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Research Article

To estimate the minimum effective dose of oxytocin required to produce adequate uterine tone in women undergoing elective caesarean delivery

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Abstract To estimate the minimum effective dose of oxytocin required to produce adequate uterine tone in women undergoing elective caesarean delivery under spinal anaesthesia.

Background: Patients undergoing caesarean delivery are at increased risk of obstetric haemorrhage. Uterine atony has been shown to be most common aetiology (30%) for PPH in patients undergoing caesarean delivery. Use of uterotonic agents decreases the incidence of PPH by approximately 40% when compared with placebo. Oxytocin is the most frequently used uterotonic agent because of less side-effects compared with all other available agents. We did the study to find out the minimal dose of oxytocin required to produce adequate uterine tone (UT) in primigravida women undergoing elective caesarean delivery.

Methods: This randomized double blind study was conducted in ninety full term primigravidas undergoing elective caesarean delivery under spinal anaesthesia. All patients received intravenous bolus of either 0.5, 1, or 2 unit oxytocin followed by infusion of 10 unit/h. UT was assessed by a blinded obstetrician as either adequate or inadequate, and using a five point scale, where 1 = atonic, 2 = partial but inadequate contraction, 3 = adequate contraction, 4 = well contracted and 5 = very well contracted at 2, 3, 6, and 9 min after oxytocin administration. Minimum effective doses of oxytocin were analysed. 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 (86%, 90% and 93% for, 0.5, 1 and 2 unit oxytocin, respectively). The prevalence of nausea and vomiting was significantly higher after 2 unit oxytocin vs 0.5 unit at 1 min (13% vs 3%).

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Conclusion: Small bolus dosages of oxytocin (0.5–2 unit) result in adequate uterine tone in primigravida women undergoing elective caesarean delivery with minimal effects on haemodynamic parameters and less incidence of nausea and vomiting.

1. Introduction

Oxytocin administration is initiated immediately after umbilical cord clamping at caesarean delivery. Though changes in haemodynamics following caesarean delivery can be because of removal of aortocaval compression, autotransfusion from uterine contraction, blood loss, use of vasopressors and emotional excitement; oxytocin has been shown to play a major role [1,2]. Oxytocin is the first line of drug for prophylaxis and treatment of uterine atony. It is administered in a wide range of doses and timing patterns. Oxytocin is the most frequently used uterotonic agent because of less side-effects compared with all other available agents.

The British National Formulary presently recommends that oxytocin should be administered in a 5-IU dose by a slow intravenous injection after delivery during caesarean section [3]. In the US, an infusion of 10 unit at the rate of 0.02–0.04 IU/min is recommended for postpartum haemorrhage. A slow intravenous bolus of 5 units of oxytocin is commonly used by obstetricians and anaesthetists (86% and 92% respectively) during caesarean delivery in UK [4]. A 5 unit intravenous bolus of oxytocin is also associated with significant side effects such as hypotension, tachycardia, flushing and chest pain [1,2]. Safety and efficacy data are lacking to support the routine dose of a 5 unit bolus of oxytocin as a standard during elective caesarean delivery. Although some authors have commented that decreasing or omitting oxytocin bolus diminishes the haemodynamic changes [1,2], but some may concern about poor uterine tone and resultant increased bleeding [4]. In a recent publication, the authors have reviewed an approach to dosing and choices of uterotonic agents for limitation of PPH [5]. Recently in an editorial by Tsen and Balki it has been suggested that oxytocin should be used in initial doses of less than 5 unit slowly followed by an initial rapid infusion of oxytocin followed by a maintenance infusion. Dosages of these infusions should be low. The authors further suggested a ''rule of 3''oxytocin protocol during caesarean delivery [6].

As the magnitude of side effects are dose related it appears prudent to use the minimum effective dose of oxytocin.

2. Methods

After approval of ethical committee ninety full term primigravidas age between 18 and 35 years belonging to American Society of Anesthesiologists (ASAs) physical status I and II, having singleton pregnancies undergoing elective caesarean delivery with Pfannensteil incision under spinal anaesthesia were included in the study. Patients having any contraindications for spinal anaesthesia, active labour or with ruptured membranes, known drug allergy to oxytocin, significant obstetric disease such as pregnancy-induced hypertension or pre-eclampsia, known risk factors for postpartum haemorrhage such as abnormal placentation or uterine fibroids, polyhydraminos, oligohydraminos and diabetes mellitus were excluded from the study.

