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AN OBSERVATIONAL COHORT STUDY OF 3 UNITS VERSUS 5 UNITS SLOW INTRAVENOUS BOLUS OXYTOCIN IN WOMEN UNDERGOING ELECTIVE CAESAREAN DELIVERY

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This study sought to compare postpartum blood loss and maternal outcomes after 3IU and 5IU oxytocin at elective caesarean delivery. In a prospective observational study, 73 women undergoing elective caesarean delivery under spinal anaesthetic received a slow I.V. injection of either 3IU (n = 35) or 5IU (n = 38) oxytocin after delivery. The main outcome was gravimetrically measured 24-hour postpartum blood loss with a non-inferiority margin of 300 mL. Uterine tone, phenylephrine dose, emesis and hypotension after oxytocin administration were secondary outcomes. Gravimetric postpartum blood loss was lower in the 3IU group (–58.8 mL [95% CI: –212.1, 94.3]) after adjusting for BMI, pre-delivery vasopressor dose, parity, and risk of uterine atony, with the upper confidence limit below the 300 mL margin in support of non-inferiority. Patients receiving 3IU had a higher (non-significant) rate of having post-delivery phenylephrine to treat hypotension (RR = 1.59 [95% CI: 0.97, 2.63]), but of those treated, the 3IU group required significantly less (–427 mcg [95% CI: –740, –114]). The 3IU group had a lower prevalence of vomiting compared to those receiving 5IU (6% versus 24%; P = 0.047). Administration of 3IU oxytocin was non-inferior compared to standard 5IU with respect to blood loss in women undergoing elective caesarean delivery.

Key words: *caesarean section, childbirth, oxytocin, postpartum haemorrhage, vasoconstrictor agents, vomiting, uterus*

INTRODUCTION

The optimal dosing of oxytocin at the delivery of the placenta in patients undergoing elective caesarean delivery is of critical importance to attain a favourable balance between effective uterine contraction to limit postpartum haemorrhage and oxytocin-induced adverse events. Uterine atony is a major risk factor for severe obstetric haemorrhage, the main cause of maternal deaths internationally (1-3). With more than 25% of babies born in Organisation for Economic Co-operation and Development countries *via* caesarean delivery (4) evidence based strategies to limit postpartum haemorrhage are urgently needed. Conversely, oxytocin causes a dose-related increase in emetic symptoms (5) and heart rate (6) and a decrease in arterial pressure (7, 8), which in rare cases, have been associated with maternal cardiovascular collapse causing death in hypovolemic patients (9). The National Institute of Health and Care Excellence guidelines recommend administration of 5IU as a 'slow bolus' at caesarean section (10). This recommendation is centred on extrapolation from 5 relatively small studies, none of which compared the effect of 5IU oxytocin with lower oxytocin doses (11-15).

The recommended dose of 5IU might be significantly higher than required for maintenance of optimal uterine tone as there are several lines of evidence to suggest that the uterus is highly sensitized to oxytocin during caesarean delivery. Firstly, uterine myometrial oxytocin receptor concentration increases considerably during pregnancy until term when there are 12-fold more receptors present (16). Secondly, it has been shown that oxytocin receptors are maximally sensitized at term due to receptor protein augmentation and increased expression of receptor RNA (17). These data could explain why oxytocin doses as low as 0.35 IU is effective for adequate uterine contraction in non-labouring women undergoing elective caesarean delivery (18). Thus, when decisions are based on the current guidelines for oxytocin administration there may be a risk of overtreatment, whereas reducing the oxytocin dose may lower the need for vasopressor intervention to treat hypotension and the risk of adverse events.

In this study we sought to determine whether low dose oxytocin at 3IU was non inferior to the recommended 5IU dosage with respect to 24 hour postpartum blood loss in women undergoing elective caesarean delivery. Further, we sought to determine if 3IU oxytocin was superior to 5IU regarding: 1) uterine tone 3 minutes after oxytocin administration; 2) reduced vasopressor requirements and 3) reduced oxytocin-induced adverse events.

