A randomised double-blind trial of minimal bolus doses of oxytocin for elective caesarean section under spinal anaesthesia: Optimal or not?

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ABSTRACT

Background: Oxytocin administration regimens are arbitrary and highly subjective. Hence, it is essential to reinvestigate the appropriate dose for effective uterine contraction with minimal bleeding and adverse effects. Aim: To determine the optimal dose of bolus oxytocin for uterine contractions for elective caesarean section under spinal anaesthesia. Methods: Ninety term mothers (37 to 41 weeks) undergoing caesarean section electively under spinal anaesthesia were considered for the trial and divided into three groups to receive oxytocin bolus of one, two or three units. The uterine tone was assessed at 2 min after oxytocin administration. Intraoperative blood loss, mean arterial pressure, heart rate and possible side effects were also compared. Paired t-test, Kruskal-Wallis test, Chi-square test and analysis of variance (ANOVA) test with Scheffe multiple comparisons were used as inferential statistics. Results: Adequate uterine contraction was seen in 66% of participants who received one unit of oxytocin, and in 83.3% of participants who received two units of oxytocin. All those who received three units of oxytocin had an adequate uterine contraction. Blood loss was inversely related to the bolus dose of oxytocin. Conclusions: Lower bolus oxytocin doses of one and two units were inadequate for uterine contraction at elective caesarean section, while three units appeared to be effective in terms of adequate uterine contraction, reduced blood loss and stable haemodynamic system and absent side effects.

Key words: Blood loss, caesarean section, heart rate, oxytocin, spinal anaesthesia, uterine haemorrhage

INTRODUCTION

The blood loss following delivery of the foeto-placental unit can cause significant haemorrhage if the uterus is not well contracted. Proactive doses of uterotonic agents are quintessential. Caesarean sections face a high risk of bleeding due to uterine atony. Pre-labour, the receptors for oxytocin are about 12 times the non-pregnant uterus.[1] Uterus at term is highly receptive to actions of oxytocin. Due to life-threatening adverse effects, many studies favour lower dose with better outcomes.[2–6] However, it is essential to reinvestigate the least permissible dose range with effective uterine contraction, reduced blood loss and least side effects.

METHODS

After obtaining clearance from the institutional ethics committee (IEC/RC/12/58 dated 26-10-2012), the details of the randomised double-blind trial were...
submitted to the Clinical Trials Registry India (CTRI Number: CTRI/2019/03/018249). All mothers who were admitted to a tertiary care centre in Puducherry, with singleton pregnancy within the age group 18 to 40 years, American Society of Anesthesiologists (ASA) class I or II and suitable to receive spinal anaesthesia and who gave consent were included. The patients with a history of allergy to oxytocin, abnormal placentation, uterine fibroids, hypertension in pregnancy, eclampsia, inherited or acquired coagulation disorders, thrombocytopenia, severe anaemia or who had undergone caesarean section twice or more were not included. Study groups were randomised to receive either one unit, two units or three units of bolus oxytocin and were grouped respectively into groups A, B and C [Figure 1]. Randomisation was by lot technique. Under strict aseptic precautions, the subject was given a spinal block with 2 mL of 0.5% bupivacaine. The surgery commenced once anaesthesia level till T6 was confirmed with neurotip. Following the standard surgical procedure, the foetus was delivered and umbilical cord clamped. The study drug diluted and labelled in 10 mL syringe, was given over 15 s. After removal of the placenta by controlled traction and completion of 2 min from the administration of the drug, the obstetrician was asked to check the tone of the uterus by manual palpation without exteriorising the uterus. The uterine tone was rated as either adequately retracted or inadequately retracted.

Then 10 units of oxytocin infusion in 500 mL normal saline was commenced at 125 mL/h. A five-point Likert scale can be used to assess the uterine tone by palpation. However, since the objective of this study is to give full contraction to the uterus to prevent blood loss, the intermediate scale becomes insignificant. If inadequate, then intramuscular methergine 0.2 mg was administered as alternative uterotonic therapy. The other uterotonics kept ready for back-up were carboprost (0.25 mg) or misoprostol (800–1000 µg).

Before giving oxytocin, the baseline heart rate, heart rhythm and mean blood pressure were recorded. Thereafter every 2 min for the next 20 min changes in the heart rate, heart rhythm and mean arterial blood pressure were recorded. Hypotension was defined as a drop in mean arterial blood pressure by more than 20% and was treated with aliquots of 6 mg ephedrine and intravenous fluids. Incidence of other side effects like nausea, vomiting, chest pain, breathlessness and flushing were monitored.

