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Comparison of Efficacy and Safety of Two Different Bolus Doses of Oxytocin During Elective Caesarean Delivery: A Prospective Randomised Controlled Study

KEYWORDS: Oxytocin, caesarean delivery, "clinically acceptable" uterine tone

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ABSTRACT ***OBJECTIVE****: To determine the optimal dose of oxytocin during elective caesarean delivery (CD) for adequate uterine tone with least haemodynamic adverse effects.*

METHODOLOGY*: 90 women undergoing CD under spinal anaesthesia were randomised to receive either oxytocin bolus (group O2-2 units, group O5-5 units) or saline followed by oxytocin infusion (5 units/ hour). Primary outcome was adequacy of uterine tone 2 minutes after initial bolus. Secondary outcomes included haemodynamic adverse events, requirement for rescue uterotonics, emesis and blood loss.*

RESULTS: *Significant differences were noted in distribution of "clinically acceptable" uterine tone at 2 minutes (56.7%, 86.7% and 93.3% for placebo, O-2 and O-5 respectively, p 0.001). The differences remained significant at 3 (p 0.01) and 5 minutes (0.004). Number of patients with hypotension at 1 minute was more in O-5 (36.7%) compared to placebo (6.7%) and O-2 (20%) (p 0.017). Need for additional uterotonic agents was higher in placebo (63%) compared to O-2 (30%) and O-5 (20%) (p 0.01). Emesis and postoperative Haemoglobin fall were maximum in placebo (p 0.043 and 0.014 respectively). Both the oxytocin groups were comparable in efficacy. Adverse effects were more with O-5.*

CONCLUSION*: 2 units oxytocin bolus followed by infusion has a favorable efficacy and safety profile in elective CD.*

INTRODUCTION

The current guidelines for oxytocin administration during caesarean delivery are diverse reflecting a lack of uniform consensus[1]. Considering the inter-ethnic variability in pharmacokinetics and lack of uniform consensus there is a need for properly designed randomized controlled trials to determine the optimal (effective and safe) dose of oxytocin during CD.

Confidential Enquiry into Maternal Deaths (CEMD-2001)2 emphasized the adverse effects of bolus dosing and concluded that oxytocin should be given only by infusion and never as bolus. However, recent trials[3, 4] have shown that a small bolus dose apart from infusion is beneficial. Considering the narrow therapeutic index, the exact dose, rate and timing of administration are of paramount importance. An evidence based protocol and standardized algorithm for oxytocin administration during elective caesarean delivery is needed to guide the clinicians in a clear manner.

The goal of the present study is to determine whether a bolus dose of oxytocin is necessary and if so, the optimal bolus dose of oxytocin which gives adequate uterine tone with least haemodynamic adverse effects during elective caesarean delivery.

AIMS AND OBJECTIVES

Comparison of effect of two different initial bolus doses (2 or 5 IU) of oxytocin with that of saline; along with regular oxytocin infusion (5 $IU.h^{-1}$) on:

1. Adequacy of uterine tone
2. Haemodynamic changes

in healthy women undergoing elective caesarean delivery under spinal anaesthesia

MATERIALS AND METHODS

It was a prospective, randomised, double blinded trial after approval from the Departmental Dissertation Committee and the Institutional Ethics Committee. Written informed consent was taken from all the patients.

Inclusion criteria:

1. Age between 18 and 40 years
2. ASA physical status 1 and 2

Exclusion criteria:

1. Previous oxytocin allergy
2. Previous postpartum haemorrhage
3. Placenta previa/ accreta
4. Multiple pregnancy
5. Polyhydramnios
6. More than 2 previous caesarean sections
7. Preeclampsia
8. Abnormal lie
9. Non-reassuring fetal status
10. Inadequate spinal anaesthesia

Premedication

Patients were kept nil per orally 6 hours (solids) and 3 hours (clear fluids) prior to surgery. They were premedicated the night before and on the morning of surgery with Tab Ranitidine 150 mg and Tab Metoclopramide 10 mg orally.

