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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,

USA). The quality of the fit was considered based on improvement in the log-likelihood value of NONMEM (an improvement of 4 of the log-likelihood value consistent with $P<0.05$ was considered significant) and visual assessment of the fit. This method of logistic regression analysis has been previously validated in other studies investigating ED_{50} and ED_{95}.[7 8]

Results

Seventy-five patients were enrolled, and 74 patients completed the study; one patient was excluded due to protocol violation (obstetrician request for supplemental oxytocin despite adequate UT) (Fig. 1). The patient characteristics were similar among the five groups (Table 1).

The percentage of patients with adequate UT at 2, 3, 6, and 9 min after bolus administration of oxytocin are shown in Table 2. There were no significant differences in the prevalence of adequate UT at 2 min between the groups. Ten out of 15 patients (66%) in the placebo group had adequate UT at 3 min compared with 15 patients (100%) receiving 3 u oxytocin ($P=0.04$) (Table 2); two patients in the placebo group received supplemental oxytocin (2.5 units) for inadequate UT at 2 min. Owing to the high prevalence of adequate UT in groups receiving placebo or 0.5 units oxytocin (73% and 100%, respectively), the transition point from inadequate to adequate UT could not be calculated using logistic regression analysis. As a result, the ED_{50} and ED_{95} for oxytocin at 2 min after bolus administration could not be derived.

The UTS values after oxytocin bolus administration at 2, 3, 6, and 9 min are presented in Figure 2. Using repeated-measures ANOVA, a group by time interaction effect was observed for UTS ($P=0.045$). Patients receiving 0 unit had significantly lower UTS at 2 and 3 min compared with those receiving 3 and 5 units oxytocin ($P<0.05$, respectively) (Fig. 2).

The total number of patients in each group who required rescue doses of oxytocin (2.5–5 units) to treat uterine atony is shown in Table 2. Fewer patients in the 3 units oxytocin group required supplemental oxytocin compared with placebo (0% *vs* 47%, respectively; $P=0.006$) (Table 2). Two rescue doses of oxytocin (total=5 units) were required to treat inadequate UT for two patients in the placebo group (at 2 and 3 min), for one patient in the 0.5 units oxytocin group (at 6 and 9 min), and for two patients in the 1 unit oxytocin group (at 3 and 6 min). One

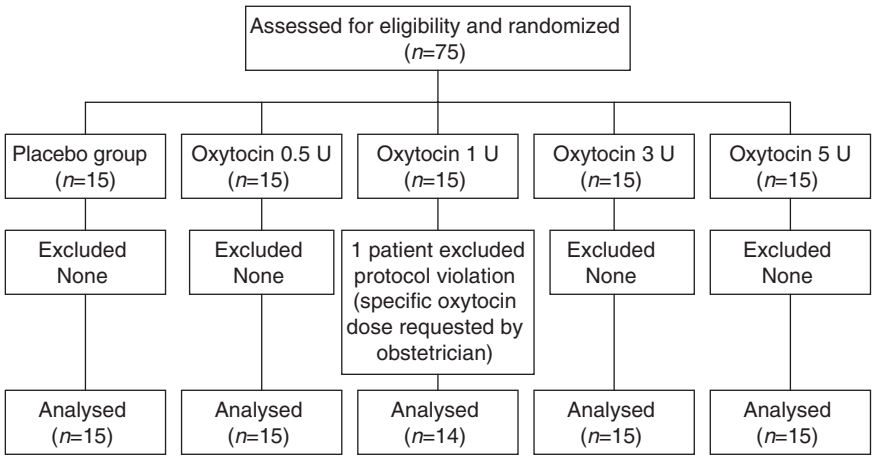

Fig 1 Schematic of algorithm for study protocol. U, units.

Table 1 Maternal patient characteristic and obstetric data. Data are presented as mean (SD) and median (inter-quartile range). CS, Caesarean delivery; HCT, haematocrit

	Oxytocin dose				
	0 unit	**0.5 unit**	**1 unit**	**3 units**	**5 units**
n	15	15	14	15	15
Age (yr)	31 (26–35)	33 (31–34)	35.5 (32–38)	33 (30–36)	32 (29–33)
Weight (kg)	80.6 (16.3)	79.1 (8.3)	82.1 (12.1)	71.9 (7.7)	73.5 (6.6)
Parity	1 (1–1)	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–2)
Previous CS	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Gestational age (weeks)	38.9 (0.6)	38.7 (1)	38.6 (0.6)	38.6 (0.7)	38.6 (0.8)
Preoperative HCT (%)	35 (2.7)	35.7 (3.1)	36 (1.8)	36.3 (2.4)	35.1 (3.1)