All the patients were examined a day before surgery and subjected to complete general physical as well as systemic examination. Routine investigations such as haemoglobin, bleeding time, clotting time and urine examination were carried out in all the patients. The purpose and protocol of the study was explained to patients and informed written consent was obtained. Patients were kept fasted for 6 h and premedicated with tablet ranitidine 150 mg orally the night before and on the morning 2 h before surgery. Upon arrival in operating room usual monitoring including non-invasive blood pressure, EKG and pulse oximetry were established. Intravenous line was secured with an 18G venous cannula and base line haematocrit was taken. Patients were preloaded with 10 ml kg^{-1} of Ringer lactate solution. Baseline maternal heart rate (HR) and non-invasive blood pressure (NIBP) were recorded as the average of three readings. The patients were divided randomly into three groups of 30 patients each using Microsoft Excel generated allocations. Opaque envelopes containing group assignments were used to ensure blinding. Group 1 (n = 30) patients received 0.5 unit of oxytocin intravenous bolus. Group II (n = 30) patients received 1 unit of oxytocin intravenous bolus. Group III (n = 30) patients received 2 unit of oxytocin intravenous bolus. All patients were given spinal anaesthesia in sitting position in L3/L4 or L4/L5 space with 25G Quincke spinal needle with 1.5 ml of 0.5% hyperbaric bupivacaine with 25 μg of fentanyl. Patients were laid supine with wedge under the right flank to achieve leftward tilt of 15°. Surgery was commenced once the block height reached T_4 to cold perception using ice. The oxytocin dose was prepared before surgery and diluted with 0.9% normal saline up to a total volume of 5 ml by a doctor not involved in the care of the patient or any data recordings, so that each anaesthetist and obstetrician were blinded to oxytocin dose. Oxytocin was administered as an intravenous bolus over a time period of 15 s after clamping of the umbilical cord and delivery of the foetus. After delivery of placenta uterine tone was assessed by the obstetrician at 2, 3, 6, and 9 min interval on a five-point scale, where 1 = atonic, 2 = partial but inadequate contraction, 3 = adequate contraction, 4 = well contracted and 5 = very well contracted [14]. As per our institutional protocol uterine massage was not done and uterus not exteriorised. If the tone was assessed as inadequate at 2 min, a 'rescue' bolus of 2.5 units of oxytocin was administered. A maximum of two 'rescue' doses of oxytocin were permitted in the event of two separate recordings of inadequate uterine tone. If uterine tone was assessed as inadequate after two rescue doses of oxytocin, then additional uterotonic drugs were administered in following order: intravenous methylergometrine 0.2 mg, intramuscular carboprost tromethamine 0.25 mg and then rectal misoprostol 800–1000 mg. After adequate uterine tone had been achieved, maintenance infusion of oxytocin

was then started (20 units of oxytocin in 500 ml 0.9%normal saline at 250 ml/h [0.16 units/min]). Measurement of NIBP and HR were taken at 2 min intervals from the time of oxytocin administration. Hypotension was defined as a decrease in mean blood pressure $\geqslant$10% of the baseline value, and each episode of hypotension was treated with an intravenous bolus of 3 mg of ephedrine. Tachycardia was defined as maternal HR $\geqslant$ 120 beats min^{-1} or $\geqslant$10% of the baseline value.

The primary study outcome measure was the assessment of either adequate or inadequate uterine tone at 2 min after administration of the initial oxytocin dose. Secondary endpoints included the number of rescue doses of oxytocin, use of additional uterotonic agents, intraoperative blood loss (measured by estimating blood collected by suction and by calculating the weight of blood on surgical swabs), haematocrit values measured before surgery and within the first 30 min after completion of surgery. Any side effects associated with oxytocin such as tachycardia, hypotension, nausea, vomiting, chest pain, headache and flushing were recorded.

At the end of study all the data was compiled and analysed statistically using analysis of variance (ANOVA) test for haematocrit, need for additional uterotonic agents and the amount of blood loss. Chi-square test was used to analyse HR, NIBP and the side effects of oxytocin.

3. Results

Ninety patients were randomised and all completed the study. Patient characteristics i.e. age, weight, haemodynamic parameters before oxytocin infusion among the group were comparable as shown in Table 1. The percentage of patients with adequate UT at 2 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 (P value $>$ 0.05).There were no significant difference in the total number of rescue doses of oxytocin and additional uterotonic drugs used as shown in Table 3. There was significant difference in incidence of nausea and vomiting in group III as compared to group I as shown in Table 2.II. Blood loss in all three groups is shown in Table 3, Table 4 shows preoperative and postoperative haematocrit. The results of both are statistically comparable in all groups. No significant hypotension and tachycardia occurred in any patient in any group as shown in Tables 5 and 6. Also there was no incidence of chest pain, headache, flushing or any ECG changes in any patient.

Table 1 Demographic data.

