 to 5 IU due to maternal deaths after cardiovascular instability with the higher dose,[26] smaller doses given rapidly can produce significant effects. Langesaeter *et al.*[19] indicated that intravenous oxytocin 5 IU "injected rapidly" resulted in hypotension (*i.e.*, >20% reduction in systolic blood pressure, as measured by an arterial line) in all 60 cases requiring a single dose and all 20 cases requiring a second dose. Thomas *et al.*[27] indicated that the intravenous administration of oxytocin 5 IU as a rapid *versus* slow bolus in healthy term parturients undergoing elective cesarean delivery produced more cardiovascular instability; similar findings have been observed with an intravenous bolus or infusion of oxytocin 3 IU.[28] These findings suggest that even small bolus doses should be administered slowly (15 to 30 s) to minimize the hemodynamic effects.[17] For the practicing clinician who seeks to avoid the preparation and slow intravenous bolus administration of an oxytocin syringe, continuous-infusion methods can be used with a lower threshold oxytocin dose (3 IU; equivalent to 50 ml of oxytocin 30 IU in 0.9% normal saline 500 ml) after which the maintenance dose is invoked. Regardless, the total oxytocin dose should be tempered in response to timed inquiry regarding the adequacy of uterine tone.

Therein lies a novel contribution of this study, which is the use of "timed inquiry" as a mechanism to limit the dose of oxytocin and potential use of alternative uterotonic agents. Inquiry, an attempt to obtain information from another in the form of a question,[22] is a vital element of effective

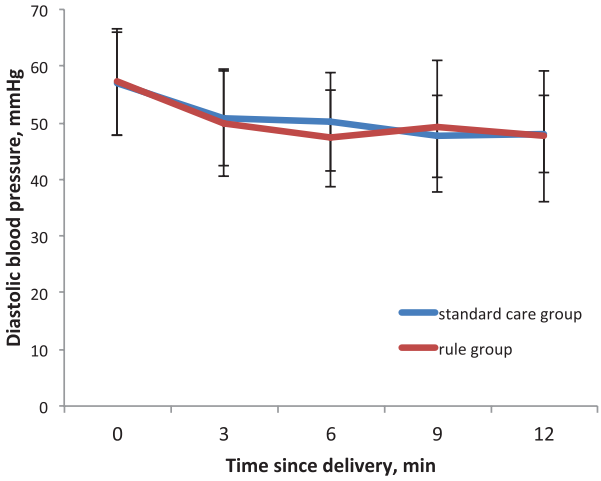

Fig. 5. Diastolic blood pressure for rule of threes and standard care groups.

communications strategies and the development and conduct of a jointly managed clinical plan.[20] Poor communication has been cited as a major contributing factor in a third of cases where delayed cesarean delivery resulted in newborn death or brain damage claim.[29] Minehart *et al.*,[20] with the use of simulated cesarean delivery cases, indicated that anesthesiologists used advocacy more than inquiry and inquired for general information and the obstetric plans in only 30 and 11% of cases, respectively. Inquiry is particularly important in the perioperative environment involving time pressure and high-stakes patient care,[20] with timed inquiry a key element in crisis situations, such as advanced life support.[30] In our study, the use of timed inquiry in both groups likely served an important communication and service role by indicating the importance of adequate uterine tone to the team and taking responsibility for an assessment at regular intervals; this may have been partially responsible for the majority of patients in both groups requiring no further oxytocin after the first inquiry and no patients requiring any uterotonic agents after 9 min, except for the oxytocin 3 IU/h maintenance infusion with establishment of adequate uterine tone. As importantly, the timed inquiry every 3 min noted in our algorithm[23] allows oxytocin to exert its uterotonic effects, and if present, potentially limit the administration and side effects associated with additional and alternative uterotonic agents. Standardized drug dosing regimens have been observed to decrease the inappropriate alterations and errors associated with drug dose, frequency, and side effects.[31]