The intraoperative bleeding was assessed by checking the volume of blood in the graduated suction canister. Around 150 to 200 mL of the canister content was attributed to amniotic fluid. The remainder was taken as blood volume. The abdominal swabs of 18 by 18 inches, fully soaked, were estimated to carry as much

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**Figure 1:** Consort diagram showing the workflow of the study
as 100 mL of blood and partially soaked had 50 mL of blood, while the four by four inches small swabs were estimated to hold as much as 5 mL of blood when fully soaked and 2 mL when partially soaked. The swabs that were soaked with amniotic fluid alone were not counted. Post-operative haematocrit was done 30 min after surgery and was compared to the pre-op values.

All data collected were entered in Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) software (Version: 20, IBM, Armonk, NY, United States of America). Descriptive statistics such as mean, standard deviation and percentages were used to describe background and outcome variables. Inferential statistics such as paired t-test, Kruskal-Wallis test, Chi-square test and analysis of variance (ANOVA) test with Scheffe multiple comparisons was used in this study. Kruskal-Wallis test and Chi-square test were used to find an association between ordinal outcome variables, nominal variables with dose. Analysis of variance (ANOVA) test with Scheffe multiple comparisons was used to compare the variation in outcome variables with dose and to compare pairwise comparison. Paired t-test was used to compare heart rate and mean blood pressure between different time intervals in each of the groups separately.

**RESULTS**

The study groups were comparable in demographic profile [Table 1]. In groups A and B, 66% and 83.3% of the participants, respectively had an adequate uterine contraction while in group C, the outcome was 100%. The difference in tone between the three groups was significant [Table 1]. The requirement of rescue doses of methergine was compared between the three groups and was found to be significant (\( P = 0.002 \)). Blood loss between the three groups was compared and there was a significant difference, with maximum blood loss in group A (mean value of 1030.9 mL), followed by group B (mean value of 770.1 mL) and least in group C (mean value of 608.6 mL) [Table 1]. The pre-operative and post-operative haematocrit values in the three groups were significant (\( P = 0.001 \)). The mean difference in the pre-operative and post-operative haematocrit was highest in group A, followed by group B. The difference was least in group C. Nausea was seen in 15 out of 90 participants. It was compared between the three groups and difference was insignificant [Table 2].

Heart rate at the time of administration of oxytocin was compared with the baseline value, the values after 2 min and the average of the values from 2–20 min taken at 2-min intervals. In group A and group B, there was a significant increase in heart rate from the value at the start of administering the dose. In group C, there was no significant change in heart rate [Figure 2]. The increase in heart rate in group A and B was probably due to significant blood loss in the two groups [Table 3]. The average heart rate (2–20 min) between the groups was compared. There was a significant difference

### Table 1: Patient demographic variables and outcome variable across study groups

| Demographic variable | Group A          | Group B          | Group C          | \( P \)  |
|----------------------|------------------|------------------|------------------|---------|
| Age (years)          | 26.6 ± 4.9       | 27.9 ± 5.6       | 25.7 ± 3.6       | 0.209   |
| Gestational age (weeks) | 38.7           | 38.3            | 38.5            | 0.366   |
| Gravidity (G\(_1\)–G\(_5\)) * | 1.8             | 2               | 2.1             | 0.360   |
| Parity (P\(_0\)–P\(_5\))† | 0.7             | 0.8             | 0.9             | 0.376   |
| LSCS frequency (1–2)  | 1.5             | 1.6             | 1.7             | 0.574   |
| Height (cm)          | 154.9           | 152.1           | 153.3           | 0.235   |
| Weight (kg)          | 76.9            | 73.2            | 73.3            | 0.304   |
| Outcome variable     |                  |                 |                 |         |
| Adequate Tone (n = 90) | 20              | 25              | 30              | 0.002   |
| Blood loss (mL)      | 1030.9 ± 245.5   | 770.6 ± 202.4   | 608.6 ± 128.2   | 0.001   |

*Gravidity one to five †Parity zero to five
between the average heart rate of group A and group C. The mean blood pressure at the time of administration of oxytocin was compared with the baseline value, the value after 2 min and the average of the values from 2–20 min taken at 2-min intervals [Figure 3]. In groups A and B, there was a noteworthy decrease in mean blood pressure compared to the baseline reading. In group C, the difference was not substantial [Table 3]. This could be due to increased bleeding in groups A and B.

