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REPORTS OF ORIGINAL INVESTIGATIONS

Up-down determination of the ED_{90} of oxytocin infusions for the prevention of postpartum uterine atony in parturients undergoing Cesarean delivery

Détermination de la DE_{90} des perfusions d'oxytocine pour la prévention de l'atonie utérine post-partum chez les parturientes subissant un accouchement par césarienne

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Abstract

Introduction *Use of the lowest effective dose of oxytocin may reduce side effects. This study was designed to determine the effective dose $(ED)_{90}$ of oxytocin infusion for an elective Cesarean delivery (CD) to prevent uterine atony.*

Methods *The participants were ASA I and II, non-obese, non-labouring adult women undergoing an elective CD at term with a singleton gestation. The spinal anesthetic technique was standardized, and a blinded infusion of oxytocin was administered after delivery. The obstetrician rated the uterine contraction as either satisfactory or unsatisfactory. The initial dose of oxytocin infusion was 0.4 $IU{\cdot}min^{-1}$, and the dose for the next subject was based on the response of the preceding subject as per a biased-coin design up-down sequential method. The ED_{90} was calculated using Firth's penalized likelihood estimation.*

Results *Fifty subjects were screened, eight subjects were excluded, and two patients were withdrawn. Seven of the 40 subjects had uterine tone that was judged unsatisfactory by the obstetrician and required additional uterotonic medications. The ED_{90}, i.e., the dose at which 90% of women were judged to have satisfactory uterine tone, was 0.29 $IU{\cdot}min^{-1}$ (95% confidence interval [CI] 0.15-0.43 $IU{\cdot}min^{-1}$).*

Discussion *In this study, we found the ED_{90} of oxytocin required to prevent uterine atony and postpartum hemorrhage after an elective CD to be 0.29 $IU{\cdot}min^{-1}$—approximately 15 IU of oxytocin in 1 L of intravenous fluid administered over a one-hour period—(95% CI 0.15-0.43 $IU{\cdot}min^{-1}$). This oxytocin infusion dose is 30% less than the clinical infusions currently in use. It remains to be seen whether this dosing will be required for higher risk individuals or for labouring parturients undergoing non-elective CD. (Clinical Trial gov. NCT00785395).*

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Résumé

Introduction *L'utilisation de la dose efficace d'oxytocine la plus basse possible pourrait réduire les effets secondaires. Cette étude a été conçue pour déterminer la dose efficace $(DE)_{90}$ d'une perfusion d'oxytocine afin de prévenir l'atonie utérine après un accouchement par césarienne (AC) non urgent.*

Méthode *Les participantes étaient des femmes adultes ASA I et II, non obèses et pas encore en travail obstétrical subissant un AC à terme d'une grossesse unique. La technique d'anesthésie rachidienne était standardisée,*

et une perfusion en aveugle d'oxytocine a été administrée après l'accouchement. L'obstétricien a évalué la contraction utérine comme étant satisfaisante ou non satisfaisante. La dose initiale de perfusion d'oxytocine était de 0,4 IU·min^{-1}, et la dose pour la patiente suivante était fondée sur la réaction de la patiente précédente, conformément à une méthode séquentielle des suites croissantes et décroissantes avec tirage biaisé à pile ou face. La DE_{90} a été calculée à l'aide en estimant la vraisemblance pénalisée de Firth.

Résultats *Cinquante patientes ont été évaluées, huit ont été exclues, et deux retirées. Parmi les 40 patientes, sept ont manifesté un tonus utérin jugé non satisfaisant par l'obstétricien et ont nécessité des médicaments supplémentaires pour améliorer le tonus utérin. La DE_{90}, soit la dose à laquelle 90 % des femmes ont été jugées comme présentant un tonus utérin satisfaisant, était de 0,29 IU·min^{-1} (intervalle de confiance [IC] 95 %, 0,15-0,43 IU·min^{-1}).*

Discussion *Dans cette étude, nous avons observé que la DE_{90} d'oxytocine nécessaire à la prévention de l'atonie utérine et de l'hémorragie post-partum après un AC non urgent était de 0,29 IU·min^{-1}, soit environ 15 IU d'oxytocine dans 1 L de liquide intraveineux administré sur une période d'une heure (IC 95 %, 0,15-0,43 IU·min^{-1}). Cette dose de perfusion d'oxytocine représente une réduction de 30 % par rapport aux perfusions cliniques utilisées actuellement. Des études futures devront déterminer si cette dose sera nécessaire pour les patientes à risque plus élevé ou pour les patientes en travail subissant un AC urgent. (Numéro gouv. d'étude clinique NCT00785395).*

Clinically, pharmacologic concentrations of oxytocin are used for induction and augmentation of labour and the prophylaxis of postpartum hemorrhage.[1] While both ergometrine and oxytocin are effective in the prevention of uterine atony and postpartum hemorrhage, oxytocin is first-line therapy due to the significant side effects associated with ergometrine, i.e., hypertension and vomiting. In fact, when oxytocin is administered in bolus doses, it also may be associated with adverse effects, including hypotension, nausea, vomiting, headache, and myocardial ischemia.[2] Oxytocin manufacturers and expert opinion no longer recommend oxytocin bolus dosing for the prophylaxis of postpartum hemorrhage; alternatively, they suggest it should be administered as a dilute rapid infusion.[2-6] Use of the lowest effective dose (ED) of an oxytocin infusion may also reduce these side effects.

