

## Comparison of uterotonic effects of three low dose oxytocin regimens; bolus plus continuous infusion, bolus or continuous infusion during elective caesarean section: A double blind randomized control trial

Jayesh Shakeet<sup>1</sup>, Rakhi Bansal<sup>2,\*</sup>, Mridul Janweja<sup>3</sup>, Sarita Janweja<sup>4</sup>

<sup>1,2</sup>Resident, <sup>3</sup>Intern, <sup>4</sup>Professor, Dept. of Anaesthesia, Dr. SN Medical College, Jodhpur, Rajasthan

\*Corresponding Author:

Email: drrakhibansal@yahoo.in

### Abstract

**Background:** Oxytocin is considered the drug of choice for managing post-partum hemorrhage resulting from uterine atony, but optimum regimen of oxytocin is yet to be uncovered. Here our primary aim was to compare the uterotonic effects (uterine tone, use of rescue drugs, and intra-operative blood loss) of three low dose different regimens of oxytocin.

**Methods and Material:** It was a double blind randomized control trial conducted in tertiary care teaching hospital. One hundred and twenty primi/second gravida mothers, age group 18-40 years, ASA grade II and height between 1.52 to 1.72 meters, scheduled to undergo elective caesarean section under spinal anesthesia were randomized in to three groups based on oxytocin regimen administered; group A- 3 IU bolus plus 5 IU infusion, group B- 3 IU bolus and group C -5 IU infusion. Fishers exact test was used to compare the proportion between the groups and quantitative data were compared by using Kruskal-Wallis test.

**Results:** At 2 minutes the percentage of subjects having adequate uterine tone (uterine tone score  $\geq 3$ ) was higher in group A (95%) and B (90%) in comparison to group C (70%) (Fisher exact test,  $p=0.006$ ). Overall median uterine tone score remained low in group C in comparison to group A and B. Frequency of use of additional uterotonic drugs was equivalent (Fisher exact test,  $p=0.09$ ) in all the groups but blood loss in group B and C was higher in comparison to group A ( $P<0.001$ ). Hemodynamic derangements and drug side effects were again proportionate in all the groups ( $P>0.05$ ).

**Conclusions:** Bolus plus continuous infusion (3IU plus 5IU) of oxytocin is better uterotonic than either infusion or bolus alone.

**Keywords:** Oxytocin, Bolus, Infusion, Uterotonic, Blood loss

### Introduction

Post-partum haemorrhage remains the principle cause of maternal deaths worldwide and uterine atony tops the list of risk factors described for it.<sup>(1,2)</sup> Oxytocin a nonapeptide secreted by neurohypophysis is considered the uterotonic of choice for managing this dreaded condition, but the protocol for its use is yet not fixed.<sup>(3,4)</sup> Several regimens of oxytocin; single bolus, repeated small boluses, bolus with continuous infusion and continuous infusion alone have been tried with a widely variable wanted (uterotonic) and unwanted (cardiovascular) results.<sup>(5,6)</sup> Bolus dose of oxytocin by inducing appropriate uterine contractions has been found to be more effective than continuous infusion in reducing post-partum bleeding but side effects like hypotension, tachycardia through its peripheral vasodilatation, and fluid retention, pulmonary oedema because of its antidiuretic property are more, on the other hand slow continuous infusion though is considered more safe but continuous exposure may lead to internalization of its receptors and reduction in therapeutic efficacy.<sup>(7-11)</sup>

In a survey it has been found that majority of anaesthesiology department prefers bolus dose over slow infusion (85.3% versus 13.9%) in Germany but the dose of bolus varies from as low as 1 IU to as high as 40 IU.<sup>(12)</sup> This is despite the fact that a dose of 10 IU bolus has produced the catastrophic side effects like myocardial ischemia.<sup>(13)</sup> The frequency 10 IU bolus administration has decreased from 87% (2001) to 12%

(2006) in UK and to 11.6% (2007) in Germany.<sup>(14,15)</sup> In a striking contrast to Europe, in USA placebo bolus followed by continuous oxytocin infusion is favoured but again the dose is not fixed.<sup>(12,16)</sup>

We hypothesized that a low dose bolus-infusion (3 plus 5 IU) regimen would combine the benefits of both the bolus and infusion with no added side effects. Here we primarily compared uterotonic effects of three different regimens of oxytocin; bolus, bolus followed by continuous infusion and continuous infusion alone in pregnant women undergoing caesarean section. In addition haemodynamic derangements (heart rate, mean blood pressure, and pulse oximeter saturation) and drug side effects (chest pain, nausea/vomiting) were also compared.