**DISCUSSION**

Oxytocin dosing in labouring mothers has been extensively studied for over three decades. The dosing has gradually evolved from a high dose to a low bolus dose. In elective caesarean, there has been a hesitancy to standardise the lowest possible dose. The UK directive on caesarean sections endorses five units of oxytocin as slow intravenous bolus dose after delivering the new-born. This may be attributed to lack of comparability in studies performed with oxytocin doses less than five units, and increased reports on serious side effects on doses greater than five units with no added benefit on the tone of uterus or reduction of haemorrhage.[13] We have used one, two and three units slow bolus doses with no increased incidence of any of the side effects. However, we noted that doses of one unit and two units were statistically pointing to inadequate uterine retraction and significant blood loss. There was a corresponding significant drop in haematocrit as well. The blood loss was significant enough to alter the expected drop in heart rate with low doses of oxytocin and there was increased heart rate and drop in blood pressure.[14] However, with three units the uterine retraction was found to be adequate and the blood loss was less compared to the other two groups.

Studies have favoured 0.35 units to three units of bolus oxytocin.[2-5] When two and five units were compared, the tone of uterus assessed at multiple intervals was adequate for both doses with no difference between groups regarding blood loss, uterine tone and the requirement for other uterotonics.[3] Besides, the haemodynamic changes were lower with two units while the heart rate was significantly higher and prolonged after five units. The decrease in mean pressure was significant in the five units group. A meta-analysis concluded that before an infusion of 20 units to 40 units in 1 L isotonic solution over 4 h, a bolus of 0.3 units to one unit administered slowly will be effective in reducing haemorrhage and minimising side effects during elective caesarean section.[15] A study on caesarean for failed induction concluded that ED90 of oxytocin is 2.99 units i.e., three units oxytocin as a ‘loading dose’ can achieve uterine tonicity before an oxytocin infusion for maintenance is continued, which may be diluted and be given as a rapid infusion to avoid a sudden drop in blood pressure.[16] ‘Rule of Threes’ proposed by Tsen and Balki, was a new approach for delivery of oxytocin in caesarean section. They proposed three units of oxytocin bolus over 30 s and additional oxytocin dosing if required twice more after 3-min interval. Maintenance infusion would be three units/hour oxytocin. Three other drugs can be given if the three doses of oxytocin do not achieve adequate contraction.[17] It is not known if the response to oxytocin is different in different ethnic groups since most of the studies favouring low

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**Table 2: Comparison of side effects between groups**

| Study Group | Side Effect |
|-------------|-------------|
| Group A (n = 30) | Nausea: 4, Vomiting: Nil, Chest pain: Nil, Arrhythmia: Nil, Flushing: Nil |
| Group B (n = 30) | Nausea: 6, Vomiting: Nil, Chest pain: Nil, Arrhythmia: Nil |
| Group C (n = 30) | Nausea: 5, Vomiting: Nil, Chest pain: Nil, Arrhythmia: Nil |
| *P* | 0.787 |

**Table 3: Comparison of heart rate and blood pressure between groups**

| Study Group | Heart Rate (per min) | Blood Pressure (mmHg) |
|-------------|----------------------|-----------------------|
|              | Mean | SD  | *P*  | Mean | SD  | *P*  |
| A            | 94.0 | 7.9 | 0.000 | 78.4 | 8.7 | 0.029 |
| B            | 90.2 | 9.5 | 0.001 | 80.2 | 7.2 | 0.045 |
| C            | 87.8 | 7.1 | 0.790 | 79.9 | 9.9 | 0.234 |

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**Figure 3:** Comparison of mean blood pressure between dose interventions.
doses were conducted in regions of the world where the multi-ethnic population was prevalent, whereas our study was confined to a semi-urban hamlet of Puducherry where the majority of the patients were natives.

Few limitations of the study need to be highlighted. Firstly, the assessment of uterine tone by the obstetrician performing the caesarean is highly subjective. However, we tried to limit this factor to some extent by having an obstetrician with a minimum of 5 years experience. Secondly, as inclusion criteria, we have used only first-time caesarean or second-time caesarean ASA grade II cases. The result may vary in case of high-risk pregnancy or more than two previous lower segment caesarean section (LSCS).

**CONCLUSIONS**

In elective caesarean sections, a bolus oxytocin dose lower than three units is inadequate for attaining optimum uterine contraction. We recommend the use of three units bolus oxytocin, followed by a maintenance dose of 10 units infusion in 500 mL normal saline at 125 mL/h, as it provides adequate uterine contraction, steady haemodynamics, nominal blood loss and lesser side effects. Thus it is high time we endorse a slow intravenous low bolus dose for oxytocin universally, especially in elective caesarean, since the debate has been on for more than three decades.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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