This study is designed to determine the minimum ED_{90} of oxytocin infusions for the prevention of uterine atony/postpartum hemorrhage and the need for additional uterotonics in low-risk parturients presenting for an elective Cesarean delivery (CD). Based on our clinical experience, we hypothesized that the ED_{90} would be from 0.3 to 0.6 IU·min^{-1}.

Methods

Institutional Research Ethics Board approval was obtained, and all subjects provided written informed consent. Fifty subjects were considered eligible and were approached to participate in this trial. Inclusion criteria included adult women aged $\geq$ 18 yr, ASA I and II, non-labouring, and undergoing an elective CD with spinal anesthesia at term (37-42 weeks) with a singleton gestation. Exclusion criteria included morbid obesity (body mass index $\geq$ 45 kg·m^{-2}) or conditions that predisposed to increased risk of uterine atony or postpartum hemorrhage. The subjects were identified from the weekly-published operating room schedule.

Standard monitoring was applied in the operating room, and the anesthetic technique was standardized. All women received antacid prophylaxis with sodium citrate 30 mL. As well, they received a standardized spinal anesthetic administered in the region of L3 and L5 in the sitting position using hyperbaric bupivacaine 12 mg with fentanyl 10-20 μg and preservative free morphine 100-200 μg. Immediately following, the patients were positioned supine with left uterine displacement to minimize aortocaval compression. After the spinal was completed, their blood pressure was measured every minute for ten minutes then every 2.5 min for the duration of the study. Each subject received an intravenous coload of crystalloid, and any spinal-induced hypotension was treated with bolus doses of phenylephrine 50-100 μg.

Following delivery and clamping of the umbilical cord, a blinded infusion of oxytocin was administered. The initial dose of oxytocin infusion (0.4 IU·min^{-1}) was chosen from the clinical range currently in use, as determined by the investigators and previous research.[7,8] Since an investigator independent of the anesthesia provider prepared the study medication, the anesthesiologist and the obstetrician were blinded to the concentration of oxytocin that was provided to them in a 500 mL bag of normal saline. The concentration was adjusted such that all infusions were administered at 500 mL·hr^{-1}. The blinded oxytocin infusion was continued for one hour, followed by an oxytocin infusion of 30 IU·1000 mL^{-1} administered at 150 mL·hr^{-1} while the patients remained in the postanesthesia care unit (PACU) (institutional standard). The oxytocin infusion was discontinued once the patients were discharged from the PACU.

Hypotension following the initiation of oxytocin was defined as a systolic blood pressure (SBP) 20% lower than the previous SBP or a SBP < 90 mmHg. The hypotension was treated with 50-100 μg of phenylephrine *iv*. We recorded any adverse effects that occurred immediately after delivery/initiation of oxytocin infusion, such as hypotension, arrhythmias, chest pain, and shortness of breath, and we noted intraoperative need for additional uterotonic medications, uterine massage, or surgical intervention. In addition, we recorded adverse events in the initial 48-hr postoperative time period, including excessive per vagina bleeding, diagnosis of postpartum hemorrhage, need for transfusion, need for return to the operating room or transfer to the intensive care unit.

With respect to the surgical approach, the obstetricians proceeded in their usual surgical manner by handing off the baby to the neonatal team, manual or assisted delivery of the placenta, removal of any further products of conception, inspection of the patient's uterus, and wiping of the uterine cavity. At any time at this point, the surgical repair of the patient's uterus was started. Three minutes after manual or assisted delivery of the placenta, the obstetrician was asked to rate the uterine contraction as either satisfactory or unsatisfactory and to indicate whether further management was necessary. If the uterine contraction was considered unsatisfactory, the anesthesiologist and obstetrician proceeded with their usual management of uterine atony, i.e., uterine massage and additional oxytocin bolus, ergometrine, or carboprost. If a part of usual practice, the obstetrician was able to exteriorize the uterus for repair once the three-minute assessment was completed. All of the obstetricians were consultants. We did not control which obstetricians participated, and the protocol was reviewed with each obstetrician prior to surgery.