MATERIAL AND METHODS

Study design

This was an observational, open label cohort study conducted at the Royal Hobart Hospital, Tasmania, between July 2011, and May, 2013. Although not a randomised clinical trial, this study was retrospectively registered (Australia New Zealand Clinical Trial Registry Number 12616000398404) and approved by the University of Tasmania Human Research Ethics Committee. Study registration facilitates public reporting, completes the set of evidence and helps prevent publication bias which favours positive or statistically significant results (19). The Department of Obstetrics and Gynaecology at the Royal Hobart Hospital endorsed the study protocol. All participants provided written informed consent after receiving a verbal explanation and reading the patient information and consent form, which include the potential risks of study participation. The study have been carried out in accordance with the Declaration of Helsinki.

Participant characteristics and flow

Women undergoing elective caesarean delivery under spinal anaesthesia were recruited. Inclusion criteria were: ASA I - II, term pregnancy (> 38 weeks) including twins, aged 18 to 40 years and scheduled for elective caesarean delivery. Exclusion criteria were: clinical history of hypertensive disorders (pre eclampsia; chronic hypertension), haemodynamic instability during pre assessment prior to caesarean delivery (systolic blood pressure < 100 mmHg), bleeding diastasis (thrombocytopenia with a platelet count less than 100 000 platelets per microliter, coagulopathies) and history of uterine atony causing post-partum haemorrhage (by interviewing the patient and by evaluating the digital medical record of their previous deliveries). One hundred and nine potentially eligible women were approached to participate in the study and flow of participants is presented in *Fig. 1*.

Primary outcome

Twenty four hour postpartum blood loss utilising a gravimetric measurement technique was chosen as the primary outcome because it has been found to be highly concordant with the gold standard spectrophobic Hb analysis (20). Adherence to a strict blood collection protocol was employed to keep unaccounted blood loss to the minimum (20). Trained research nurses performed the gravimetric measurement protocol: at the delivery amniotic fluid was carefully suctioned first, followed by switching the suction to another bottle in order to independently collect the blood and minimise amnion fluid contamination. Sucker bottles were transparent with measurement marks in millilitres. Plastic drapes with pockets were used to collect blood. All swabs had a standardised weight and were weighed postoperatively on the same calibrated scale. Sanitary pads utilised during the first 24 hours postoperatively were collected and weighed, with 1 g weight gain equivalent to a 1 ml blood loss.

Sample size calculations were based on blood loss data from Sheehan *et al.* (21) (mean ± S.D., 843 ± 487 ml) and an inferiority