Randomisation and Blinding:

Patients were randomly allocated to one of the following three groups by computer generated random number table

1. **Group O-2:** received oxytocin 2 units as a bolus IV
2. **Group O-5:** received oxytocin 5 units as a bolus IV
3. **Group S:** received saline bolus (Control)

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Intraoperative management:
Routine monitoring was done and baseline vitals recorded.. A peripheral intravenous line was secured using an 18 gauge intravenous cannula and lactated Ringer's solution was administered at a rate of 10 $mL.kg^{-1}$ rounded off to the nearest 50 mL. The calculated amount of fluid was infused over 15 minutes beginning with the administration of the subarachnoid block.

Spinal anaesthesia was administered under strict aseptic precautions using 25 gauge Whitacre needle at L2-3 or L3-4 inter-spinous space. Adequate level of block was ensured before starting the surgery. Sensory level following spinal was tested using spirit soaked cotton swab every 5 minutes till baby delivery. Patients were placed in supine position with left uterine displacement using a wedge under the right pelvis. Routine administration of oxygen was not practiced unless maternal oxygen saturation dropped below 95%.

Opaque sealed envelopes containing group allocation were opened by the anaesthesia technician posted for the case (who was not involved further in the study) and he/ she loaded the study drug (oxytocin or saline) as per the group allocation. The study drug was loaded in a 5 mL syringe and made up to a total volume of 5 mL using 0.9% saline and labeled in a blinded manner. Soon after umbilical cord clamping, the study drug was injected intravenously over 15 seconds as per the group allocation. Subsequently, all patients received oxytocin infusion at 5 $IU.h^{-1}$ using an infusion pump. Routine uterine massage was avoided after the baby delivery. Delivery of the placenta was done by manual continuous cord traction.

Haemodynamic assessment and management
Hypotension following spinal anaesthesia was managed using intravenous phenylephrine boluses of 50 µg. Blood pressure and heart rate just before the administration of the study drug was considered as baseline. Blood pressure and heart rate were measured from the time of administration of the study drug: every minute for the initial 5 minutes; then every 2.5 minutes for the next 15 minutes and thereafter every 5 minutes till the uterus was sutured and interiorized.

Hypotension defined as "a decrease in Mean Arterial Pressure (MAP) more than 20% from the baseline value" or a MAP < 60 mmHg (whichever is greater) was treated with an IV bolus of phenylephrine 50µg and the dose was repeated if inadequate.

Maternal tachycardia was defined as "Heart rate (HR) increase of >20% from baseline" and bradycardia as "HR decrease of > 20%".

Assessment of uterine tone:
Uterine tone was assessed by the consultant obstetrician (blinded to group allocation) at 2, 3, 5, 10, 15 and 20 minutes after delivery of baby by manual palpation of the uterus. Uterine tone was assessed using "Five-point" scale (1 atonic, 2 partial but inadequate contraction, 3 adequate contraction, 4 well contracted, and 5 very well contracted)

Score of $\geq$ 3 was considered "clinically acceptable". During assessment, if the uterine tone was found to be inadequate, alternative uterotonic therapy was administered in the following order of preference:

1. Oxytocin 2.5IU as intravenous bolus (maximum of two doses),
2. Methyl ergonovine 0.2 mg (methergine; intramuscular)
3. Prostaglandin $F_{2\alpha}$ 0.25mg (Carboprost, intramuscular)

Total blood loss was estimated using visual assessment of suction bottles, sponges and drapes. Postoperative haemoglobin was estimated. The occurrence of nausea and vomiting, before and after the oxytocin bolus was assessed and recorded. Routine intraoperative use of antiemetics was avoided. An emetic symptom with stable blood pressure was treated with rescue antiemetic (one or more doses of IV ondansetron 4 mg). The study was terminated for each case after adequate uterine tone was achieved and abdominal closure started.

Outcomes measured
Primary outcome:

Adequacy of uterine tone at 2 minutes after administration of the study drug

Secondary outcomes:
- Heart rate / blood pressure
- Additional uterotonic agent requirements
- Intraoperative blood loss
- Phenylephrine requirements
- Occurrence of nausea/ vomiting and need for antiemetics

STATISTICAL ANALYSIS
The study data was analysed using SPSS version 16 for Windows. Sample size was calculated to be 84 (28 patients in each group) for a power of study (80%) with a level of significance (5%). Hence, a total of 90 healthy women, 30 in each group were recruited for the study.

