ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 10 | October - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A RANDOMIZED STUDY COMPARING THE EFFICACY AND SAFETY OF TWO DIFFERENT BOLUS DOSES OF OXYTOCIN DURING CAESAREAN DELIVERY

Anaesthesiology

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ABSTRACT

Background: Typically, oxytocin is used to induce uterine contractions during caesarean delivery. The intravenous administration of oxytocin is known to have negative side effects, including tachycardia, hypotension, and alterations in electrocardiograms (EKGs), which can be harmful in high-risk patients. In this study, we contrasted the outcomes of two oxytocin dosages. **Methods:** A total of 70 patients—35 in each group—were receiving an I.V. bolus of 2 or 5 units of oxytocin while undergoing elective caesarean sections under spinal anaesthesia. An hourly infusion of five units of oxytocin was then administered. Evaluation of uterine tone, the need for further uterotonic drugs, changes in hemodynamics, and adverse pharmacological effects were compared between the two groups. **Results:** The two groups' patients had similar characteristics. At two minutes, uterine tone ratings remained similar. The difference between the two groups at the fifth minute was statistically significant. At the fifth minute, there was a substantial change in the clinically acceptable uterine tone measured over the entire trial time. At the first minute, the percentage rise in the mean maternal HR was observed to differ significantly (p=0.002). No significant difference in maternal tachycardia existed across the groups. When the systolic blood pressure was compared to the baseline at 1, 2, 3, 4, 15, 18, and 21 minutes, there was a discernible difference in the percent drop. There was a noticeable difference in the diastolic blood pressure during the entire trial period. Only few cases had side effects like nausea and vomiting, there was no appreciable difference. **Conclusion:** In healthy adult women having an elective caesarean section, a 2-unit oxytocin bolus followed by an infusion of 5 units per hour had a positive effectiveness and safety profile.

KEYWORDS

Anaesthesia, Oxytocin, Caesarean delivery, hemodynamic change, uterine tone

INTRODUCTION

The most popular uterotonic substance used globally to produce optimal uterine tone and prevent postpartum haemorrhage is oxytocin. Lowering the amount has been more popular over the past 10 years in an effort to lessen the negative effects of oxytocin, such as nausea, hypotension, chest discomfort, alterations in the EKG, and maternal death. The best method for administering oxytocin, nevertheless, is still debatable. Randomized experiments with oxytocin have shown that the extent of these cardiovascular adverse effects appears to be dosage [1,2] and administration rate [3] dependent. The medicine must be administered as a brief infusion, according to the oxytocin producer, to maintain cardio-vascular stability. An acceptable uterine tone can be achieved with bolus dosages less than 5 IU, and there is a significantly lower risk of negative side effects. The most significant cause of maternal morbidity is post-partum haemorrhage(PPE), which is defined as a blood loss of at least 500 ml after vaginal birth and at least 1000 ml after CS and/or the requirement for blood transfusion within 24 hours of delivery [4,5]. Given that PPH is more prevalent after CS than after vaginal delivery [6] and that the rate of CS is rising, it is anticipated that PPH incidence will rise as well. In this randomised research, we compare the effectiveness and safety of two different bolus doses of oxytocin used during either a planned or unplanned caesarean delivery. The varied and empirical nature of the existing recommendations for oxytocin administration during caesarean delivery again reflects the absence of a unified consensus. As a result, many trials have been conducted and there are divergent views among anaesthesiologists regarding the ideal amount of oxytocin to administer after caesarean section. There are not many statistics about the Indian population. Given the interethnic variation in pharmacokinetics, it may be necessary to further confirm the doses for Indian women having elective caesarean deliveries. Higher dosages of oxytocin can result in harmful circulatory alterations such tachycardia, hypotension, and ST abnormalities, while lower levels can increase uterine haemorrhage because of decreased uterine tone. The 2001 Confidential Enquiry into Maternal Deaths (CEMD) report highlighted the negative effects of bolus dosage and came to the conclusion that oxytocin can only be administered intravenously. However, some of the most recent studies have shown that a tiny bolus dose, in addition to the infusion, can be helpful. The precise dose, pace, and timing of administration are of utmost relevance given the limited therapeutic index. To provide doctors with clear direction, an evidence-based methodology and standardised algorithm for administering oxytocin during elective caesarean delivery are required. The purpose of this randomised study was to compare the efficacy and safety of two different oxytocin bolus doses used during either a planned or unplanned caesarean delivery. And to observe, which of the two oxytocin bolus doses causes adequate uterine contractions with the fewest adverse effects and haemodynamic side effects during an elective caesarean delivery?