Table 2 Prevalence of adequate UT at 2, 3, 6, and 9 min after oxytocin administration and total number of patients requiring supplemental oxytocin during the study period. Data presented as *n* (%). *Obstetrician unable to perform manual assessment of UT for one patient. †3 units oxytocin *vs* 0 unit oxytocin at 3 min; *P*=0.04. ‡Obstetrician unable to perform manual assessment of UT due to peritoneal closure for one patient. ¶Obstetrician unable to perform manual assessment of UT due to peritoneal closure for four patients. §3 units oxytocin *vs* 0 unit oxytocin; *P*=0.006

	Oxytocin dose				
	0 unit	**0.5 unit**	**1 unit**	**3 units**	**5 units**
Time=2 min	11/15 (73%)	15/15 (100%)	13/14 (93%)	14/14* (100%)	14/15 (93%)
Time=3 min	10/15 (66%)	14/15 (93%)	12/14 (86%)	15/15 (100%)†	14/15 (93%)
Time=6 min	15/15 (100%)	13/15 (87%)	12/14 (86%)	15/15 (100%)	15/15 (100%)
Time=9 min	15/15 (100%)	14/15 (93%)	11/13‡ (85%)	11/11¶ (100%)	14/14 (100%)
Patients requiring supplemental oxytocin	7/15 (47%)	3/15 (20%)	3/14 (21%)	0/15 (0%)§	2/15 (13%)

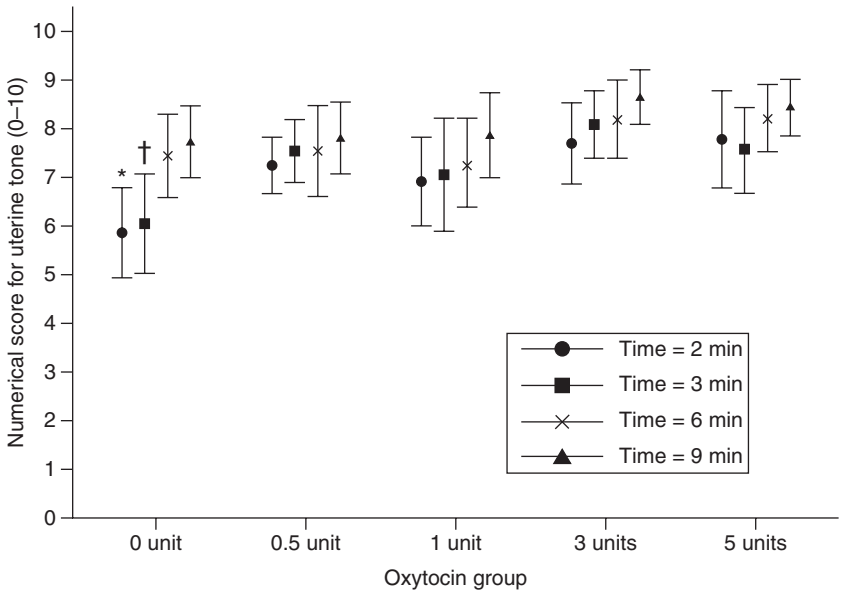

Fig 2 Numerical scores for UT according to manual assessment by the obstetrician using a numerical scale of 0 (absent UT) to 10 (optimal UT) for groups receiving 0, 0.5, 1, 3, and 5 units oxytocin. Data presented as mean (95% confidence intervals). *0 unit oxytocin *vs* 3 units oxytocin at 2 and 3 min after bolus administration; $P<0.005$. †0 unit oxytocin *vs* 5 units oxytocin at 2 and 3 min after bolus administration; $P<0.05$.

patient in the 1 unit oxytocin group received i.m. methylergonovine maleate (0.2 mg) at 9 min, due to refractory uterine atony after 5 units of 'rescue' oxytocin.