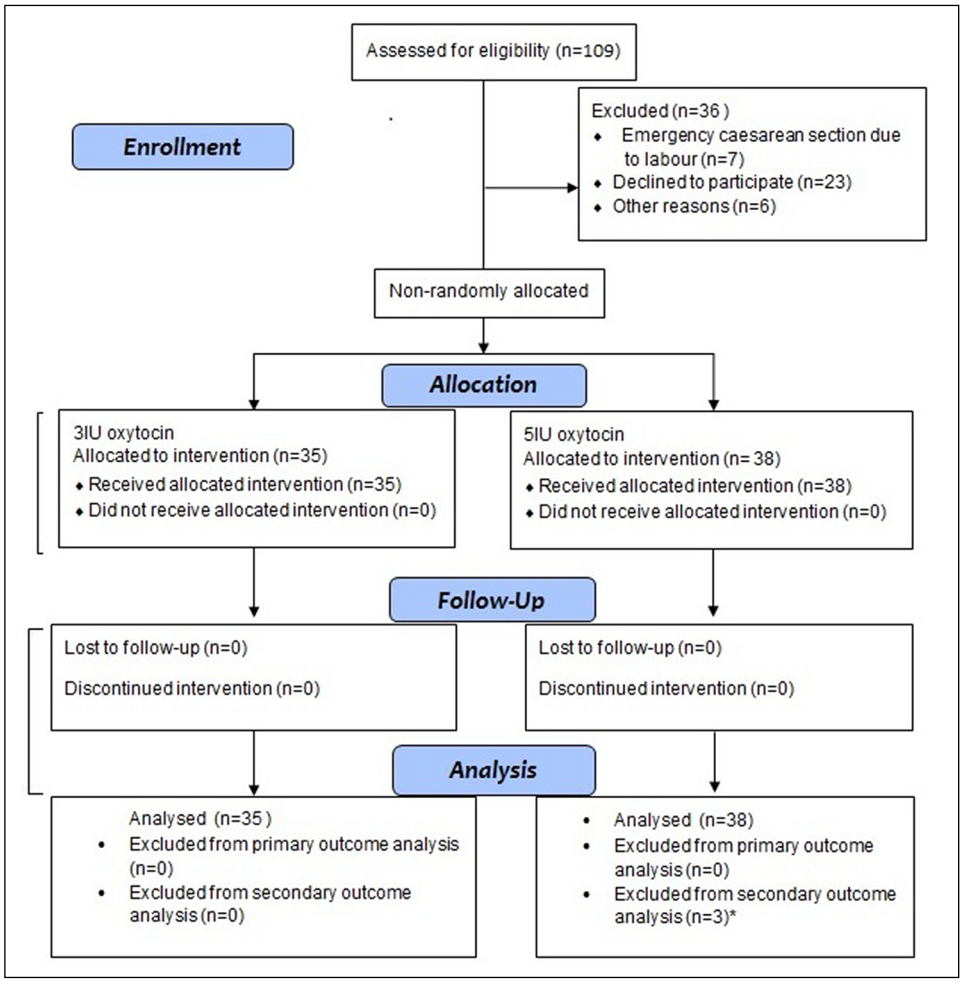

Fig. 1. Participant flow diagram. *Vasopressor infusion was not immediately discontinued at delivery as specified by protocol in 3 patients in 5IU oxytocin group.

margin of 300 ml deemed as clinically significant. With $\beta = 0.20$ and $\alpha = 0.05$, 33 patients were required for each group to ensure that the upper limit of a one-sided 95% confidence interval would be below the non-inferiority limit of 300 ml.

Secondary outcomes

There were five secondary outcomes after oxytocin administration: 1) adequacy of uterine tone at 3 minutes ; 2) need for additional uterotonic agents in the first 30 minutes after delivery ; 3) cumulative phenylephrine dose between the time points of oxytocin administration and the completed uterine closure; 4) vomiting, defined as the ejection of stomach content or dry retching and; 5) hypotension, defined as a mean arterial pressure (MAP) ≤ 65 mmHg in the first 10 minutes after oxytocin administration.

Study procedures

The anaesthesia technique was standardised for all patients. On arrival to theatre a 16G cannula was secured and 2 g cephazolin administered. Non-invasive monitoring included pulseoximetry and ECG. Brachial BP was recorded by automated device (Datex-Ohmeda S/5 Anesthesia Monitor, GE Healthcare, 572 Swan Street, Victoria, Australia) under resting conditions. Baseline MAP was calculated as the mean of 5 MAP readings, 2.5 minutes apart with patients in the supine left lateral table tilt position.

All patients were co-loaded with 1000 ml of crystalloid with non-invasive blood pressure cycling in 3 minute intervals. Spinal anaesthesia was established in the sitting position at the L3/4 or L4/5 level using a 25G pencil point needle. A combination of 11 mg 0.5% hyperbaric bupivacaine with 10 mcg fentanyl and 125 mcg morphine was injected intrathecally. Patients were immediately positioned supine, with 15 degree left lateral table tilt and non-invasive blood pressure cycling in 1 minute intervals. Simultaneously, a phenylephrine infusion was commenced at 50 mcg per minute and adjusted accordingly to maintain MAP within 10% of baseline. Intraoperative hypotension, with a MAP threshold of 65 mmHg, was treated by 50 to 100 mcg boluses of phenylephrine.

Surgery commenced when the sensory block reached T4 to cold sensation. The surgical procedure was standardised to allow uterine closure in two layers and avoiding exteriorization of the uterus unless clinically indicated. At umbilical cord clamping either 3IU or 5IU oxytocin as a slow bolus over 60 seconds was administered and further haemodynamic data was recorded. The study followed a pragmatic approach similar to real world anaesthetic practice by allowing the attending anaesthetists to determine the administered dose. The dose was decreased to avoid hypotension primarily. Previous work indicate that quick bolus administration of 5IU oxytocin result in occurrence of hypotension in 45% of patients; whereas 3IU has a lower prevalence of up to 25% (22). Each attending anaesthetist diluted the 3IU or 5IU oxytocin with 0.9% saline to a total of 5 ml ensuring that patients, research nurses and obstetricians were blinded to the treatment dose. The obstetricians and anesthesiologists were blinded to the primary outcome.