The initial dose of oxytocin infusion was 0.4 IU·min^{-1}, and the dose for the next subject was based on the response of the preceding subject, as per a biased-coin design (BCD) up-down sequential method (UDM).[9] If the uterine contraction/tone was judged as unsatisfactory during the initial three-minute assessment, i.e., there was a need to administer additional uterotonics, the dose was stepped up in the next patient. The dosing change was in increments of 0.1 IU·min^{-1}. If the uterine contraction/tone was judged as satisfactory, i.e., no uterine atony was observed and there was no need for additional uterotonics, the next patient was randomized with a probability of 0.1 to the next lower dose and with a probability of 0.9 to the same dose. The primary outcome measure was the response of effective uterine contraction as either satisfactory or unsatisfactory as determined by the obstetrician blinded to the oxytocin infusion dose.

The ED_{90} with 95% confidence interval (CI) was calculated using Firth's penalized likelihood estimation using SAS 8.0 (SAS Inc., Cary, NC, USA).[10] Based on previous experience with this statistical method[11] and convenience of patient recruitment within a specific time period, a sample size of 40 patients was selected.

Results

Fifty subjects were screened for participation from June to August 2008. Eight subjects were excluded prior to providing informed consent because they did not meet inclusion and/or exclusion criteria after further review (obesity [three], multiple gestation, malpresentation, age, failed induction of labour, language barrier). Two of the 42 subjects were withdrawn from the study because they both required a general anesthetic after a failed spinal anesthesia. Subject demographics and clinical characteristics are listed in the Table 1.

Forty subjects received a blinded infusion of oxytocin following delivery by CD. Seven of the 40 subjects had uterine tone that was judged unsatisfactory by the obstetrician and required additional uterotonic medications. The dosage of oxytocin infusions ranged from 0.1-0.4 IU·min^{-1}. Figure 1 illustrates the oxytocin infusion doses assigned and the subsequent dose assignment based on uterine tone assessment and the BCD of the UDM. Two subjects developed hypotension post infusion and required administration of vasopressors. No transfusions of blood products or colloids were required, and those subjects with unsatisfactory uterine tone responded to an oxytocin bolus of 5 IU.

The ED_{90}, i.e., the dose at which 90% of women were judged to have satisfactory uterine tone, was 0.29 IU·min^{-1} (95% CI 0.15-0.43 IU·min^{-1}), as determined with Firth's penalized likelihood estimation method. Using Firth's bias reduction logistic regression, the probability of a successful

Table 1 Demographic data of randomized subjects receiving oxytocin infusions

Variable	Mean / Median
Age (yr)	32 ± 5
Weight (kg)	85 ± 15
Height (cm)	164 ± 6
BMI (kg·m^{-2})	31.8 ± 5.1
Gravidity	2 (2, 3)
Parity	1 (1, 2)
Sensory block @ 10 min	T4 (T3, T4)
Anesthesia – delivery interval (min)	26 ± 5

Mean ± standard deviation / median (interquartile range). BMI = body mass index

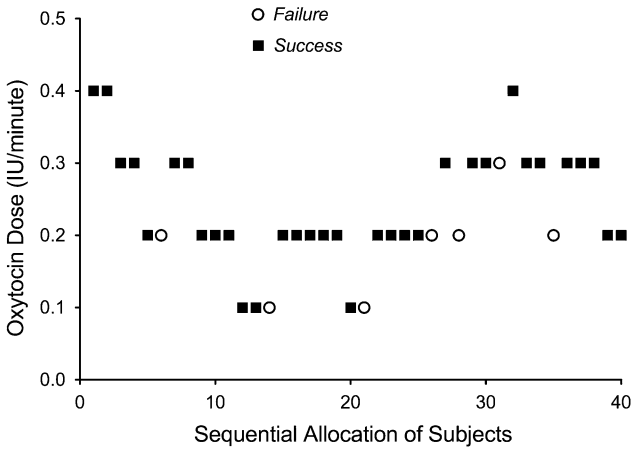

Fig. 1 Oxytocin dose frequencies, patients' responses, and subsequent dose allocation

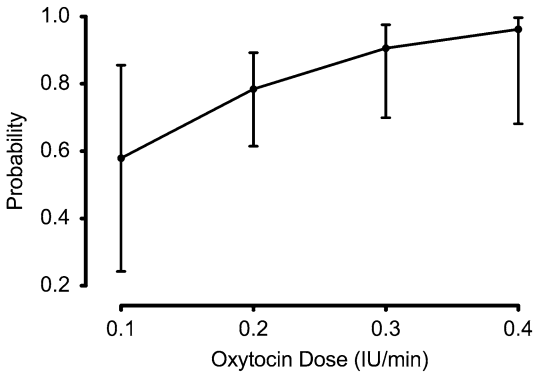

Fig. 2 Fitted probabilities of successful responses at the specific oxytocin doses tested using Firth's bias reduced penalized maximum likelihood logistic regression 95% confidence intervals

response at 0.3 IU·min^{-1} was 90.6% (95% CI 69.9-97.6 %) (Figure 2).[A]