Group	Weight in kgs (mean ± SD)	Age in years (mean ± SD)
I (n = 30)	62.20 ± 2.47	21.90 ± 2.28
II (n = 30)	60.83 ± 3.31	22.00 ± 1.93
III (n = 30)	61.90 ± 4.36	22.13 ± 2.31

Table 2 Study parameters.

Group	Adequate UT at 2 min	RDO	AUD	Nausea and vomiting
I (n = 30)	26	5 (86%)	1	1
II (n = 30)	27	4 (90%)	0	2
III (n = 30)	28	3 (93%)	0	4

RDO: rescue doses of oxytocin.
AUD: additional uterotonic drugs.

Table 3 Estimated blood loss in the three groups.

Group	Blood loss in ml (mean ± SD)
I (n = 30)	840.60 ± 110.44
II (n = 30)	815 ± 108.59
III(n = 30)	786.5 ± 128.79

Table 4 Preoperative and postoperative haematocrit.

Group	Preop Hct (mean ± SD)	Postop Hct (mean ± SD)
I (n = 30)	29.166 ± 1.80	24.51 ± 2.42
II (n = 30)	28.9 ± 2.36	24.33 ± 2.68
III (n = 30)	29.03 ± 2.34	24.45 ± 2.64

Table 5 Heart rate at time of delivery and 2 min after oxytocin bolus.

Group	HR in beats/min at time of delivery (mean ± SD)	HR in beats/min 2 min after oxytocin bolus (mean ± SD)
I (n = 30)	90.76 ± 8.240	96.63 ± 9.942
II(n = 30)	89.55 ± 6.3555	95.70 ± 6.654
III(n = 30)	90.06 ± 6.113	97.46 ± 6.640

Table 6 Mean arterial pressure at time of delivery and 2 min after oxytocin bolus.

Group	MAP (mmHg) at time of delivery (mean ± SD)	MAP (mmHg) 2 min after oxytocin bolus (mean ± SD)
I (n = 30)	86.61 ± 4.874	83.10 ± 4.967
II (n = 30)	89.40 ± 4.848	82.58 ± 4.592
III (n = 30)	89.60 ± 4.538	81.18 ± 4.151

4. Discussion

Our results show that small bolus doses of oxytocin (0.5–2 unit) result in adequate uterine tone in primigravida women undergoing elective caesarean delivery with minimal effects on haemodynamic parameters and less incidence of nausea and vomiting. Adequate uterine tone was achieved with 0.5 IU of oxytocin with less incidence of nausea and vomiting as compared to 2 IU of oxytocin administration. There was no difference in the blood loss & pre and postoperative haematocrit values between the groups.

The most important finding of our study is that in healthy primigravida undergoing elective caesarean delivery under spinal anaesthesia, oxytocin in the dose as small as 0.5 unit is

effective in producing adequate uterine tone. The results of our study are similar to that done by Butwick et al. [7] in which adequate uterine tone was achieved with 0.5 unit of oxytocin at 2 min after delivery. However, the number of patients in their study was less and adequate uterine tone was achieved in 93%, 87%, and 93% of the patient at the interval of 3, 6, 9 min but in our study at various intervals mean adequate uterine score kept on increasing. Moreover our study was conducted on primigravida.

The results of our study are similar to a previous study done by Carvalho et al. [8] in which ED90 of oxytocin was estimated to be 0.35 units However, their study was single-blinded; in contrast to our study(double blinded). Moreover oxytocin related side-effects such as nausea (38%), vomiting (17%), and flushing (63%) were noted in their study, which is in contrast to our study. The reason may be slow speed of injection of oxytocin (15 s) in our study. Our results are comparable to another study in which adequate uterine tone was achieved with 2 unit of oxytocin [9]. The results are in contrast with another study done by Sarna et al. [10] where adequate uterine tone was achieved with 5–20 unit of oxytocin with no difference in estimated blood loss between the groups, but the authors did not determine the minimum effective dose of oxytocin. Our results are different from other two studies using very low dose of oxytocin (0.1 and 0.29 units). Out of these the first study was conducted on women with cardiac disease undergoing caesarean section [11]. In their study oxytocin was administered in boluses from 0.05 to 0.5 unit and adequate uterine tone could be achieved. In the later study ED90 of oxytocin was found to be 0.29 IU/min [12]. However, the estimate was imprecise, as illustrated by wide ranging 95% CI (0.15–0.43 IU/min).

The frequency of use of additional uterotonic agents was not statistically different between the groups. We chose the need for additional uterotonic drug as determined by surgeons according to their usual clinical practice. This is in accordance with previous studies [7,8].