Only fully qualified obstetricians or senior trainees with at least 5 years' experience assessed uterine tone every 3 minutes by palpation until uterine closure. Inadequate uterine tone was treated using the following standardised protocol as recommended by the guidelines from the Royal College of Obstetricians and Gynaecologists on the prevention and treatment of postpartum haemorrhage: oxytocin 5IU over 60 seconds, ergometrine 250 ug IVI, oxytocin 40IU in 1000 ml normal saline at 250 ml/hour and 5-methyl prostaglandin F2-alpha (Hemabate; carboprost) 250 mcg intramyometrial (23). A research nurse recorded both nausea and vomiting as binary outcomes, which included dry retching (yes/no). A visual analogue scale was not employed to determine the severity.

Table 1. Baseline demographic and clinical characteristics of study participants before oxytocin administration. Values are mean (S.D.) or numbers (proportion). IU; international units.

Variable		Standard Oxytocin 5IU (n = 38)	Low-dose Oxytocin 3IU (n = 35)	P-value
Age (years)		29.6 (5.5)	30.4 (5.3)	0.467
Gestation (weeks)		38.8 (0.51)	38.9 (0.48)	0.188
Parity (n)				0.047
	0	1 (2.6%)	5 (14.3%)	
	1	27 (71.1%)	14 (40.0%)	
	2	7 (18.4%)	11 (31.4%)	
	3+	3 (7.9%)	5 (14.3%)	
Body mass index (kg/m^2)		30.0 (7.0)	28.2 (7.3)	0.287
Smoking status (current or former) (n)		8 (21.1%)	11 (32.4%)	0.277
Risk factor for uterine atony (n)		7 (18.9%)	10 (28.6%)	0.335
Vomiting (n)		0	0	1.00
Hematocrit (%)		0.36 (0.03)	0.35 (0.02)	0.629
MAP before oxytocin (mmHg)		96.2 (10.1)	95.7 (7.7)	0.823
Heart rate before oxytocin (beats min^{-1})		83 (11)	84 (10)	0.745
Phenylephrine dose before oxytocin (mcg)		1281 (448)	1268 (425)	0.905

Statistical analysis

Descriptive statistics of the study groups at baseline; means and standard deviations or 95% confidence intervals (95% CI) are presented except where indicated. Geometric means and standard error of the mean (S.E.M.) are presented for skewed outcomes. Group differences were assessed using the two sample equal-variance t-test and chi-squared or Fisher exact tests where required. The primary outcome was regressed on oxytocin dose (3IU versus 5IU) adjusted for BMI, pre-delivery vasopressor dose, parity and the presence of a uterine atony risk factor. A logarithmic transformation of the outcome variable was required after assessment of model residuals, back-transformed (geometric) means and 95% confidence intervals are presented, and these limits were used to assess non-inferiority. Post-delivery administration of vasopressor dose was analysed in two-stages; no transformation was suitable since 40 participants did not receive any post-delivery vasopressor. Firstly, post-delivery vasopressor use was analysed using log-binomial regression to estimate the risk of usage between treatment groups. Further, only those who received vasopressor post-delivery were analysed separately using linear regression after logarithmic transformation to estimate the difference in dose between treatment groups, back transformed estimates are presented. Both models were adjusted for BMI, pre-delivery vasopressor dose, parity and the presence of a risk factor for uterine atony. Propensity weighting was used in all regression models to adjust for the non-random allocation of participants to treatment groups. A logistic regression model with the covariates; age, weight, previous caesarean section, seniority of obstetrician, seniority of anaesthetist, was used to generate propensity weights. All patients received their allocated treatment intervention, with one minor protocol violation regarding vasopressor administration. We conducted all analyses on an intention to treat basis (ITT); a sensitivity analysis was further conducted on a per-protocol (PP) basis to examine the effect of the protocol violation. All models were checked for violation of model assumptions. A P-value of 0.05 was considered significant. Data were analysed using SPSS statistics 21 (IBM, Armonk, NY), and STATA 12.1 (StataCorp LP, Texas, USA).

RESULTS

Patient characteristics and flow

A total of 73 patients were enrolled. Of these patients, 35 received 3IU oxytocin and 38 received 5IU. *Table 1* presents the characteristics of the study patients. All patients had a singleton pregnancy except for one in the 5IU group who had a twin pregnancy. There were no significant between-group differences in MAP, emetic signs or vasopressor requirements before oxytocin administration (P > 0.11 for all). There was a minor protocol violation occurring among 3 women in the 5IU group where the vasopressor infusion post-delivery was not immediately ceased. *Table 2* details the unadjusted primary and secondary outcome data after oxytocin administration.

