Oxytocin Requirements at Elective Cesarean Delivery: A Dose-Finding Study

José C. A. Carvalho, MD, PhD, Mrinalini Balki, MD, John Kingdom, MD, and Rory Windrim, MD

OBJECTIVE: Oxytocin is frequently used by intravenous bolus and infusion to minimize blood loss and prevent postpartum hemorrhage at cesarean delivery. Current dosing regimens are arbitrary whereas large doses may pose a serious risk to the mother. The purpose of this study was to estimate the minimum effective intravenous bolus dose of oxytocin (ED90) required for adequate uterine contraction at elective cesarean in nonlaboring women.

METHODS: A randomized, single-blinded study was undertaken in 40 healthy term pregnant women presenting for elective cesarean under spinal anesthesia. Oxytocin was administered by bolus according to a biased coin up-and-down sequential allocation scheme with increments or decrements of 0.5 IU. Uterine contraction was assessed by the obstetrician, who was blinded to the dose of oxytocin, as either satisfactory or unsatisfactory. After achieving sustained uterine contraction, an infusion of 40 mU/min of oxytocin was started. Oxytocin-induced adverse effects and intraoperative complications were recorded and blood loss was estimated. Data were interpreted by parametric analysis based on logistic regression model and nonparametric analyses at 95% confidence intervals (CIs).

RESULTS: The ED90 of oxytocin as determined by logistic regression model fitted to the data was estimated to be 0.35 IU (95% CI 0.18–0.52 IU), with nonparametric estimates of 97.1% (95% CI 84.9–99.8%) response rate at 0.5 IU, and 100% (95% CI 92.2–100%) at 1.0 IU. The estimated blood loss was 693 ± 487 mL (mean ± standard deviation).

CONCLUSION: The bolus dose of oxytocin used at elective cesarean deliveries in nonlaboring women can be significantly reduced while maintaining effective uterine contraction. Alteration in practice will likely reduce the potential adverse effects of this drug when given in large bolus doses, but may require modification of the techniques to remove the placenta. (Obstet Gynecol 2004;104:1005–10. © 2004 by The American College of Obstetricians and Gynecologists.)

In many institutions, oxytocin is routinely administered by intravenous bolus and infusion at cesarean delivery after delivery of the fetus. Oxytocin promotes uterine contraction, thereby reducing blood loss from the placentatic site. However, when given in large doses and as a rapid bolus, oxytocin is associated with various adverse effects, including hypotension, nausea, vomiting, chest pain, headache, flushing, and myocardial ischemia. For these reasons, the manufacturer’s instructions do not recommend bolus administration.

A variety of regimens for administration of oxytocin have been described previously but appear to be empirical. Furthermore, the minimum effective dose of oxytocin at cesarean delivery has not yet been established. The purpose of our study was therefore to estimate the minimum effective dose (ED90) of oxytocin required to produce adequate uterine contraction at elective cesarean delivery in nonlaboring women.

MATERIALS AND METHODS
After obtaining approval from the Research Ethics Board at Mount Sinai Hospital, a randomized, single-blinded study was performed with 40 healthy term pregnant women scheduled for elective cesarean delivery. Patients were recruited between October 1, 2003, and January 21, 2004, and 20 surgeons were involved in the study. All patients with conditions that predispose to uterine atony and postpartum hemorrhage such as placenta previa, multiple gestation, preeclampsia, macrosomia, hydramnios, uterine fibroids, history of uterine atony and postpartum bleeding, or bleeding diathesis were excluded from the study. A written informed consent was obtained from the patients before enrollment in the study. All patients received 30 mL of 0.3 mol/L sodium citrate orally, 30 minutes before the institution of spinal anesthesia. Baseline blood pressure (BP) and heart rate were calculated as the mean of 3 readings, 2 minutes apart, recorded in the admitting unit using an automated noninvasive BP device. An 18G peripheral intravenous line was inserted and 10 mL/kg of lactated Ringer’s solution was given as preload.