The prevalence of hypotension in the study groups at 1 min is shown in Figure 3. Only one of 15 patients in the placebo group (7%) had hypotension compared with seven patients in the 5 units oxytocin group (47%) (*P*=0.035). No significant differences in the proportion of patients with hypotension between the study groups were found at 2, 3, 6, and 9 min. One patient who received 5 units oxytocin developed tachycardia (HR=120 beats min^{-1}) at 1 min; tachycardia was not observed in any of the other study groups at 1 min or in any study group at 2, 3, 6, or 9 min. Nausea was reported in two patients at 6 min (after 0 and 5 units oxytocin, respectively); no patient vomited during the study period. No episodes of shortness of breath, chest pain, arrhythmias, or flushing were observed.

The time intervals between delivery and uterine exteriorization, and between uterine exteriorization and placental delivery (Table 3) were similar among the groups.

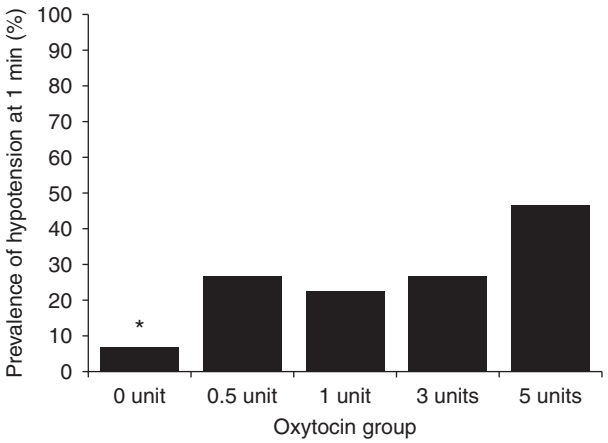

Fig 3 Prevalence of hypotension at 1 min after bolus administration of oxytocin for groups receiving 0, 0.5, 1, 3, and 5 units oxytocin. *0 unit oxytocin *vs* 5 units oxytocin; *P*=0.035.

Total i.v. crystalloid volume infused, blood loss, and pre- and postoperative HCT values also were similar among the study groups (Table 3).

Table 3 Perioperative surgical data, total i.v. fluid volume administered, and postoperative haematocrit values. Data presented as mean (SD), median (inter-quartile range). CD, Caesarean delivery; EBL, estimated blood loss (excluding blood on surgical swabs); HCT, haematocrit; PD, placental delivery; UE, uterine exteriorization

	Oxytocin dose				
	0 unit (n=15)	0.5 units (n=15)	1 unit (n=14)	3 units (n=15)	5 units (n=15)
Delivery–UE time (s)	51 (37–58)	43 (32–77)	38 (22–59)	53 (35–60)	45 (30–58)
UE–PD time (s)	40 (22–55)	37 (24–47)	33 (20–51)	36 (26–52)	38 (25–51)
I.V. crystalloid (ml)	1980 (409)	1860 (415)	1942 (621)	1880 (350)	1703 (452)
EBL (ml)	800 (256)	836 (175)	764 (237)	707 (117)	697 (120)
Weight of blood on surgical swabs (g)	957 (412)	843 (327)	929 (574)	720 (294)	776 (261)
Post-CD HCT (%)	30.3 (2.3)	31.8 (2.8)	32.7 (2.6)	32.3 (2.6)	31.7 (3.3)

Discussion

Our results indicate that adequate UT can be achieved with small bolus doses (0.5–3 units) of oxytocin in patients undergoing elective CD. We also observed a surprisingly high prevalence of adequate UT (73%) at 2 min in the placebo group. Although the ED_{50} and ED_{95} of oxytocin could not be calculated using logistic regression analysis, the results of this study suggest that the use of 5 units oxytocin as a standard dose to achieve adequate UT during elective CD is excessive and re-evaluation of dosing requirement is necessary.

Patients undergoing CD are at increased risk of obstetric haemorrhage,[9] and uterine atony has been shown to be the most common aetiology (>30% patients undergoing CD).[9 10] Oxytocin is commonly administered after vaginal delivery and CD to reduce the risk of postpartum haemorrhage.[11] Despite widespread use, there are limited data to guide optimal oxytocin dosing for patients undergoing elective CD. A recent UK survey reported that a slow i.v. bolus of 5 units oxytocin is commonly used by obstetricians and anaesthetists (86% and 92%, respectively) during CD.[4] However, safety and efficacy data are lacking to support the routine use of a 5 units bolus of oxytocin as a standard of care during elective CD.