### Material and Methods

This prospective randomized double blind control trial was carried out over a period of one year in a tertiary care teaching hospital, after obtaining approval from the Institutional Ethics committee and informed written consent from the patients. All primi and second gravida mothers, in the age group of 18-40 years, with ASA grade II and height between 1.52 to 1.72 meters, scheduled to undergo elective caesarean section under spinal anaesthesia were included. Patients with placenta praevia, chorioamnionitis, multiple gestations, foetal abnormalities, polyhydramnios, uterine fibroid, hypertension, diabetes mellitus, coagulopathies or taking anti-coagulant drugs, neurological,

neuromuscular, cardiovascular or psychiatric disorders, and those not fit for spinal anaesthesia or in active labour were excluded.

Demographic details including age, weight, and height, and vital parameters including mean blood pressure (MAP), heart rate and oxygen saturation (SpO<sub>2</sub>) were recorded during pre-anaesthetic examination. On arrival in the operation theatre, multi-parameter monitor was attached for continuous monitoring of heart rate, non-invasive blood pressure, SpO<sub>2</sub>, and ECG. A good venous access was secured with 18G cannula. All patients were pre-medicated with injection ranitidine 150 mg intravenously followed by preloading with 10 ml/kg of lactated Ringer's solution over 30 minutes.

Spinal anaesthesia was induced using 25G spinal needle with patient in the sitting position in L3-L4 inter-space and location of subarachnoid space was confirmed by loss of resistance technique and free flow of CSF. Immediately after intra-thecal administration of 2ml of 0.5% injection bupivacaine (hyperbaric), the patient was placed in the supine position with a wedge under the right flank to achieve a leftward tilt of 15° and oxygen supplementation at a rate of 5 L/min was started via a face mask. Surgery was allowed to proceed after loss of sensation to pinprick up to T4 level.

Using pre-sealed opaque envelopes prepared and drawn by an independent observer, all the selected candidates were randomly assigned (as per computer generated random number table) in to the following three groups; Group "A"- oxytocin 3 ml bolus followed by oxytocin infusion 5 ml over 10 minutes (total 8 IU oxytocin), Group "B"- oxytocin 3ml bolus followed by injection normal saline infusion 5 ml over 10 minutes (total 3 IU oxytocin), and Group "C"- Injection normal saline 3ml bolus followed by oxytocin infusion 5ml over 10 minutes (total 5 IU oxytocin). Bolus intravenous dose was administered over a time period of 5s to 10 s after clamping of the umbilical cord. Both for bolus and continuous infusion final concentration of oxytocin was kept same (1IU/ml). All the drugs were prepared by a person not involved in the study. The obstetrician and anaesthetist involved in each case were also blinded to the group assignment.

Immediately after delivery, the attending obstetrician performed manual uterine massage. The time of umbilical cord clamping was taken as 'zero minute' for timing of all events. Placenta was delivered by controlled cord traction. Uterine tone was assessed by direct visualization and manual palpation of the uterus by the attending obstetrician initially at 2 & 3 minutes and then at three minutes interval for 15 minutes following cord clamping at a five point scale; 1=atonic, 2=partial but inadequate contraction, 3=

adequate contraction, 4= well contracted and 5= very well contracted.<sup>(17)</sup> In all the casestone was assessed by a single obstetrician to reduce the observer bias. First dose of rescue uterotonic drugs were administered at 3 minutes and subsequently at 3 minutes interval to maintain the adequate uterine contraction (uterine tone score - at least three) in the following order: 5 unit oxytocin, again repeat dose of 5 unit oxytocin, ergometrine 0.25 mg (all intravenous), then intramyometrial prostaglandin.

Blood loss was estimated by counting the number of soaked lapads and by measuring the suction volume (excluding amniotic fluid). A note of nausea/vomiting and chest pain as complained by the patient was also made. Emetic symptoms were initially treated by correction of hypotension, followed by rescue antiemetic drug (ondansetron 4 mg) if necessary. Hypotension (reduction of MAP  $\geq$  30% from baseline) was corrected by injection mephentermine 6mg intravenously. ECG changes and chest pain were noted and were treated accordingly.

Uterotonic effects (tone, need of rescue uterotonic drugs and blood loss) were our primary outcomes. Secondary outcomes included hemodynamic responses and drug related side effects.

Keeping adequate uterine tone (score  $\geq$ 3) at 2 minutes as the primary outcome, a pilot study was undertaken on 20 subjects' 10 each in bolus plus infusion and continuous infusion groups to ascertain the sample size, and it showed adequate uterine tone in 9/10 and 6/10 in these groups respectively. Expecting adequate uterine tone in 90% in bolus plus infusion group in comparison to 60% in infusion alone group, and keeping alpha error 0.05 (both sided) and 80% power, the sample size was calculated to be 32 subjects in each group, we enrolled 40 candidates in each group.