All baseline characteristics were tested for comparability among the three groups. Categorical data was analysed using Chi-square test. One way ANOVA was used to detect statistically significant differences in means among the three groups. Post-hoc tests for multiple comparisons between the groups were done using Bonferroni (homogenous data) and Games-Howell test (non-homogenous distribution). ANCOVA was used to compare the percentage change in heart rate and MAP from baseline among the three groups. A p value of less than 0.05 was considered statistically significant

RESULTS
None of the patients were excluded from the study. The three groups were comparable with respect to patient characteristics**.** Majority of the patients (Group S 22/30, Group O-2 23/30 and Group O-5 24/30, p 0.83) had sensory block at T4 level. Rest of them had level of block at T6.

Table 1: Patient characteristics

Variables	Group S n= 30 Mean (Range)	Group O-2 n= 30 Mean (Range)	Group O-5 n= 30 **Mean (Range)**	***p* value**
Age (years)	26.1 (20-34)	27.13 (21-36)	29 (21-38)	0.06
Weight (kg)	61.37 (50-92)	63.45 (46-88)	63.67 (49-75)	0.48
Estimated fetal weight (kg)	2.9 (2.5-3.5)	2.93 (2.4-3.3)	2.9 (2.5-3.4)	0.95
Gestational age (weeks)	37.97 (37-40)	37.97 (36-40)	37.77 (37-39)	0.52
Baseline Hb (g/dl)	12.04 (10.2-13.2)	11.89 (9-14)	12.27(10.4-14.4)	0.37

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Adequacy of uterine tone

Majority of patients in oxytocin bolus groups had "clinically acceptable" uterine tone at 2 minutes (26 and 28 in group O-2 and O-5 respectively) when compared to saline group (17). Further inter-group comparisons showed significant difference between the saline group and both the oxytocin bolus groups. {O-2 vs S - odds ratio (OR) 4.97 (95% Confidence interval (CI): 1.39 - 17.82), p 0.01 and O-5 vs S - OR 10.71 (95% CI: 2.15- 53.35), p 0.001}. The two oxytocin bolus groups were comparable (O-5 vs O-2: OR 2.154 (95% CI: 0.36-12.74), *p* 0.389)

There were more number of patients with "clinically acceptable" uterine scores in oxytocin groups compared to saline group during initial 5 minutes. Beyond 5 minutes, all three groups were comparable.

Table 2: Number of patients with "clinically acceptable" uterine tone during entire study period among the three groups

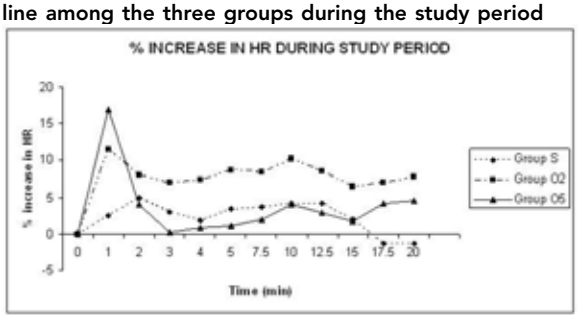
Time interval (min)	Group S (n = 30)	Group O-2 (n = 30)	Group O-5 (n = 30)	***p* value**
2	17	26	28	0.001 *
3	19	27	27	0.01 *
5	19	28	27	0.004*
10	26	29	29	0.20
15	25	22	27	0.49
20*	28	25	28	1.0

*During assessment time intervals, surgery was completed before 20 minutes in 2 patients each in group S and group O-5 and 5 patients in group O-2.