After skin disinfection and local infiltration, a subarachnoid puncture was performed in the sitting position at L2–3 or L3–4 interspace using a 27G Whitacre needle. Anesthetic blockade of up to a T4 dermatomal level was
achieved using 12–15 mg 0.75% hyperbaric bupivacaine and 100 μg preservative-free morphine, injected over 60 seconds. The patient then was immediately positioned supine, with left uterine displacement using a wedge under the right buttock. All patients received supplemental oxygen via nasal prongs at the rate of 4 L/min until the delivery of the fetus.

Standard monitoring included electrocardiography, noninvasive BP, heart rate, and oxygen saturation via pulse oximeter. Systolic BP and heart rate were recorded every minute until the end of the operation. Systolic BP was maintained within 10% of the baseline values with aliquots of 0.1 mg phenylephrine. Patients not responding to phenylephrine were treated with increments of 5 mg ephedrine. Hypotension was defined as a decrease in systolic BP greater than 20% of the baseline value, despite the use of a prophylactic vasopressor.

Oxytocin was administered as an intravenous bolus, immediately upon delivery of the fetal anterior shoulder. The dose of oxytocin for each patient was determined by the response of the previous patient to a larger or smaller dose, according to a biased coin up-and-down sequential allocation scheme designed to cluster doses close to ED_{90}. If a patient did not respond adequately to the initial bolus of oxytocin, that initial dose was increased by 0.5 IU for the next patient. If the patient responded to the initial bolus, the dose for the next patient was decreased by 0.5 IU with a probability of 1/9; otherwise it remained unchanged. The “biased coin” allocation after each successful response was implemented using a computer generated list of random responses: “Maintain Previous Dose” (8/9) or “Reduce Dose by 0.5 IU” (1/9), prepared by the biostatistician in the unit. One exception was the first patient in the study, for whom the starting dose of oxytocin was arbitrarily chosen as 0.5 IU. Oxytocin was administered from a syringe containing 0.5 IU/mL, 1 mL over 5 seconds.

The obstetrician was asked to allow assisted spontaneous delivery of the placenta, without uterine massage, and to keep the uterus inside the abdominal cavity until sustained uterine contraction was achieved. Once delivery of the placenta occurred, the obstetrician commenced closing the uterine incision. The obstetrician, blinded to the oxytocin dose, assessed uterine tone every minute by palpation and rated the degree of uterine contraction as satisfactory or unsatisfactory. If uterine tone remained unsatisfactory at 3 minutes, an additional bolus of 0.5 IU was administered upon the obstetrician’s request. After achieving sustained uterine contraction, an infusion of 40 mU/min oxytocin was started. An antibiotic, 1 g cefazolin diluted in 20 mL normal saline, was administered over a 5-minute period. Oxytocin infusion was continued at the same rate until discharge from the recovery room. Hemoglobin and hematocrit levels were recorded before surgery and at 48 hours after surgery to calculate intraoperative blood loss.

For the purpose of this study, the minimum effective dose was defined to be that at which adequate response would occur in 90% of patients (ie, ED_{90}). Parametric analysis was based on a logistic model and estimated using the LIFEREG procedure in SAS 8.2 (SAS Institute, Cary, NC). Patients who did not respond to the initial oxytocin bolus were treated as being interval-censored between the first and second dose. The goodness-of-fit of the logistic model was assessed using the likelihood ratio \( \chi^2 \) of that model compared with the saturated model (estimated using a generalized gamma model because there were only 3 dose levels).

Evidence of an association between the initial oxytocin dose and response time was assessed using both the Jonckheere-Terpstra test and a test for trend using logrank scores. The later test treated the response times as censored for the patients who did not respond to the initial bolus. Exact 2-sided \( P \) values were used for both tests. The 95% confidence intervals (CIs) on which the nonparametric analysis of the cumulative response was based were calculated using the exact Blyth-Still-Casella method. The Jonckheere-Terpstra test was also used to test for an association between estimated blood loss and initial oxytocin dose. All nonparametric analyses used StatXact 5 (Cytel Software, Cambridge, MA).