Fisher exact test was used for comparative analysis of categorical data. As most of our continuous data did not follow normal distribution (Shapiro Wilks test,  $p < 0.05$ ), we preferred Kruskal-Wallis test for comparison of these variables among three groups. Post adhoc analysis was done by Mann-Whitney test for comparison between two groups. For all statistical purposes both side  $p$  value  $< 0.05$  was taken as significant.

## Results

With no exclusion, total 120 enrolled patients were divided in to three groups A, B and C; each comprising of 40 patients. Baseline demographic and clinical parameters were comparable in all the three groups ( $p > 0.05$ ) (Table 1).

**Table 1: Comparison of clinical and demographic characteristics**

Characteristics	Group A (n-40)	Group B (n-40)	Group C (n-40)	P# value
Age (years)	24 (22-25.75)	21 (20-24.75)	23 (21-24.75)	0.063
Weight (Kg)	61 (58-64)	60 (57.25-63.75)	60 (55.25-63.75)	0.494
Height (cm)	163 (159-165.75)	163 (160-166)	164 (160.5-166)	0.408
Duration of surgery (minutes)	35 (30-35)	35 (30-35)	35 (30-35)	0.559
HR per minute	91.5(84.5-95.75)	90.5(85-97)	92(86-98.75)	0.937
MAP (mmHg)	96 (90.25-100)	93(88-101)	94.5 (91.25-98.75)	0.865
SPO <sub>2</sub>	100(99-100)	100(100-100)	100(99-100)	0.225

All figures have been presented as median, figure in parenthesis indicates interquartile range (25<sup>th</sup> to 75<sup>th</sup> centile), HR- heart rate, MAP- mean arterial pressure, # Kruskal-Wallis test

Prevalence of adequate uterine tone (score  $\geq 3$ ) at 2 minutes was 95% (38/40), 90% (36/40), and 70% (28/40) in group A, B and C respectively (Fisher exact test,  $p=0.006$ ), but 3 minutes onwards this difference subsided (Fisher exact test,  $p>0.05$ ) (Table 2). From 2 to 12 minutes overall uterine tone in group A and B was comparable (Mann-Whitney Test,  $p>0.05$ ), and in both the groups (A and B) it was better than group C (Mann-Whitney test,  $p<0.05$ ), but at 15 minutes it was comparable in all the groups (Table 3). Additional uterotonic drugs were required in 2/40(5%), 7/40(17.5%), and 8/40(20%) in group A, B and C respectively (Fisher exact test,  $p=0.09$ ). Most of them required single dose of oxytocin except for one candidate each in group B and C who required two rescue dosage of oxytocin (Table 2 & 3). Intra-operative blood loss (more than 500 ml) was noted in

7.5% (3/40), 22.5% (9/40), and 67.5% (27/40) cases in group A, B and C respectively (Fisher exact test,  $p<0.000001$ ).

**Table 2: Number of candidates who displayed adequate uterine tone (score  $\geq 3$ )**

Time in minutes	Group A	Group B	Group C	P\$ value
2	38	36	28	0.006
3	38	36	32	0.117
6	40	37	39	0.070
9	40	39	40	0.327
12	40	40	40	1
15	40	40	40	1

\$ - Fisher exact test

**Table 3: Comparison of uterine tone score- median (25<sup>th</sup> to 75<sup>th</sup> Interquartile range)**

Time in minutes	Group A	Group B	Group C	P# value	A Vs B	B VsC	A Vs C
2	3(3-4)	3(3-4)	3 (2-3)	<0.0001	P1=0.412 P2=0.825	P1<0.0001 P2=0.0001	P1<0.0001 P2<0.0001
3	4(3-4)	4 (3-4)	3 (3-3)	<0.0001	P1=0.385 P2=0.771	P1<0.0001 P2<0.0001	P1<0.0001 P2<0.0001
6	4(4-4)	4(4-4)	3 (3-4)	<0.0001	P1=0.226 P2=0.453	P1=0.0001 P2=0.0001	P1<0.0001 P2<0.0001
9	4 (4-5)	4 (4-5)	4 (3-4)	<0.0001	P1=0.277 P2=0.555	P1=0.0009 P2=0.0017	P1<0.0001 P2<0.0001
12	5 (4-5)	5 (4-5)	4 (4-5)	0.0358	P1=0.401 P2=0.802	P1=0.0202 P2=0.0404	P1=0.0089 P2=0.0178
15	5 (5-5)	5 (4.25-5)	5(4-5)	0.1243			

# - Kruskal-Wallis test, P1 & P2 – Mann-Whitney test

Prevalence of hypotension was 67.5% (27/40), 77.5%(31/40) and 60%(24/40) in group A, B, and C respectively but this difference amongst the groups was not significant (Fisher exact,  $p=0.250$ ) and change in mean blood pressure, heart rate and SpO<sub>2</sub> remained comparable in all the three groups intra-operatively (Kruskal-Wallis test,  $p>0.05$ ). Drug side effects; nausea/vomiting and chest pain respectively 20% (8/40), 15% (6/40) in group A, 12.5% (5/40), 15% (6/40) in group B, and 7.5% (3/40), 10%(4/40) in group C were comparable (Fisher exact test,  $p=0.261$ , and 0.839 respectively). At 24 hours follow up in post-operative ward none of the mother developed post-partum haemorrhage (blood loss  $\geq 1000$ ml).