The results of our study indicate that estimated blood loss and difference in preoperative and postoperative haematocrit are independent of the doses of oxytocin used which is in accordance with previous studies [7,9,10]. In one study blood loss was more than 1 l (marker of PPH) in all the groups using either placebo, 0.5, 1, 3 or 5 unit bolus of oxytocin [7]. This is in contrast to our study in which blood loss was less than 1 l in all the groups. The difference could be because of smaller sample size and inclusion of multigravidas in their study.

In our study no hypotension was observed in any group at any time indicating that low dosages are associated with haemodynamic stability during caearean delivery. These findings are in contrast to a study in which hypotension occurred in 7% of the patients receiving 2 U of oxytocin [9]. The difference can be because we included only primigravida in our study whereas in their study patients were multigravida. Surprisingly in a study using 5–20 unit of oxytocin no haemodyanamic instability was observed. The reason can be attributed to small patient population and infusion of oxytocin used in their study [10].

In our study no tachycardia was observed with any of the doses of oxytocin used. Tachycardia was observed in other studies using higher doses of oxytocin [1,2]. However, in a study, tachycardia was seen even in patient receiving 2 unit of oxytocin [9]. The reason could be attributed to observation of hypotension in their study which could have produced resultant tachycardia. Other studies examining the effect of oxytocin did not comment upon change in heart rate [10,13].

In our study there was significant difference in the occurrence of nausea and vomiting in patients receiving 2 unit of oxytocin as compared to patient receiving 0.5 unit of oxytocin. These results are similar to a previous study in which nausea and vomiting occurred with 2 unit of oxytocin [9]. Our findings are in contrast to another study done where high incidence of nausea and vomiting (37.5% and 12.5% respectively) was observed with low doses of oxytocin [8]. This can be attributed to rapid speed of injection of oxytocin used in their study.

In our study no flushing was observed in any patient. This is similar to other studies in which no flushing was observed with low dose of oxytocin [7,9]. This observation is in contrast to a previous study where there occured a high incidence of flushing (62.5%) with a small dose of oxytocin [8]. The authors attributed this high incidence of flushing to the potent vasodilating properties of oxytocin.

No patient in our study complained of headache and lightheadedness. However, in a study headache and lightheadedness was observed in 0.7% of the patient with the use of 5 unit of oxytocin [14]. The authors commented that these side effects could be due to the coadministration of vasodilatory drugs enhancing the adverse effect of bolus dose of oxytocin as in their study GA was also provided to some of the patients. Other studies using low dose of oxytocin did not comment upon incidence of headache and lightheadedness [8,9].

Transient ECG changes (ST segment, T wave abnormalities) and subjective symptoms e.g. chest discomfort and pain has been described following 10 unit of oxytocin during caesarean delivery [15]. This can be because of profound hypotension, tachycardia and coronary vasoconstiction causing mismatch between myocardial oxygen demand and supply, leading to myocardial ischaemia. Since we used very low dose of oxytocin, so none of our patient experienced any ST segment or T wave changes on ECG or complained of chest pain.

We chose spinal anaesthesia as an anaesthetic technique for our patients because general anaesthesia is a risk factor for uterine atony [16,17]. Most of the studies investigating the oxytocin dosages for uterine atony have used regional anaesthesia except for a few where anaesthetic technique was not standardised. Our study was conducted on healthy primigravida without any risk factor for PPH for the purpose of homogenicity.

One limitation of our study was that we studied only primigravida patients with no clinical risk factor for uterine atony. The requirement of oxytocin may be influenced by the parity and in patient with risk factors for uterine atony/obstetric haemorrhage. The study was undertaken in patients undergoing elective caesarean delivery. During emergency caesarean delivery, uterine response greatly decreases; higher doses of oxytocin with early use of alternative uterotonics may be required [13]. Also the blood loss was measured by visual assessment of suction chamber, weighting the surgical swabs and by change in preoperative and postoperative haematocrit values. The visual estimated blood loss may be inaccurate [18] and the changes in haemoglobin and haematocrit are difficult to interpret because of large fluid shifts that occur around the time of delivery [19]. However, most of the studies evaluating the response of small doses of oxytocin had adopted the same method for estimation of blood loss [7,9,14]. Another limitation of our study was that uterine massage was not performed

and uterus was not exteriorised; may be the dosage of oxytocin can be reduced further if these measures were undertaken.

In summary, our results show that small bolus doses of oxytocin result in adequate UT at 2 min in primigravidas undergoing elective caesarean delivery with less haemodynamic side effects. Since the study was conducted on primigravidas so the results cannot be assumed to be equivocal for multigravidas and patient having risk factors for uterine atony. Therefore further studies are required to assess whether the current dosing would be adequate for high risk parturients or for labouring women undergoing emergency caesarean delivery as the dosing of oxytocin should be administered according to specific patient group.

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