Blood loss was estimated by the difference in hematocrit values assessed before and at 48 hours after cesarean delivery, according to the following formula: EBV (preoperative hematocrit – postoperative hematocrit)/reoperative hematocrit, where EBV indicates estimated blood volume (in milliliters), measured as the patient’s weight in kilograms \( \times 85 \) (Shook PR, Schultz JR, Reynolds JD, Spahn TE, DeBaldi P. Estimating blood loss for cesarean section: how accurate are we? Anesthesiology 2003;98 suppl 1:SOAP A2). Any adverse effect before and after delivery such as hypotension, arrhythmia, nausea, vomiting, chest pain, shortness of breath, headache, and flushing was recorded.

The primary outcome was the uterine response to the initial intravenous bolus of oxytocin, rated by the obstetrician as satisfactory or unsatisfactory. Secondary outcomes were the calculated blood loss and the oxytocin-related adverse effects.

Based on our clinical experience, we expected that 50% of patients would respond to an initial oxytocin bolus of 0.5 IU, and 90% to 1.0 IU. Assuming that the actual response was described by a 2-parameter logistic curve with these properties, a simulation of the proposed sequential allocation scheme determined that 80% of the time, the minimum effective dose (ED_{90}) could be esti-
mated with a standard error of less than 0.21 IU, if a sample of 30 patients was used. With 40 patients, the standard error of ED90 would be less than 0.18 IU, 80% of the time. The simulation used 10,000 replications.

RESULTS

Forty term pregnant women (age 35.2 ± 4.1 years; weight 79.3 ± 17.1 kg; height 162.8 ± 9.1 cm; mean ± standard deviation) were studied. Three patients received no initial oxytocin bolus, 31 patients received 0.5 IU, and 6 patients received 1 IU of initial bolus of oxytocin (Table 1). Based on the logistic regression model fitted to the data, it was estimated that the dose at which 90% of the women would respond (ED90) was 0.35 IU (standard error 0.09 IU). The 95% CI for ED90 is 0.18–0.52 IU. Figure 1 presents the fitted response curve with the corresponding 95% CI. The likelihood ratio test comparing the logistic model (2 degrees of freedom) with the saturated model (3 degrees of freedom) produced a $\chi^2$ statistic of 0.035 (1 degree of freedom) with a $P$ value of .85. Therefore, there was no evidence of lack-of-fit in the logistic model.

There was strong evidence of a trend in decreasing response time with initial increasing dose ($P = .005$ based on the Jonckheere-Terpstra test) (Table 1). If the actual response time is treated as censored for the 3 patients who did not respond to the initial dose (because their response time would presumably have been longer, had the additional bolus not been given), the evidence in favor of a trend is even stronger ($P = .001$). However, this result is mainly due to the slow response at the zero dose, and there is no evidence that the 0.5 IU and 1.0 IU doses differ from each other with respect to response time ($P = .19$). Most patients (33 out of 37) developed adequate uterine contraction within 3 minutes at 0.5 IU and 1 IU of initial oxytocin dose, whereas patients who received no oxytocin either required more than 3 minutes or did not respond.

The proportion of patients responding at each dose level (or a lower dose) is a nonparametric alternative to the logistic model, and is plotted in Figure 1. Table 2 gives the empirical estimate at each dose, with 95% CIs. This nonparametric approach is basically in agreement with the logistic model, with ED90 expected to be less than 0.5 IU, although the more conservative conclusion, based on the lower range of the 95% CI, is that it may lie

<table>
<thead>
<tr>
<th>Minutes for response</th>
<th>Initial oxytocin dose</th>
<th>0.0 IU</th>
<th>0.5 IU</th>
<th>1.0 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>5</td>
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<td>7</td>
<td>0</td>
<td>1*</td>
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</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>31</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates the 3 patients who did not respond to the initial dose.
between 0.5 IU and 1.0 IU. It is unlikely that the ED$_{90}$ is greater than 1.0 IU, because the probability of the response rate at 1.0 IU being less than 90% is only 0.015. The mean estimated blood loss was 693 ± 487 mL, as calculated from the preoperative and postoperative hematocrit values. There was some evidence that estimated blood loss increased with initial oxytocin dose. Estimated blood loss varied from 175 mL at the initial dose level of 0.0 IU to 692 mL at 0.5 IU and 1,006 at 1.0 IU ($P = 0.04$).