METHODS

Study Design

This is a prospective, single-centre, randomised trial that is being conducted in A.J. Institute of Medical Sciences during the period of November 2016 to October 2018. Recruitment for the study began and would last for two years. The Institutional Ethics Committee gave their approval to the project. While neither of us is involved in the patients' care, we make sure the study medicine is administered correctly, the hemodynamic parameters are sent, and intraoperative data is collected.

Selection and withdrawal of participants

Participants are found by selecting the daily list of patients scheduled for a CS and at the pre-anaesthesia visit. The patients are informed of all details relevant to trial participation by the study team or the anaesthetist in charge, and they are then recruited to take part.

Informed Consent

The anaesthesia or obstetric team routinely evaluates eligibility to determine whether the patient is competent to give consent to participate in the trial. All participants were asked for their written, informed consent. Participants are made fully aware of the voluntary nature of the trial and their right to withdraw at any time.

Selection Criteria

Inclusion Criteria

Healthy pregnant women with a singleton who are having a planned or

unplanned caesarean section (CS) after at least 37 full weeks of gestation and who are older than 18 years old and in good health and who have given written informed consent are eligible.

Exclusion Criteria

Applying the following exclusion standards: Maternal comorbidities like severe cardiovascular conditions like pre-eclampsia, emergency caesarean section (CS), kidney or liver disorders, coagulopathies, as well as epilepsy, uterine malformation, foetal malformation, known hypersensitivity to oxytocin, unplanned caesarean section (CS) brought on by foetal distress, and the inability to read and understand the participant's information.

Sample size

To detect a mean difference of uterine tone score 1, standard deviation of 1 (0.05 of alpha-error and power of study 80%, beta-error 0.2) the minimal sample size or group will be 60 assuming equal sample size. Considering 10% drop-out rates, we decided to study in 35 subjects for each group. Hence, a total of 70 healthy adult women, 35 in each group undergoing elective Caesarean delivery under Spinal anaesthesia were recruited for the study.

Study procedure

Intraoperative Management

Routine monitoring such as electrocardiogram, non-invasive blood pressure and pulse oximetry were established, once the patient was shifted inside the operation theatre and baseline vitals were recorded. Mean arterial pressure was recorded and upper and lower limits (20% above and below the baseline) were calculated and noted down for reference. A peripheral intravenous line was secured using an 18-gauge IV cannula and lactated Ringer's solution was administered at a rate of 10 mL.kg-1 rounded off to the nearest 500 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 by the concerned anaesthesiologist posted for the case using 25-gauge Whitacre spinal needles at L2-3 or L3-4 interspinous space. Amount of spinal drug and patient position used for spinal subarachnoid block was left to the discretion of the concerned anaesthesiologist. Adequate level of anaesthesia block was ensured before starting the surgical procedure. Sensory level following spinal level was tested using spirit-soaked cotton swab every 5 min till baby delivery by anaesthesia resident posted for the case. Patients were placed in supine position with left uterine displacement using a wedge under the right pelvis during surgery. 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 (observer 2) posted for the case (who is not involved further in the study) and he/ she loaded the study drug as per the group allocation. The study drug was loaded in a 5mL syringe and made up to a total volume of 5 mL using 0.9% saline and labelled in a blinded manner. Immediately following baby delivery, soon after umbilical cord clamping, the study drug was injected intravenously over 15 seconds by observer 1 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 following the baby delivery was by manual continuous cord traction rather than manual evacuation. Observer 1, patient and obstetrician were blinded to the patients' group allocation.

