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Minimum effective bolus dose of oxytocin during elective Caesarean delivery

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Background. The aim of this study was to determine the lowest effective bolus dose of oxytocin to produce adequate uterine tone (UT) during elective Caesarean delivery (CD).

Methods. Seventy-five pregnant patients undergoing elective CD under spinal anaesthesia were randomized to receive oxytocin (0.5, 1, 3, 5 units) or placebo. UT was assessed by a blinded obstetrician as either adequate or inadequate, and using a verbal numerical scale score (0–10; 0, no UT; 10, optimal UT) at 2, 3, 6, and 9 min after oxytocin administration. Minimum effective doses of oxytocin were analysed (ED_{50} and ED_{95}) using logistic regression. Oxytocin-related side-effects (including hypotension) were recorded.

Results. There were no significant differences in the prevalence of adequate UT among the study groups at 2 min (73%, 100%, 93%, 100%, and 93% for 0, 0.5, 1, 3, and 5 units oxytocin, respectively). The high prevalence of adequate UT after placebo and low-dose oxytocin precluded determination of the ED_{50} and ED_{95}. UT scores were significantly lower in patients receiving 0 unit oxytocin at 2 and 3 min compared with 3 and 5 units oxytocin ($P<0.05$, respectively). The prevalence of hypotension was significantly higher after 5 units oxytocin *vs* 0 unit at 1 min (47% *vs* 7%; $P=0.04$).

Conclusions. The routine use of 5 units oxytocin during elective CD can no longer be recommended, as adequate UT can occur with lower doses of oxytocin (0.5–3 units).

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Oxytocin is routinely administered during elective Caesarean delivery (CD) to initiate and maintain adequate uterine contractility after placental delivery. The uterotonic effect of oxytocin is important in reducing blood loss from the site of placental attachment and decreasing the risk of postpartum haemorrhage. However, adverse haemodynamic effects are known to occur after i.v. oxytocin, notably tachycardia, hypotension, and ECG changes.[1–3] Although many practitioners use 5 units oxytocin during elective CD,[4] there is limited evidence to substantiate this practice. Smaller bolus doses of oxytocin are associated with reduced frequency of adverse effects;[2 3] however, few studies have investigated the dose-related effects of an oxytocin bolus for achieving adequate uterine tone (UT) during elective CD.[2 5 6]

The aim of this study was to estimate the minimum effective dose of oxytocin required to produce adequate UT at 2 min for 50% (ED_{50}) and 95% (ED_{95}) of patients undergoing elective CD with spinal anaesthesia.

Methods

After obtaining Institutional Review Board approval and written informed consent, 75 healthy term patients (≥37 weeks gestation) undergoing elective CD were enrolled in this randomized, double-blind, placebo-controlled, dose-ranging study. The study was conducted at Lucile Packard Children's Hospital (Stanford, CA, USA), and patients were enrolled over a 10-month period (July 2008–April 2009).

Inclusion criteria were ASA I or II, age between 18 and 40 yr, singleton pregnancies, and elective CD with a Pfannensteil incision. All enrolled patients received spinal

anaesthesia. Exclusion criteria included active labour, ruptured membranes, known drug allergy to oxytocin, multiple gestation, significant obstetric disease (including pregnancy-induced hypertension or pre-eclampsia), known risk factors for postpartum haemorrhage (including abnormal placentation, multiple gestation, uterine fibroids, history of postpartum haemorrhage or uterine atony, and previous classical uterine incision), inherited or acquired coagulation disorder, and thrombocytopenia (platelet count $<100\times10^9$).

In the preoperative period, an 18 G peripheral i.v. cannula was inserted and all patients received 500 ml hetastarch (Hospira, Lake Forest, IL, USA) within 30 min before spinal anaesthesia. Baseline haematocrit (HCT) values were taken in the preoperative period. All patients were premedicated with i.v. metoclopramide 10 mg and ranitidine 50 mg. Baseline maternal heart rate (HR) and non-invasive arterial pressure (NIAP) were recorded as the average of three readings at admission in the preoperative period.

Before spinal anaesthesia, standard monitoring included ECG, NIAP, and pulse oximetry. Measurement of NIAP and HR was taken at 1 min intervals from the time of oxytocin administration. Hypotension was defined as a decrease in mean AP $\geq$10% of the baseline value, and each episode of hypotension was treated with an i.v. bolus of 100 μg phenylephrine. Tachycardia was defined as a maternal HR $\geq$120 beats min^{-1}. Crystalloid solution (lactated Ringer's) was infused during the intraoperative period, with the aim of using a total crystalloid volume of $\leq$2 litre. Intraoperative fluid management was at the discretion of the supervising anaesthetist who was not involved in the study.