A previous study by Carvalho and colleagues[6] estimated the ED_{90} of oxytocin to be 0.35 units in patients undergoing elective CD. However, Carvalho's study was single-blinded, oxytocin was administered during delivery of the fetal shoulder, and spontaneous-assisted delivery of the placenta was performed without uterine massage. It is possible that the dose–response of oxytocin occurs independent of these variations in surgical technique.

Sarna and colleagues[12] studied the effect of different oxytocin infusions (total dose range=5–20 units) during elective CD, and observed no differences in the incidence of adequate UT between the high- and low-dose oxytocin regimens. However, the study did not formally assess oxytocin doses <5 units, and drug–responses were likely delayed due to oxytocin delivery by infusion.

No previous investigations have studied the effects of a placebo on UT during elective CD. The relatively high prevalence of adequate UT in the placebo group (73%) at 2 min may be related to the routine use of uterine massage after delivery. Despite the high prevalence of adequate UT in the placebo group, our results do not justify omitting prophylactic oxytocin administration. Nearly 50% of patients receiving placebo required rescue oxytocin during the study period. Numerical scores for UT were also significantly lower in the placebo group compared with the groups receiving either 3 or 5 units oxytocin at 2 and 3 min after administration. These results suggest that prophylactic oxytocin administration and uterine massage are both important. The efficacy of uterine massage was also demonstrated by a previous study in patients after spontaneous vaginal delivery.[13] Uterine massage plus routine active management of the third stage of labour using oxytocin was associated with decreased blood loss and a lesser requirement for additional uterotonics compared with routine active management. The uterine massage technique was not standardized in this study and efficacy of the technique may vary between obstetricians.

Important haemodynamic side-effects have been associated with oxytocin administration. In our study, the incidence of hypotension at 1 min was significantly greater in patients receiving 5 units oxytocin compared with 0 unit. These results are consistent with previous studies that showed maximal decreases in AP and systemic vascular resistance occur within 1 min of oxytocin bolus administration.[14 15] Previous studies have shown that bolus doses of oxytocin ≥5 units are associated with hypotension.[1–3] There were no significant differences in the prevalence of hypotension or tachycardia among the study groups receiving 0.5–3 units.

Other oxytocin-related side-effects (nausea, vomiting, and flushing) occurred rarely in our study, which is in contrast to the study by Carvalho and colleagues[6] which noted high rates for each side-effect (38%, 13%, and 63%, respectively). These findings may be related to differences in the speed of injection of oxytocin [slower injection time in our study (15 s)] and subsequent drug onset time. We found no differences in estimated blood loss or HCT values (pre- or post-CD) among the study groups; however, it is likely that rescue doses of oxytocin prevented prolonged periods of uterine atony and excessive

blood loss in patients with inadequate UT. Mean total blood loss values (estimated blood loss+weight of blood on surgical swabs) were higher than expected in all study groups (>1000 ml). However, no patients had postoperative HCT values <24%, and no patients required red cell transfusion or required surgical intervention to treat refractory uterine atony. The visual assessment of blood loss in the suction chamber and on surgical swabs is commonly utilized to estimate blood loss, although these subjective assessments of blood loss are known to be inaccurate.[16]

We acknowledge that there are several limitations to our study. Calculation of the ED_{50} and ED_{95} of oxytocin was not possible due to the high prevalence of adequate UT at 2 min after placebo and low boluses of oxytocin (0.5–1 unit). As a result, the small sample sizes in our study limit data interpretation of observed between-group differences in UT. In addition, the analyses of the oxytocin response and side-effects ≥2 min after administration may have also been confounded by patients receiving rescue doses of oxytocin; however, for ethical reasons, we could not allow inadequate UT and bleeding to persist untreated. The assessment of UT in our study was performed by attending obstetricians; however, there are no clinically validated or objective methods for assessing UT. Subjective assessments have been utilized in previous studies assessing UT during CD.[5 6 12]

In summary, our results show that small bolus doses of oxytocin (0.5–3 units) are associated with a high prevalence of adequate UT at 2 min in patients undergoing elective CD. Although adequate UT is possible with uterine massage and no oxytocin administration, this outcome can be more successfully achieved using oxytocin. We believe that the routine use of 5 units oxytocin during elective CD can no longer be recommended, as adequate UT can occur with lower bolus doses of oxytocin (0.5–3 units) and important cardiovascular side-effects (notably hypotension) can also be minimized. Further work is necessary to assess optimal modes of oxytocin administration to achieve and maintain UT during CD in healthy patients and patients at-risk of developing uterine atony.

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