Heart rate changes and maternal tachycardia

Eleven patients in group O-5 and 5 in O-2 had tachycardia in the first minute after the study drug compared to none in the saline group (p < 0.001). Significant % change in mean maternal heart rate from baseline was noted only during the first minute after study drug administration (Group S 2.57%, Group O-2 11.4% and Group O-5 16.91%, p < 0.001). Inter-group comparisons showed significant differences { S *vs* O-2, p 0.023; S *vs* O-5, p < 0.001; O-2 *vs* O-5, p 0.054}. Rest of the study periods, all the three groups were comparable

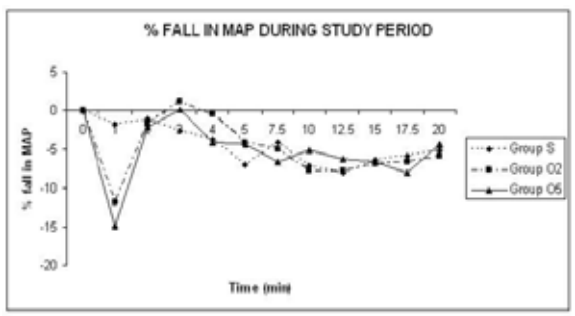
Figure 1: Percentage increase in heart rate from baseline among the three groups during the study period



Mean arterial pressure and maternal hypotension

Eleven patients in group O-5 and 6 in O-2 had hypotension in the first minute after the study drug compared to 2 in the saline group (p 0.017). Significant % fall in mean of MAP was noted only during the first minute after study drug administration. (Group S 1.79%, Group O-2 11.83% and Group O-5 14.89%, p < 0.001). Inter-group comparison showed significant differences {S *vs* O-2, p 0.001; S *vs* O-5, p < 0.001; O-2 *vs* O-5, p 0.75}. Rest of the study periods, all the three groups were comparable.

Figure 2: Percentage change in mean arterial pressure from baseline among the three groups during the study period



Need for additional uterotonic agents

The number of patients requiring additional uterotonic drugs was less in the oxytocin bolus groups compared to the saline group. Inter-group comparison showed significant differences {O-2 vs S: OR 4.03 (95%CI: 1.37- 11.83), p 0.01; O-5 vs S: OR 6.90 (95% CI: 2.16 – 22.09), p 0.001}. There was no statistical difference between oxytocin groups {O-5 vs O-2: OR 1.71 (95% CI: 0.52 - 5.62), p 0.37}.

Table 3: Comparison of number (proportion) of patients who needed additional uterotonic drugs:

Drug	Group S (n=30)	Group O-2 (n=30)	Group O-5 (n=30)	***p* value**
First rescue: oxytocin 2.5 IU	19	9	6	0.01*
Second rescue: oxytocin 2.5 IU	15	5	4	0.002*
Methyl ergonovine	13	4	4	0.007*
PG F 2α (Carboprost)	4	1	-	0.064

Nausea and vomiting

Eleven patients in group S, 3 in O-2 and 6 in O-5 developed either nausea or vomiting during the study period. (p 0.043). Inter-group comparison showed significant differences {S vs O-2: OR 5.211 (95% CI: 1.278 - 21.237), p 0.015 ; S vs O-5: OR 2.316 (95% CI: 0.724 - 7.407), p 0.15 ; O-2 vs O-5: OR 0.444 (95% CI: 0.100-1.974), p 0.278 }. The occurrence of nausea and vomiting correlated with the use of additional uterotonic drugs. It occurred in 15/ 21 patients requiring methyl ergonovine (p 0.001) and 4/5 patients requiring all rescue additional uterotonic agents including PG F 2α (p 0.001).

Table 4: Other secondary outcomes

Variable	Group S (n = 30)	Group O-2 (n = 30)	Group O-5 (n = 30)	***p* value**
Number requiring Phenylephrine	11	16	17	0.252
Estimated blood loss (mL) (SD)	571.67 (138.76)	560 (134.8)	558.33 (145.08)	0.92

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Intraoperative fluids (mL) (SD)	1551.67 (421.30)	1390 (264.70)	1556.67 (359.05)	0.123
Reduction in haemoglobin (SD)	0.85(0.66)	0.62(0.48)	0.43(0.39)	0.014*

DISCUSSION

The reported trials [3-10] about oxytocin use in elective caesarean delivery have differed with respect to the type (bolus, infusion, bolus followed by infusion), dosage, rate of drug administration (both in bolus and infusion), timing , outcome measures and protocols for use of additional uterotonic agents.