Spinal anaesthesia was performed at the L3–4 interspace with the patient in the sitting position with a 25 G Whitacre needle by an anaesthetist who was not involved in the study. Women were given spinal anaesthesia with hyperbaric bupivacaine 1.6 ml (0.75%), fentanyl 10 μg, and morphine 200 μg. The patient was then moved to the supine position with left lateral uterine displacement. Surgery was allowed to proceed after achieving a T6 sensory level to pinprick. The obstetrician and anaesthetist involved in each case were blinded to the oxytocin dose assignments.

After enrolment, patients were randomized using Microsoft Excel-generated random number allocations into one of the five possible groups to receive 0, 0.5, 1, 3, or 5 units oxytocin. Opaque envelopes containing group assignments were used to ensure blinding of the investigators. The oxytocin dose was prepared before surgery and diluted with 0.9% normal saline up to a total volume of 5 ml by an anaesthetist not involved in the study. Oxytocin was administered as an i.v. bolus over a time period of 15 s after clamping of the umbilical cord and delivery of the fetus. After delivery of the fetus, the obstetrician manually removed the placenta and subsequently performed uterine massage. Uterine exteriorization was performed at the discretion of the attending obstetrician.

UT was assessed by the attending obstetrician at 2, 3, 6, and 9 min after oxytocin administration by manual palpation of the uterus. The obstetrician provided two subjective assessments of UT at each time point: (i) adequate or inadequate UT, (ii) a UT score (UTS) using a verbal numerical scale score (0–10; 0, no UT; 10, optimal UT). If the tone was assessed as adequate at 2 min, then an oxytocin infusion was commenced [10 units oxytocin in 250 ml 0.9% normal saline at 125 ml h^{-1} (0.08 units min^{-1})]. If the tone was assessed as inadequate, then a 'rescue' bolus of 2.5 units oxytocin was administered. A maximum of two 'rescue' doses of oxytocin were permitted in the event of two separate recordings of inadequate UT during the study period. If UT was assessed as inadequate after two rescue doses of oxytocin, then alternative uterotonic therapy was administered (i.m. methylergonovine maleate 0.2 mg; i.m. carboprost tromethamine 0.25 mg; rectal misoprostol 800–1000 μg) at the discretion of the attending anaesthetist and obstetrician. After the study period, all patients received a maintenance infusion of i.v. oxytocin (0.16 units min^{-1}).

The primary study outcome measure was the assessment of either adequate or inadequate UT at 2 min after administration of the initial oxytocin dose. Secondary endpoints included UTS, intraoperative blood loss (measured by estimating blood collected by suction and by calculating the weight of blood on surgical swabs), the number of rescue doses of oxytocin, side-effects associated with oxytocin (including tachycardia, hypotension, nausea, and vomiting), and HCT values measured before surgery and within the first 30 min after completion of surgery.

Patient characteristics, obstetric, and perioperative data are presented as mean (SD) or median (IQR). Data were assessed for normal distribution of variance using normality plots and the Kolmogorov–Smirnov test. Data were analysed using analysis of variance (ANOVA) or the Kruskal–Wallis tests as appropriate. Repeated-measures ANOVA with group as the between-subject factor and time as the within-subject factor was used. *Post hoc* comparisons were made using the Tukey honestly significant difference test. Categorical data were analysed using Fisher's exact test. A *P*-value of <0.05 was considered to be statistically significant. Data were analysed using SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Adequate UT and inadequate UT were assessed as binary outcomes. The corresponding bolus dose of oxytocin was fitted to the following version of the Hill equation: probability of adequate UT$=\text{dose}^{\gamma}/(\text{dose}^{\gamma}_{50}+\text{dose}^{\gamma})$, where dose is the bolus dose of oxytocin (in units), dose_{50} the dose of oxytocin at which there is a 50% probability of achieving adequate UT, and γ the slope of the response curve and describes the shape of the data distribution. The binary endpoints used for logistic regression analysis were adequate UT compared with inadequate UT. A naïve pooled analysis was performed with each subject providing one data point for the fit. ED_{50} and ED_{95} were estimated using NONMEM® version V (GloboMax, Hanover, MD,