## Discussion

All over the world widely varying regimens of oxytocin are being used to prevent blood loss among parturient mothers during caesarean section. The mechanism of action of these regimens also differs; bolus causes constriction of venous sinuses, leading to placental separation and placental bed haemostasis and infusion maintains the uterine tone.<sup>(16,18)</sup> Now carbetocin; a synthetic oxytocin with a longer half-life is also preferred in some countries for this purpose, but the high cost restricts its use in resource limited settings, and oxytocin continues to be the drug of choice.<sup>(16,19)</sup>

We compared three low dose regimens of oxytocin; bolus followed by continuous infusion (group A), bolus alone (group B) and continuous infusion alone (group C). The higher prevalence of adequate uterine tone (uterine tone score  $\geq 3$ ) at 2 minutes in group A and B in comparison to group C reflects an early uterotonic effect of bolus. But at 3 minutes onwards as adequate uterine tone was equivalent, the use of rescue drugs remained proportionate in all the groups. Overall uterine tone score remained low in group C in comparison to group A and B. Two reasons can be cited for more bleeding in group C; first less frequency of adequate uterine tone in first two minutes or second uterine score of 3 was not adequate to control the bleeding. Addition of continuous infusion to bolus neither adversely affected the hemodynamic responses nor increased the drug related side effects in comparison to bolus or infusion alone.

The major strengths of our study were adequate sample size and comparison of three regimens of oxytocin using a low and fixed dose in a well-defined population. There were certain limitations like blood loss was estimated rather than measured. This method becomes more unreliable when loss is more than 1000ml, which is not the case in present study. Moreover other methods like, gravimetric method is also subject to technical error because of contamination with amniotic fluid, and change in haematocrit is also affected by quantity of intravenous fluid administered.<sup>(20,21)</sup> For assessment of uterine tone instead of tocodynamometer or intrauterine pressure catheter,<sup>(22)</sup> we chose a clinical method which was observer dependent. But these devices are not widely available, and the present uterine tone score has been used in previous study also. Lastly the technique of uterine massage was not standardized which also can influence the uterine tone.

Our findings are supported by Kim et al<sup>(5)</sup> who also observed better uterine tone in bolus-continuous infusion (2 or 5 IU bolus followed by continuous infusion of 10 IU) group in comparison to continuous infusion alone (20 IU in continuous infusion group), but in contrast to us, they found more increase in heart rate in bolus group and more fall in MAP in 5 IU bolus group, all probably because of higher dose of oxytocin.

Clinical side effects (nausea, vomiting, and use of antiemetic drugs) were also comparable in all the groups, similar to our results.

In contrast to our results, Thomas<sup>(8)</sup> et al observed no difference in blood loss between bolus (5IU) and continuous infusion (5 IU) groups but more derangement of hemodynamic parameters in the former again probably because of the fact that the dose used by them was higher than that used by us (5 IU vs 3 IU). Bhattacharya<sup>(23)</sup> again found comparable uterine tone in both the bolus and continuous infusion groups but with more deranged hemodynamic parameters in bolus group, despite the use of low dose (3 IU in both bolus and continuous infusion).

In a study by Sheehan<sup>(16)</sup> addition of bolus (5IU) to continuous infusion (40IU over 4 hours) didn't reduce the major obstetric haemorrhage but reduced the requirement of additional uterotonic drugs again a divergence from our findings, probably their threshold for the use of rescue uterotonic drugs was lower than that of us.

The expression of oxytocin receptors reaches its maximum at term, but in labouring women continuous exposure leads to desensitization of its receptors and thus increases oxytocin requirement by nine times in comparison to non-labouring women. Thus even a small dose of oxytocin should be effective in planned caesarean section because of lack of its prior exposure.<sup>(24)</sup> In the present study low dose combination regimen (3 IU bolus plus 5 IU infusion) produced the best wanted (more uterine tone, less blood loss) effects with no increase in unwanted (hemodynamic derangements, drug related side effects) effects in healthy parturient mothers undergoing caesarean section under spinal anaesthesia. As the effects of oxytocin may vary from person to person, this regimen needs to be tested in other populations also before a wider application.

## Conclusion

Low dose combination regimen of oxytocin (3 IU bolus plus 5IU infusion) is better (more uterotonic, reduced blood loss with no increase in hemodynamic derangements, or drug related side effects) than either bolus or infusion alone in healthy parturient mothers undergoing Caesarean section under spinal anaesthesia.

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