Primary outcome

Gravimetric postpartum blood loss was lower in the 3IU group (–58.9mL [95% CI: –212.1, 94.3]) after adjusting for BMI, pre-delivery vasopressor dose, parity, and risk of uterine atony (*Table 3*). The upper 95% confidence limit for the adjusted difference between 3IU and 5IU (below) does not include the clinically important blood loss difference of 300 ml, indicating non-inferiority. The adjusted analysis identified BMI as a statistically significant predictor of gravimetrically measured blood loss: 18.3mL (95% CI: 8.0, 28.6; P = 0.001) per kg/m^2 (*Table 3*). On the per-protocol analysis the gravimetric blood loss was –28.3mL [95% CI: –167.4, 110.8]

Secondary outcomes

All women had adequate uterine tone 3 minutes after oxytocin administration (P = 1.00), however there was a high prevalence of

Table 2. Outcome data after oxytocin administration at 3IU compared with 5IU. Geometric mean and SEM are presented for skewed data. Values are number (proportion).

Variable	Standard Oxytocin 5IU (n = 38)	Low-dose Oxytocin 3IU (n = 35)	P-value
Unadjusted mean gravimetric blood loss (ml)*	689 (53.7)	655 (53.3)	0.661
Nausea	23 (62.2 %)	15 (42.9%)	0.101
Vomiting	9(24.3%)	2 (5.7%)	0.047†
Chest pain	3 (8.1%)	0 (0.0%)	0.240†
SOB	2 (5.4%)	1 (2.9%)	1.000†
Headache	2 (5.6%)	3 (8.6%)	0.674†
Flushing	7 (18.9%)	9 (25.7%)	0.488
Patients who received phenylephrine after oxytocin administration	14 (36.8%)	19 (54.3%)	0.135
Total phenylephrine dose after oxytocin administration in the those patients who received phenylephrine (mcg)*	500 (135)	103 (24)	0.001
Adequate uterine tone at 3 minutes after oxytocin administration	38 (100%)	35 (100%)	1.00
Uterotonic use after oxytocin administration	19 (50.0%)	16 (45.7%)	0.814

†Fishers exact test used for these analyses, *Geometric mean and S.E.M. for skewed data.

Table 3. The effect of oxytocin group (3IU and 5IU) on gravimetric blood loss as determined by multiple regression adjusted for BMI, pre-delivery vasopressor and risk of uterine atony after propensity adjustment (back-transformed coefficients shown).

Model variables	Beta	95% CI	P-value
Oxytocin dose (3IU/5IU)	–58.9	–212.1, 94.3	0.446
Body mass index (kg/m^2)	18.3	8.0, 28.6	0.001
Pre-delivery vasopressor dose (mcg)	0.082	–0.104, 0.268	0.381
Risk uterine atony (Y/N)	67.8	–105.0, 240.7	0.425
Parity (per additional birth)	–38.6	–94.2, 16.9	0.176