The adverse effects in both the predelivery and post-delivery periods measured during the study are shown in Table 3. Hypotension occurred in 37.5% and 30% of patients before and after delivery, respectively. The dose of phenylephrine required was 0.43 ± 0.27 mg before delivery and 0.37 ± 0.38 mg after delivery. The median maximum height of the spinal block, as assessed by pinprick, was T-4.

**DISCUSSION**

Practice varies widely in the administration of oxytocin at cesarean delivery. The British National Formulary presently recommends that oxytocin should be administered in a 5-IU dose by slow intravenous injection after delivery during cesarean.³ In the United States, an infusion of 10 IU at a rate of 0.02–0.04 IU/min is recommended for postpartum hemorrhage.⁴,⁵ Despite these statements, there has been no evidence to support the effectiveness of a particular dose. In the clinical trials referred to by the authors of Why Mothers Die 1997–1999, there is no trial cited involving differing doses of oxytocin.⁶ Our trial is novel in that it assessed the minimum effective dose of oxytocin to be used at cesarean delivery in nonlaboring women.

The most important finding of our study is that, in a healthy woman undergoing elective cesarean delivery with regional anesthesia, a dose of oxytocin as small as 0.35 IU is effective in producing adequate uterine contraction.

The physiologic effects of oxytocin are most likely limited by the density of oxytocin receptors in the uterine muscle, rather than by the steady-state plasma concentration of oxytocin.¹¹ Because of the effects of estrogen, the uterine oxytocin receptor population density increases progressively during pregnancy to reach a peak at term.¹² Therefore, the uterus becomes very sensitive to the effects of oxytocin while preparing for parturition. This could explain the uterine response to low doses of oxytocin that was observed in our study.

The response to oxytocin at cesarean delivery after failure to progress in oxytocin-augmented labor, or at cesarean delivery after failed induction, may be attenuated in comparison with the findings in this study. In such circumstances, we would predict that higher doses of oxytocin may be required and that alternate-pathway uterotonic medications, such as ergot derivatives, misoprostol, or carborprost, would be more likely to determine adequate uterine tone. This issue would be clarified further by molecular characterization of myometrial oxytocin receptor density in relation to indication for cesarean delivery, blinded to the clinical response of the patient to intravenous oxytocin.

Although most regimens of oxytocin have been shown to provide satisfactory results, large doses, including serial boluses, are associated with adverse effects such as hypotension, nausea, vomiting, dysrhythmias, ST-T segment changes, pulmonary edema, and severe water intoxication with convulsions.¹,² In our study, the

<table>
<thead>
<tr>
<th>Oxytocin dose (IU)</th>
<th>Cumulative number of responses</th>
<th>Cumulative number of trials</th>
<th>Estimated percentile (%)</th>
<th>95% CI (%)</th>
<th>$P^*$</th>
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<td>0.0</td>
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<td>33.3</td>
<td>1.7–86.5</td>
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<td>34</td>
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<td>84.9–99.8</td>
<td>0.133</td>
</tr>
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<td>1.0</td>
<td>40</td>
<td>40</td>
<td>100.0</td>
<td>92.2–100</td>
<td>0.015</td>
</tr>
</tbody>
</table>

CI, confidence interval.

$^*$ $P$ value for response $< 90\%$ (that is, small $P$ values support response rates of $> 90\%$).

| Table 2. Empirical Response Curve at Each Dose
<table>
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<tr>
<td>Oxytocin dose (IU)</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>0.0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
</tr>
</tbody>
</table>

CI, confidence interval.