Study treatment with trial drug

Seventy patients, with 35 in each group, underwent elective caesarean sections while under spinal anaesthesia. Following the delivery of the baby, the patients were given an I.V. bolus of 2 or 5 units of oxytocin, followed by an oxytocin infusion of 5 units per hour. In terms of uterine tone evaluation, the requirement for further uterotonic medicines, haemodynamic alterations, and negative medication effects, the two groups were compared.

Premedication

Patients were kept nil per orally 8 hours for solids and 3 hours for clear fluids prior to the surgery. They were premedicated on the night before and on the morning of surgery with Tab Ranitidine 150 mg and Tab Metoclopramide 10 mg orally.

Concurrent Medication

If there is insufficient uterine tone, the patient was treated in accordance with industry best practises. Six alternatives are available: uterine massage, Sulprost 4-8 mcg/min, 600 mcg rectal misoprostol, oxytocin infusion 20-40 U/2 h, BakriTM balloon, and surgical intervention. Depending on the degree of uterine atony, the treating obstetrician may decide to use one or more of these treatments.

Observers of the study

Three observers were involved in this study:

Observer 1: Researcher performed preoperative evaluation, obtained written informed consent from all patients, recorded intra operative haemodynamics, interventions, and assessments

Observer 2: Anaesthesia technician posted, who loaded the drugs as per group allocation

Observer 3: Consultant obstetrician, performing Caesarean delivery, who assessed the uterine tone

Randomisation and blinding

Patients were randomly allocated to one of the following 2 groups by computer generated random number table and sequentially numbered opaque sealed envelopes. On the day of the surgery, the sealed envelope was opened by the anaesthesia technician (Observer 2) posted for the case and he/she loaded the study drugs as per the group allocation.

The 2 groups were as follows:

Group O-2: Patients receiving oxytocin 2 units as a bolus

Group O-5: Patients receiving oxytocin 5 units as a bolus

Along with regular oxytocin infusion of 5 IU^{-h}

Uterine tone measurement

By manually palpating the uterus and using a LAS scale of 0 to 100, the obstetrician evaluates the uterine tone. The gold standard for determining uterine tone in routine clinical practise is manual uterine palpation.

Four-point scale used for uterine tone assessment:

1= Atonic
2= Partial but inadequate contraction
3= Adequate contraction
4= Well contracted

Score of more than or equal to 3 is considered clinically adequate.

Score of > 3 was considered “clinically acceptable”. During assessment, if the uterine tone was found to be inadequate, then alternative uterotonic therapy was administered in the following order of preference.

Follow up

A follow-up appointment is scheduled for each participant two days after surgery to rule out any potential oxytocin side effects and to make sure no new issues have emerged.

Outcome Measured In The Study Are As Follows:

Primary outcome

Adequacy of uterine tone at 2 minutes after administration of the initial oxytocin bolus dose.

Secondary outcomes

Haemodynamic changes

Haemodynamic measurement method

We decided on hemodynamic stability, which is shown by the lowest mean arterial pressure and greatest heart rate within the first five minutes following Carbetocin administration. We have chosen to take blood pressure non-invasively using a cuff on the upper arm after weighing our alternatives for continuous invasive and non-invasive blood pressure measures. We found the continuous non-invasive procedures' precision and accuracy to be insufficient to support their use in the setting of this trial. Although an intra-arterial catheter has a minimal risk of problems [25], the possibly serious side effects do not warrant invasive blood pressure monitoring.

Data monitoring

The research team would handle monitoring and assessed how the study is going, confirm the case report forms' (CRFs') accuracy and thoroughness, and make sure that all protocol requirements and investigator responsibilities are being met. Every two months, the trial's progress is assessed. After three months, the general distribution of uterine tone was evaluated blindly, that is, without taking group

assignment into account. By analysing the intraoperative course and figuring out the causes of low uterine tone, extreme levels were further studied.