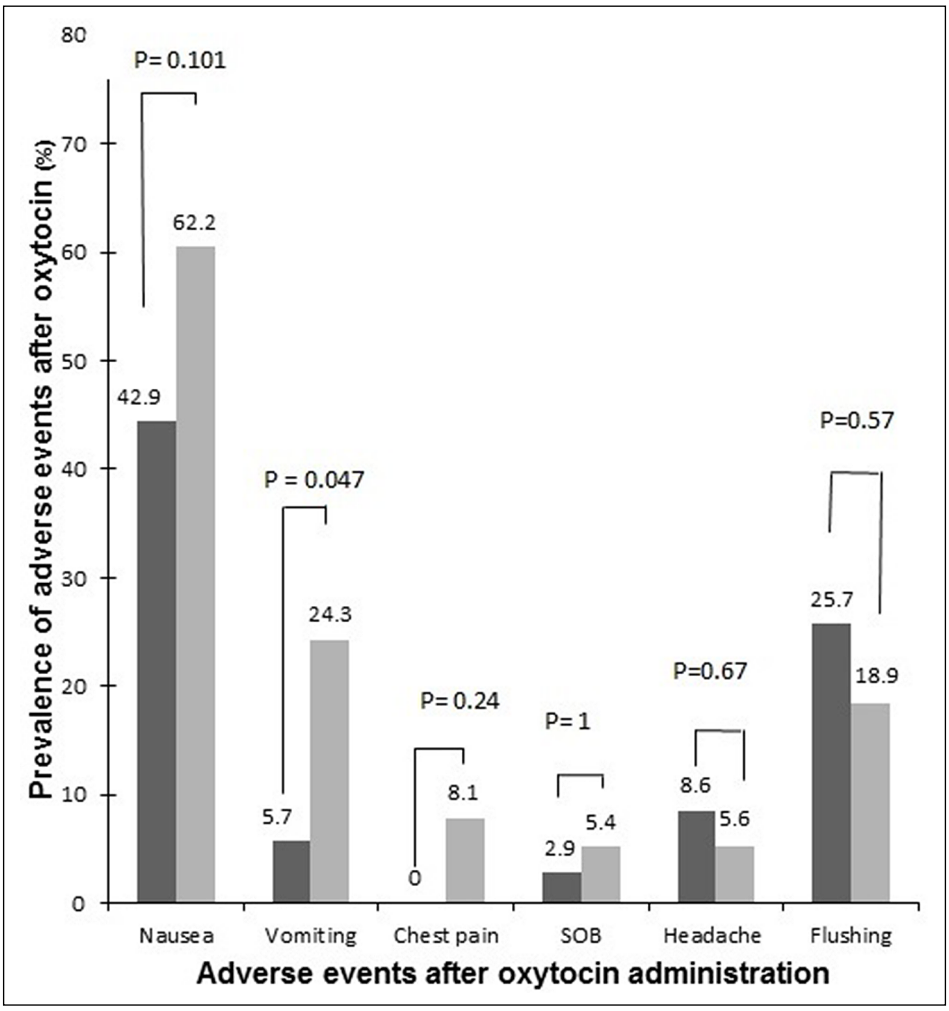

Fig. 2. Prevalence of adverse events after oxytocin administered at 3IU (dark grey square) compared with 5IU (light grey square). Women in the 3IU oxytocin group were less likely to vomit compared to those who received 5IU (P < 0.05). There was no significant difference between the groups in the prevalence of nausea, chest pain, shortness of breath (SOB) or flushing (P > 0.05).

subsequent additional uterotonics including ergometrine 250 µg IVI, oxytocin 40 IU in 1000 ml normal saline at 250 ml/hour and 5-methyl prostaglandin F2-alpha 250 mcg intramyometrial was used in both groups (3IU: 49% [17/35] versus 5IU: 50% [19/38]). This difference was not significant between groups (RR = 0.99 [95% CI: 0.59, 1.67; P = 0.974]). No factor in the sample was predictive of additional uterotonic agent use.

Vasopressors

Women in the 3IU oxytocin group were more likely (not-significant) to receive post-delivery phenylephrine (RR = 1.59 [95% CI: 0.97, 2.63]; P = 0.068), but of those women who had phenylephrine post-delivery the 3IU oxytocin group required a significantly lower dose in comparison to the 5IU oxytocin group (–427.1 mcg [95% CI: –740.3, –113.9]; P < 0.001), adjusted for BMI, pre-delivery vasopressor, parity and uterine atony risk. These outcomes were relatively unchanged on the per-protocol analysis; risk of phenylephrine (RR = 1.77 [95% CI: 1.04, 3.00]; P = 0.034) and phenylephrine dose (–358.4 mcg [95%CI: –657.6, –59.2]; P < 0.001). There was no significant difference between the groups in the prevalence of hypotension (P = 0.89) (*Table 3*).

Vomiting and nausea

Women in the 3IU oxytocin group were significantly less likely to vomit compared to those who received 5IU (*Fig. 2*, P = 0.047). None of the women who were excluded due to the protocol violation vomited (PP analysis 3IU: 6% [2/35] versus 5IU: 26% [9/34], P = 0.023). There was no significant difference between the groups in the prevalence of nausea (P = 0.101);

however, the per-protocol analysis showed a significantly higher prevalence of nausea in the 5IU group (3IU: 43% [15/35] versus 5IU: 68% [23/34], P = 0.038).

DISCUSSION

The principle finding of this study was that 3IU (low dose) oxytocin, as compared to 5IU (recommended dose), was non-inferior with respect to the primary outcome of postpartum blood loss. Administration of 3IU resulted in significantly lower prevalence of vomiting and vasopressor requirements in those women who required vasopressor intervention whilst maintaining effective blood pressure control and uterine tone. Altogether these findings suggest that 3IU oxytocin can be considered effective for routine clinical use in women presenting for elective caesarean delivery.