The salient features of the present study included:

1. The bolus dose was diluted up to 5 mL and slowly administered over 15 seconds (to reduce cardiovascular side effects) soon after umbilical cord clamping
2. All patients received oxytocin infusion at 5 $IU.h^{-1}$
3. Placenta was extracted by controlled cord traction
4. Uterine massage was not practiced (could confound the uterotonic action of the bolus oxytocin).
5. Hypotension during the surgery was corrected with phenylephrine instead of ephedrine (ephedrine could potentially confound the oxytocin induced tachycardia)

The efficacy was assessed by the incidence of "clinically acceptable" uterine tone, need for additional uterotonics, estimated blood loss and haemoglobin changes. The safety profile included the haemodynamic adverse effects and need for phenylephrine bolus doses.

The results of the study indicate that adequate uterine tone can be achieved with a bolus dose of oxytocin bolus compared with saline. There was a significantly higher incidence of "clinically acceptable" uterine tone at 2 minutes (86.7% in O-2, 93.3% in O-5) compared with saline group (56.7%). Groups O-2 and O-5 were comparable. These data were similar to observations of Butwick *et al*[3] (placebo 73%, 3 units bolus 100% and 5 units bolus 93%). In our study, lower incidence of adequate uterine tone in the saline group with greater need for rescue uterotonics implies that oxytocin infusion alone may be insufficient for achieving adequate uterine tone.

In terms of haemodynamic adverse effects, there was a significant % increase in mean heart rate (HR) as well as % decrease in MAP in the first minute compared to baseline values in the groups receiving oxytocin when compared to saline.. Hypotension requiring therapeutic intervention occurred in 2 (6.7%) in saline group, 6 (20%) in O-2 and 11 (36.7%) in O-5.The difference was statistically significant between saline and O-5 whereas O-2 and saline group were comparable. Butwick *et al*[3] reported the incidence of hypotension to be placebo (7%) and 5 units oxytocin (47%). Similarly, Sartain *et al*[4] noted greater increase in mean HR and reduction in MAP in the 5 units oxytocin group compared with the 2 units group. The findings from both these studies corroborate the data from the present study. One can firmly conclude that 2 IU bolus is relatively safer compared to a 5 IU bolus.

The need for rescue uterotonics was also more in saline (63.3%) compared to oxytocin bolus groups (O-2 30%, O-5 20%). Butwick *et al*[3] reported a lower requirement for additional uterotonics (saline 47%, 3 unit group 0% and 5 unit group 13%). Requirement for additional uterotonics was comparable in O-2 and O-5 groups in our study. The incidence of nausea/ vomiting was lesser in the O-2 group. The relatively lower incidence compared to data from Carvalho *et al*[5] (38% nausea, 13% vomiting) can be explained by the slower rate of administration of oxytocin bolus (over 15 seconds) in the present study. The incidence of nausea / vomiting in the present study increased with the use of additional uterotonics.

There was no significant difference between the three groups on comparing the estimated blood loss, requirement of phenylephrine bolus doses and need for intraoperative fluids. The estimated blood loss might be comparable between the three groups inspite of the higher incidence of inadequate uterine tone in the saline group due to the use of rescue uterotonic agents. The fall in haemoglobin was significantly lesser in the O-2 and O-5 groups compared to saline. This can again be attributable to the fact that better uterine tone was achieved in the groups receiving oxytocin when compared to saline. Importantly, the O-2 and O-5 groups were comparable with respect to fall in haemoglobin.

One limitation of the study was that interpretation of data and comparison between the three groups during the latter part of the study (after 5 minutes) was hampered by the administration of rescue doses of uterotonic drugs. However, this could not be withheld due to ethical reasons. The observations may also not be applicable for emergency caesareans and caesarean delivery under general anaesthesia

CONCLUSION

Oxytocin in the dosage of 2 IU as an initial bolus followed by infusion of 5 IU per hour after delivery of fetus, has a favourable efficacy and safety profile in healthy adult women undergoing elective caesarean delivery

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