Data Management

All patient information will be archived anonymously. A three-digit patient-identity (ID) that is exclusive to each patient will be given to them. In order to evaluate inquiries in the event of improbable values, the patient's ID, name, and date of birth will be saved separately in a different file. Data access is restricted to study team members only.

Statistical analysis

Baseline characteristics line Parity, Gravidity, Gestational Week, Risk Factors for PPH, Number of Previous CS, Planned or Unplanned CS, Reason for CS, Experience Level of the Obstetrician, were give as frequency and percentage. Continuous variables were expressed using the mean (SD) or median and categorical variables were described using count (percentage).

RESULTS

Table 1 Baseline Characteristics of the patients

Variables	Groups		P- value
	Group O-2 n=35 Mean ± SD (Range)	Group O-5 n=35 Mean ± SD (Range)	
Age in years	28.69 ± 3.795 (21 - 38)	26.0 ± 3.290 (19 – 33)	0.062
Weight in kg	64.23 ± 2.658 (59 - 62)	62.89 ± 4.898 (52 – 69)	0.159
Height in cm	158.77 ± 2.86 (150 – 165)	157.77 ± 2.860 (150 – 165)	0.179
Baseline Hb g/dl	11.443 ± 0.5611 (10.4 – 12.6)	11.491 ± 0.6099 (10.4 – 12.8)	0.730

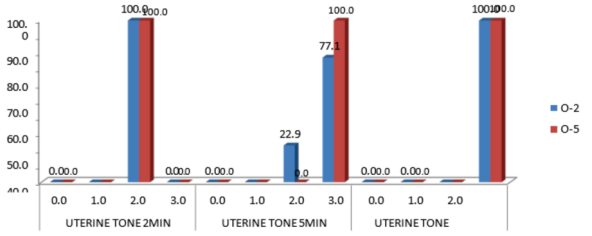
p-value <0.05 was considered as significant

This study included a total of 70 pregnant patients, 35 in each group, who were scheduled for an elective caesarean delivery under spinal anaesthesia. Throughout the whole time of the trial, no patients were excluded. Patients had a baseline mean haemoglobin of 11g.dL-1, a mean age of 26 years (range: 19-38 years), and a mean body weight of 62 kg (range: 52-69 kg) (range: 10.4-12.8). In terms of patient characteristics, the two groups were comparable. None of the patients needed sedation or analgesics during the research period because all had appropriate spinal levels for surgery. Further research was conducted for the same since intraoperative blood loss was tolerable and comparable between the two groups. During the trial period, none of the patients needed a colloid or a blood transfusion. [table-1]

Table 2: Uterine tone at different time interval after initial bolus of oxytocin:

	Groups		P # value
	Group O-2 (n=35)	Group O-5 (n=35)	
Uterine tone after 2 minutes			
1	0	0	0.573
2	35	35	
3	0	0	
4	0	0	
Uterine tone after 5 minutes of oxytocin			
1	0	0	0.002
2	8	0	
3	27	35	
4	0	0	
Uterine tone after 15 minutes			
1	0	0	0.238
2	0	0	
3	35	35	
4	0	0	

Table 2 shows the percentage of patients in the two groups that have uterine scores that are different after 2, 5, and 15 minutes following the delivery of the study drug (the initial oxytocin boluses). Following the delivery of the infant and the clamping of the umbilical chord, an oxytocin bolus was administered. The consultant obstetrician who oversaw the caesarean delivery used the "four-point scale" to evaluate uterine tone. The primary result was evaluated using the uterine tone score 2 minutes after the oxytocin dose. Throughout the two minutes, both groups' uterine tone scores stayed at 2. All patients in group O-5 and the majority in group O-2 had scores of 3 at the intervals of 5 and 15 minutes, respectively (table 2).