The first indication that very low oxytocin doses were effective in elective caesarean delivery was provided in a study on 20 women by Zarzur who found that 3IU oxytocin in 500 ml 5% dexstrose solution, administered after delivery at 0.024 IU per minute (1.44 IU per hour) provided a satisfactory outcomes with no hypotension, nausea or vomiting (24). Unfortunately the sample size was too small to draw firm conclusions. Subsequently it was found that 0.35 IU (95% CI 0.18 – 0.52IU) was effective in producing adequate uterine contraction in 90% (ED90) of non-labouring women (n = 40), suggesting that oxytocin doses could be significantly reduced in elective caesarean delivery (18). Results from other studies in non-labouring women undergoing elective caesarean suggest that adequate uterine tone can be achieved with small doses between 0.5IU and 3IU (5, 22). This is concordant with this current study. Further studies should be conducted to confirm these findings and to assess the effectiveness of lower than guideline recommended oxytocin doses in the setting of emergency caesarean section.

A clear benefit of using lower oxytocin doses is the reduction of adverse events specifically related to nausea and vomiting. Sartain *et al.* found that intravenous bolus administration of 5IU over 5 to 10 seconds caused more nausea in comparison to 2IU over 5 to 10 seconds oxytocin in 80 non labouring women undergoing elective caesarean delivery [5IU 33% (13/40) versus 5% (2/40); P = 0.003] (5). In that study, despite not finding a significant difference in the occurrence of vomiting between the groups, it is of note that the trend was towards a higher prevalence in the 5IU group [5IU 15% (6/40) versus 2IU 3% (1/40); P = 0.1] (5). In comparison, our study examined the effects of oxytocin administered as a slow bolus over 60 seconds, and while vomiting was increased with 5IU, there was no significant between-group difference in nausea (albeit the per-protocol analysis showed a significantly higher prevalence of nausea in the 5IU group).

A further advantage of administering a lower oxytocin dose is the drop in the quantity of vasopressor needed to treat oxytocin induced hypotension. The low oxytocin group required significantly less phenylephrine in order to control blood pressure after oxytocin administration. Largely these outcomes further support the consideration of lower oxytocin doses as the standard of care in elective caesarean delivery.

The observation that low doses of oxytocin are clinically effective should be viewed in light of the complexity of hormonal regulation and actions including those of oxytocin during pregnancy. As illustration, it should be noted that oxytocin and steroid hormones have been shown to have modulatory effects, which influence the uterine expression of aquaporins in pregnant experimental animals during gestation (25). Furthermore, a unique association exists between adiponectin and the expression of acute regulatory protein and reproductive hormones in porcine uterus factors stimulated by insulin (26). Finally, an interrelationship between puerperal bovine uterine health status and the frequent development of endometritis of bacterial origin reflect the expression of proinflammatory cytokines (27). These additional mechanistic subclinical and clinical observations in both patients and experimental animals add more physiological and pharmacological information to the present work and explain various aspects of complexity of pregnancy and hormonal regulation both *in vivo* and *ex vivo*.

Limitations

Oxytocin 5IU is the standard of practice in our obstetric unit and 3IU oxytocin was considered a significant deviation from the standard practice. Therefore, a non-randomised controlled trial design was used. Even though measures were taken to minimize error from numerous potential sources (i.e. blinding of all investigators, anesthesiologists and obstetricians to the study-endpoints; propensity score matching analysis) and there were no differences in clinical characteristics between groups, the observational design may have introduced error.

Conclusions

To our knowledge, this is the first study powered to detect whether low dose (3IU) is non-inferior to recommended dose oxytocin (5IU) regarding 24-hour blood loss administered as a slow bolus in patients undergoing elective caesarean delivery. This study found that administration of 3IU oxytocin was non-inferior to the current standard of 5IU with respect to blood loss in women undergoing elective caesarean delivery. Moreover, 3IU oxytocin reduced the need for vasopressors and the prevalence of vomiting. Importantly the initial bolus was not followed by an oxytocin infusion. These findings suggest that lowering the oxytocin dose to 3IU may be considered effective for routine clinical use in patients undergoing elective caesarean delivery.

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Conflict of interest: None declared.

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