Our study found no differences in blood loss or change in hematocrit, which was not surprising, given the efficacy of low oxytocin doses in providing adequate uterine tone and the unreliability of clinical estimations of blood loss.[32] Similarly, Thomas *et al.*[27] observed no differences in blood loss with oxytocin 5 IU given as a bolus *versus* an infusion, which is in agreement with other oxytocin dosing protocol comparisons.[25,33–35] Electrocardiography alterations were not different between groups but were observed in a few patients; one patient in the continuous-infusion group experienced new-onset atrial fibrillation. Oxytocin has been associated with a wide variety of electrocardiography changes that may be related to altered myocardial supply–demand ratios[36] or coronary vasospasm.[37] A randomized trial of oxytocin 10 *versus* 5 IU in healthy patients undergoing elective cesarean delivery showed a 13.9% absolute risk reduction for ST depression with the lower dose.[38] Therefore, the use of smaller doses of oxytocin may prove particularly beneficial in patients with preexisting cardiac abnormalities or those unable to tolerate tachycardia or tachyarrhythmias. Finally, no differences were observed in facial or chest flushing, nausea, or headache; by contrast Sartain *et al.*[35] observed more nausea and antiemetic use with oxytocin 5 IU (32.5%) *versus* 2 IU (5%; $P = 0.003$) administered over 5 to 10 s. The lower incidence of these side effects observed in our study and others[18] is likely related to the dose and rate of oxytocin delivery.

We recognize some inherent limitations in our study. First, we used an intravenous bolus dose of oxytocin 3 IU in our healthy patient population undergoing *elective* cesarean delivery, whereas Carvalho *et al.*[10] indicated in a similar population that the ED_{90} of oxytocin was 0.35 IU (95% CI, 0.18 to 0.52 IU). However, Butwick *et al.*[18] in a randomized controlled trial of oxytocin doses ranging from 0 to 5 IU indicated that doses up to 3 IU were required to produce a high prevalence of adequate uterine tone, and even in the 5 IU group, additional rescue doses of oxytocin were sometimes needed. As importantly, we desired a single uterotonic agent algorithm adequate for both elective and labor arrest cesarean delivery populations to limit dosing errors and confusion in our teaching institution; studies with our "rule of threes" algorithm are currently being conducted in a greater diversity of patient populations and settings. Second, our use of a "wide-open" continuous infusion may have resulted in varying amounts of oxytocin being infused. We accepted this possibility in the design of our study because we wanted to replicate actual clinical practice; however, this variation was partially mitigated through the use of 18-gauge intravenous catheters inserted into a lower arm (not antecubital) location in all patients. Third, in all studies evaluating uterine tone including ours, subjectivity and variability in uterine palpation may exist. However, our results on the timing to adequate uterine tone were similar in both groups, and all participants were blinded to the group allocation and thus a uniform bias is unlikely. We are not aware of another readily available, reliable, and objective method of clinical uterine tone measurement. Finally, we acknowledge that our study population was composed of healthy women undergoing elective cesarean delivery with spinal anesthesia; as demonstrated by others, the oxytocin requirements for women undergoing cesarean delivery for labor arrest who have been exposed to oxytocin are typically higher.[11] Moreover, in women at high risk for uterine atony or postpartum hemorrhage, it is anticipated that additional alternative uterotonic agents and interventions may be required.

In summary, we conclude the use of intravenous oxytocin 3 IU administered as a bolus dose over 15 s, as present in our "rule of threes" uterotonic agent algorithm, results in a lower total dose of oxytocin than a continuous-infusion oxytocin protocol in women undergoing elective cesarean delivery. Moreover, we suggest that the use of "timed inquiry" to assess adequate uterine tone can serve as a method to limit additional doses of uterotonic agents.

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Competing Interests

The authors declare no competing interests.

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Laughing Gas for the "Pulpit Clown"?

Nicknamed the "pulpit clown" by his detractors, Reverend Doctor Thomas De Witt Talmage (1832–1902) was a clergyman whose fiery sermons and theatrical gestures "entertained" parishioners and visitors by the thousands on Sundays in Brooklyn, New York, from 1869 to 1894. In this illustration from the irreverent American magazine *Puck*, the "pulpit clown" is seen preaching to congregation members dressed more as if they were attending the opera. In the *lower right*, a mischievous cherub is depicted releasing a bag of laughing gas from behind the curtain. (Copyright © the American Society of Anesthesiologists, Inc.)

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