Graph-1: Comparision Of Uterine Tone Between The Groups

Table-3: "Clinically acceptable (uterine score > 3)" uterine tone during entire study period after initial bolus of oxytocin:

Time interval(min)	Groups		p-value
	Group O-2 (n = 35)	Group O-5 (n = 35)	
2	0	0	0.002
5	27	35	
15	35	35	

Distribution of patients in each group with clinically acceptable uterine tone 2 minutes after the initial oxytocin boluses is shown. A clinically acceptable uterine contraction was defined as one with a uterine tone score of less than 3. According to the study's protocol, patients who had insufficient uterine contractions at each evaluation interval received an additional uterotonic medication. Two minutes after the initial bolus of oxytocin, none of the patients had uterine tone that was adequate. The majority of the patients (27 vs. 35 in O-2 and O-5, respectively) obtained satisfactory uterine scores throughout the fifth minute of the test. All of the patients had satisfactory scores by the 15th minute. Testing proportions were used in the statistical analysis, which revealed significant results only at the fifth minute of analysis (p=0.002). (Table-3)

Table-4: Distribution of maternal tachycardia at different time interval

Time interval (min)	Group O-2 (n = 35)	Group O-5 (n = 35)	P value
1	0	0	-
2	0	0	-
3	0	0	-
4	0	0	-
5	0	0	-
8	0	0	-
11	0	2	0.078
15	0	2	0.078
18	0	0	-
21	1	0	0.159

The above table-4 shows how many patients in each of the three groups experienced maternal tachycardia during the course of the trial. The baseline for the subsequent change was the patient's heart rate just prior to the study drug injection. After the study medication was administered, maternal tachycardia was defined as a 20% rise in heart rate from the baseline. One patient from the O-2 group and two patients in the O-5 group both had considerable change.

Table:5 Comparison of SBP at different time interval

Time interval (min)	Group O-2 n = 35 Mean (%)	Group O-5 n = 35 Mean (%)	p value
1	-5.35	-12.99	0.000
2	-5.78	-14.52	0.000
3	-6.44	-12.64	0.000
4	-6.78	-10.60	0.041
5	-7.74	-10.67	0.214
8	-7.15	-10.74	0.046
11	-7.23	-9.58	0.209
15	-6.62	-11.33	0.000
18	-5.73	-10.47	0.001

The above table shows the average systolic blood pressure's % change from the starting point over the course of the study. The baseline for the subsequent changes was the systolic blood pressure immediately prior to the administration of the research medication, oxytocin bolus. For

statistical analysis, percentage change from the starting point was taken into account. Both groups experienced a decrease in systolic blood pressure, although the O-5 group experienced a greater reduction.

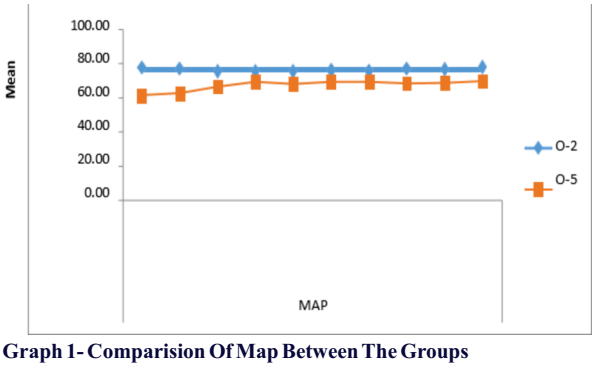
Table- 6 Comparison of DBP at different time interval

Time interval (min)	Group O-2 (n = 35) Mean (%)	Group O-5 (n = 35) Mean (%)	P-value
1	-12.66	-39.94	0.000
2	-13.33	-37.03	0.000
3	-16.45	-30.71	0.000
4	-15.82	-25.16	0.001
5	-15.46	-28.50	0.000
8	-14.16	-26.26	0.000
11	-14.63	-26.34	0.000
15	-12.46	-27.28	0.000
18	-13.88	-26.34	0.000
21	-10.57	-23.87	0.000

The above table depicts the % change in mean diastolic blood pressure from baseline during the course of the trial. The initial alterations were compared to the diastolic blood pressure that was measured soon before the research drug, oxytocin, was injected. For statistical analysis, percentage changes from the starting point were taken into account. Diastolic blood pressure decreased in all groups, although O-5 group experienced a greater reduction.