Discussion

In this study, we found 0.29 IU·min^{-1} to be the ED_{90} of oxytocin required to prevent uterine atony and postpartum hemorrhage after an elective CD; however, the estimate was imprecise, as illustrated by the wide-ranging 95% CI (0.15-0.43 IU·min^{-1}). This oxytocin infusion dose is 30% less than clinical infusions currently used (0.4 IU·min^{-1}),[7,8] and it is roughly equivalent to placing 15 IU of oxytocin in 1 L of intravenous fluid and administering the infusion over a one-hour period. This dose is approximately 50% of the current dose used at our institution.

The ED_{50} is the minimally effective dose that results in a desired clinical effect in 50% of patients in whom the drug is administered. The UDM is a method used commonly to determine the ED_{50} of intrathecal local anesthetics, intrathecal opioids, intravenous opioids, intravenous anesthetics, and inhalational anesthetics.[9] The UDM is used to choose the drug dose levels, to select the sample size of subjects from a target population, and to specify the definition of a positive response. Earlier UDM studies sought the ED_{50} of various drugs, e.g., inhalational anesthetics, that was, by definition, effective in 50% of subjects. Anesthesiologists were left to extrapolate the results to doses that were more clinically useful, i.e., ED_{90} or ED_{95}, that would be effective in 90-95% of patients. With small sample sizes used to calculate an ED_{50} in UDM studies, the assumption of a traditional sigmoidal dose-response curve may be incorrect, and using such an assumption to extrapolate an ED_{90} or an ED_{95} may lead to erroneous estimates.[9] The BCD allows the researcher to set the quantile effect dose of interest, i.e., 90%, 95%, or even 50%. Essentially, this allows for a more precise calculation of the upper-tail of the traditional sigmoidal dose-response curve rather than relying on an extrapolation from an ED_{50}. Our preliminary simulations and experience with this method led us to the conclusion that the ED_{90} would give us results with reasonable precision. Arguably, striving for the ED_{95} may lead to results that are slightly more clinically relevant. However, simulations with our sample size of 40 subjects indicated significantly less precision. If we were to attempt to determine the ED_{95}, likely the confidence intervals would have been more wide-ranging than our current results and, consequently, would have lacked any clinical significance.

The context of the particular cohort should be taken into account when considering the results of this study. This preliminary study involved healthy women with no risk factors for uterine atony or postpartum hemorrhage undergoing elective CD. Therefore, it is possible that the dose of oxytocin in this low-risk group is significantly lower than the current dosing used for the general population of women presenting for elective CD. It remains to be seen whether the current dosing would be required for higher risk individuals or for labouring parturients undergoing non-elective CD. Perhaps dosing of oxytocin may need to be tailored toward specific patient groups.

In addition, our results were influenced by our outcome measure. The subjective estimation of uterine tone by the obstetrician is an invalidated measure. However, we did limit the assessment to either satisfactory or unsatisfactory and requiring additional uterotonics. Given the lack of a more rigorous measure of uterine tone, we felt this clinical outcome measure would return sound clinical results.

[A] The resulting logistic model for Firth's method is $y_{Firth} = -0.6538 + 9.73 \bullet x$.

During the study period, two subjects (5%) experienced a brief episode of hypotension after the infusion of oxytocin was started. Both episodes of hypotension did not appear related temporally to the administration of the oxytocin infusion. The first subject had a low blood pressure reading eight minutes after the infusion was started (0.3 IU·min^{-1}), and it was reversed quickly with a vasopressor. There were no preceding or subsequent episodes of hypotension during the CD and study period. It was felt that this spurious low blood pressure reading may have been artifact and, given the timing, likely not due to oxytocin. The second subject (0.2 IU·min^{-1}) experienced multiple episodes of hypotension treated successfully with small (50 μg) aliquots of phenylephrine prior to delivery and initiation of the oxytocin infusion. The hypotension was considered likely secondary to her T1 spinal blockade.

In conclusion, this study may provide some preliminary evidence that the current infusion dose of 0.4 IU·min^{-1} may be higher than the ED_{90} dose required to prevent uterine hemorrhage and post partum uterine atony in low-risk patients undergoing an elective CD. In this subset of low-risk patients having an elective CD, an infusion of oxytocin at a lower infusion rate (15 IU of oxytocin in 1 L of intravenous fluid administered over a one-hour period) may provide sufficient uterine contractility while possibly reducing maternal side effects, including hypotension. However, given our estimate's lack of precision, further work is required on this issue.

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Conflicts of interest None declared.

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