$^*$ $P$ value for response $< 90\%$ (that is, small $P$ values support response rates of $> 90\%$).
most common adverse effects after the administration of oxytocin were hypotension (30%), nausea (37.5%), vomiting (12.5%), and flushing (62.5%). The high incidence of intense flushing after such small doses of oxytocin illustrates the potent vasodilating properties of this drug. The high incidence of nausea and vomiting after delivery may be associated with hypotension or with visceral stimulation secondary to exteriorization of the uterus for surgical repair. The study design does not allow further elaboration on this question. This issue is the subject of ongoing research.

The hypotensive action of oxytocin, demonstrated in animal models, is believed to be mediated by the direct effect on oxytocin receptors in the heart and the indirect effect of the release of atrial natriuretic peptide, brain natriuretic peptide, and nitric oxide in the cardiovascular tissues. Recent evidence from in vitro studies on human atrial tissue has shown that the hypotensive effect observed after bolus administration of a commercial oxytocin preparation may largely be due to the negative inotropic and vasodilatory effect of the preservative chlorbutanol. In a case report described by Thomas and Cooper, a 10 IU bolus of oxytocin administered to a hypovolemic mother at cesarean delivery was thought to have contributed to her death. Because oxytocin has dose-dependent adverse effects, it appears prudent to use the minimum effective dose.

Few studies have compared different doses of oxytocin during elective cesarean delivery. Sarna et al compared 5, 10, 15, and 20 IU doses of oxytocin administered intravenously at the rate of 1 IU/min after cord clamping, and determined that the degree of uterine contraction, estimated blood loss, and the difference in preoperative and postoperative hematocrit values were similar among groups. Although their study suggests that it is unnecessary to administer more than 5 IU of oxytocin, the researchers did not determine the minimum effective dose of oxytocin. In addition, they did not record potential adverse effects in the 4 study groups. With only 40 patients, 10 per group, their numbers were too small for an equivalence study.

Zarzur suggested that 3 IU of oxytocin in 500 mL 5% dextrose solution, administered immediately after delivery at 80 drops/min (0.024 IU/min) provides a satisfactory outcome, with no hypotension, nausea, or vomiting (Zarzur E. Intravenous oxytocin in patients undergoing elective cesarean section [letter]. Anesth Analg 1998;86:1334). Unfortunately, the small size of his study of 20 patients limited the power of his conclusions.

The results of our study show that the ED90 for oxytocin during elective cesarean is 0.35 IU with a logistic regression model at 95% CI. Findings of the nonparametric analysis are also in agreement with the logistic model where the ED90 is expected to be less than 0.5 IU. There is no significant difference between 0.5 IU and 1 IU with respect to response time for adequate uterine tone. None of the patients in the study required more than 1 IU oxytocin to produce effective uterine contraction. This evidence lead us to conclude that satisfactory uterine contraction at elective cesarean delivery can be achieved by administering doses of intravenous oxytocin no larger than 1 IU.

The surgical protocol followed in the study (ie, beginning oxytocin with shoulder delivery, awaiting satisfactory uterine contraction, and assisting delivery of the partially expelled placenta) is not a widespread practice. More typically, the placenta is extracted immediately after delivery of the fetus. Our approach resulted in a longer fetus-to-placenta delivery interval, during which time the lower doses of oxytocin used in this study may have had sufficient time to cause an effective uterine contraction. Therefore implementation of a regimen using lower doses of oxytocin at elective cesarean delivery may require reevaluation of the surgical practice surrounding delivery of the placenta.

REFERENCES


Reprints are not available. Address correspondence to: José C. A. Carvalho, MD, PhD, Department of Anesthesia, Mount Sinai Hospital, 600 University Avenue, Room 781, Toronto, Ontario, M5G 1X5, Canada; e-mail: jose.carvalho@uhn.on.ca.