All the patients had adequate spinal level for surgery and none of patients required any form analgesics or sedation during the study period. Intraoperative blood loss was acceptable and comparable between the two groups, so further analysis was done for the same. None of the patients required any blood transfusion or colloid usage during study period.

Comparison of mean artrial pressure



Graph 1- Comparision Of Map Between The Groups

The mean arterial pressure just before the injection of study drug oxytocin bolus was taken as baseline for the subsequent changes.

Comparison of percentage change of mean maternal heart rate

The below table shows the average maternal heart rate's % change from the study's baseline value. For the ensuing alterations, the maternal heart rate immediately prior to the infusion of the study medication oxytocin bolus served as the baseline.

Table-8: Comparison of percentage change of mean maternal heart rate from baseline:

Time interval (min)	Group O-2 n = 35 Mean (%)	Group O-5 n = 35 Mean (%)	p-value
1	3.06	0.96	0.002
2	3.85	2.71	0.092
3	5.31	5.07	0.767
4	6.40	6.20	0.701
5	6.71	7.36	0.855
8	5.78	6.37	0.612
11	4.02	2.95	0.604
15	4.19	2.09	0.251
18	2.90	0.24	0.145
21	2.79	-1.20	0.097

Table-9:Comparison of side effects after oxytocin

The above table shows the number of patients in two groups, who required phenylephrine boluses to hypotension during caesarean delivery which includes the both before and after the study drug administration (i.e., initial bolus of oxytocin or saline). There was only one patient in O-5 group had nausea and vomiting during study period which was statistically not significant

DISCUSSION

Due to uterine atony, pregnant women receiving CD are more likely to experience an obstetric haemorrhage. The mainstay of uterine atony treatment is oxytocin. [7] It has been demonstrated that routinely using oxytocin as a preventative measure can cut the risk of postpartum haemorrhage by up to 40%.[8] The population of uterine oxytocin receptors gradually rises throughout pregnancy and peaks at term. Oxytocin receptors are typically 12 times stronger in late pregnancy, just before the start of labour, and roughly 80 times higher in a uterus that is not pregnant. Low doses of oxytocin may be most effective while avoiding the negative effects of high doses of oxytocin since the non-labouring uterus at term is still more sensitive to oxytocin. [9] In this study, we chose mothers who were not in labour but underwent elective CD in the hopes of getting a positive outcome with a modest dose of oxytocin. The commencement of labour results in an increase in the uterine sensitivity to oxytocin and a diffuse and heterogeneous expression of oxytocin receptors. [9] It is common practise to increase the oxytocin dosage on the belief that bigger doses will cause uterine contractions to be more powerful. In labouring mothers who are already using oxytocin, greater doses of the hormone are unlikely to significantly enhance uterine contractions during CD. In our study, there was increase in maternal heart rate in both groups from the baseline. As per the study protocol, there was only statistical difference only at 1st minute after the baseline measurement. A total of 3 patients (O-2: 1; O-5: 2) had significant changes in heart rate in the later part study period. There were significant number of patients in group O-5 had hypotension and none in O-2 group. This could be due to larger bolus dose of oxytocin. But there was no associated significant maternal tachycardia in both groups; this could be due the phenylephrine boluses used to treat hypotension. Even though, there was some variation in study methodology in other studies, our study results comparable to them with regard to hemodynamic changes. Many studies reported the incidence of hypotension in their study to be placebo (7%) and 5 units oxytocin (47%). The reduction in MAP and speed of recovery are dose dependent. The findings from both these studies corroborate the data from the present study. there was only one patient complained of nausea and vomiting during study period (O-5). Large dosages of oxytocin that are administered quickly have been known to cause a number of negative side effects, including hypotension, nausea, vomiting, headaches, flushing, myocardial ischemia, alterations in the ST-T segment, pulmonary edema, and severe water intoxication with convulsions.[9]

CONCLUSION

To sum up, among healthy adult women undergoing elective caesarean delivery, a 2-unit oxytocin bolus followed by an infusion of 5 units per hour had a positive effectiveness and safety profile.

Conflict of interest

Nil

Funding: Self

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