

Comparison of Varying Bolus Doses of Oxytocin in Patients Undergoing Caesarean Spinal Delivery

Muhammad Salman Maqbool, Ayesha, Huda Shafqat

ABSTRACT:

Objective: To determine the lowest effective bolus dose of oxytocin to produce adequate uterine tone during elective caesarean delivery avoiding side effects.

Study design and setting: A study was conducted at Rawal General and Dental Hospital, from 10th Oct, 2018 to 27th May, 2019.

Methodology: Patients undergoing elective cesarean spinal delivery were randomly divided by computer generated numbers (n=155) into 5 groups A, B, C, D and E receiving 0.5, 1, 3, 5 and 10 units of injection oxytocin as bolus respectively after delivery of baby. Uterine contraction was assessed by gynecologist by manual palpation of uterus on a linear scale. Value of ≥ 8 was considered adequate and ≤ 8 inadequate uterine tone respectively. Heart rate, non-invasive blood pressure and oxygen saturation were noted before and after oxytocin bolus. All patients received oxytocin infusion. The primary outcome measure was the assessment of uterine tone at 2 minute of oxytocin bolus. The secondary outcome variables included shortness of breath, chest discomfort, top-up bolus administered, hemodynamic variables, epigastric discomfort and oxytocin related effects (tachycardia, epigastric discomfort and hypotension).

Results: The use of 5 units oxytocin (group-D) showed most optimal uterine contractions, 61.3% in comparison to commonly used 10 units bolus dose (group-E) 48.4% with minimal side effects like, less tachycardia (12.9% versus 72.9%) and hypotension (12.9% versus 32.3%), no top-up bolus dose was required in 54.8% cases and no complain of epigastric discomfort was observed.

Conclusion: Low doses of oxytocin are effective in terms of uterine contraction with minimal side effects.

Keywords: Caesarean section, Maternal hemodynamics, Oxytocin, Phenylephrine, Uterine atony.

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INTRODUCTION:

Caesarean section rate in developed countries varies from 20-25%.¹ Uterine atony has been stated as the main cause of obstetric hemorrhage in up to 30% in patients undergoing cesarean delivery.² Uterotonics are drugs that initiate and maintain adequate uterine contractility after placental delivery thereby helpful in reducing blood loss from the site of placental attachment and decreases incidence of post-partum hemorrhage by up to 40%.³ Oxytocin is the most common uterotonic drug used in caesarean deliveries.⁴ Just after

delivery of baby a bolus of oxytocin is given that is usually followed by infusion. In addition to its beneficial effects, its side effects include tachycardia, hypotension, epigastric discomfort, headache, flushing and chest pain.⁵

Tachycardia and increased cardiac output are considered to be a reflex response to hypotension, however it may have a deleterious effect in patients with compromised cardiac status.⁶ Oxytocin has a weak anti-diuretic effect which is associated with fluid retention and pulmonary edema.⁷

In United Kingdom the use of oxytocin bolus is a standard treatment although doses vary from 5 to 10 units⁸ (IU) as bolus that is usually followed by slow intravenous (IV) infusion, though top-up bolus may be required.⁹ There is paucity of literature regarding effective dose of oxytocin particularly in developing countries. Recent studies have proven effectiveness of low dose oxytocin bolus ranging from 1 to 3 units.¹⁰ Even cardiovascular collapse and death has been reported following rapid administration and high dose of oxytocin.¹¹

Phenylephrine is alpha adrenergic receptor agonist and is vasopressor of choice to prevent and treat post-spinal hypotension during cesarean section. A dose of 100µg is commonly used and it results in increased blood pressure

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along with reflex decrease in heart rate thus it may prove effective for prevention of hypotension and tachycardia associated with oxytocin use.¹² Mohta M, et al. pointed in study that prophylactic phenylephrine 100 µg showed no change in systolic, diastolic and mean arterial pressure in initial 3 minutes following oxytocin use, whereas other group in study receiving saline showed significant fall in mean and diastolic blood pressure though heart rate showed little change in both groups for same time period of observation.¹³ Significant variability occurs among health care physicians (obstetrician and anesthetist) as regard uterotonic agent administration in parturient undergoing cesarean section as stated by Orbach-Zinger S and colleagues¹⁴ in their study, highlighting the importance of developing national guidelines for oxytocin use which will reduce use of high bolus dose and increase patient safety. In a randomized controlled study done, at Maula Baksh Teaching Hospital, Sargodha, 2 units oxytocin was compared with 5 units oxytocin in patients undergoing cesarean section, they concluded that 2 units oxytocin causes significantly less tachycardia (32% versus 61.33%) and hypotension (4% versus 17.33%) as compared to 5 units oxytocin.¹⁵ Primary purpose of the study was to evaluate and compare adequacy of uterine tone assessed by attending obstetrician (by manual palpation of uterus) at two minutes of receiving varying bolus dose of oxytocin in parturient undergoing cesarean spinal delivery rated on linear scale of 1-10 (1 being minimum and 10 being maximum). A value of ≥ 8 and ≤ 8 was taken as adequate and inadequate uterine tone respectively. The study rationale is the need of time to have a base for using lower bolus doses of oxytocin (clinically effective) rather than commonly used higher dose which have adverse effects as stated. Uterine atony can result in severe post-partum hemorrhage, gravid hysterectomy and maternal morbidity. The study algorithm was designed to cover inadequate uterine tone (uterine atony) with 'rescue' bolus of two units of oxytocin and repeated once if needed. Further uterine atony was addressed by adding oxytocin to ongoing infusion. It was hypothesized that 5 unit is better than commonly used 10 units of oxytocin with fewer side effects. Keeping in view above considerations, this study was aimed to compare and evaluate clinical effects of differing oxytocin bolus in patients undergoing cesarean spinal delivery.

METHODOLOGY:

A study was conducted at Rawal General and Dental Hospital, Islamabad from 10th Oct, 2018 to 27th May, 2019. The approval of study was obtained from Institutional Dean and Head Research Ethics Committee, Rawal Institute of Health Sciences issued letter No. RIHS-REC/032/18. Total 155 patients (31 in each group) were enrolled in this study. All patients were planned for elective caesarean delivery with a Pfannenstiel incision, placed in American Society of Anesthesiologists (ASA) physical status class 1-3.¹⁶ Subjects were randomly divided into five groups by using computer

generated numbers. Pre-anesthesia evaluation and informed written consent was taken in all cases. Excluded cases were allergic to oxytocin, known risk factors for post-partum hemorrhage (including abnormal placentation, history of uterine atony), inherited or acquired coagulation disorder, preeclampsia, HELLP syndrome, fixed cardiac output state e.g. aortic stenosis, shock. In operation theatre after placing two 18G intravenous lines, baseline vitals (non-invasive blood pressure, heart rate and oxygen saturation) were noted. All patients received a crystalloid fluid as "co-load"¹⁷ of 500 ml ringer lactate. Spinal anesthesia was managed by team of two consultant anesthesiologists with more than eight years post-fellowship experience using injection bupivacaine spinal 0.5% hyperbaric (12 mg) in sub-arachnoid space over a period of 10 seconds and placed supine afterwards. The sensory and motor block was evaluated by pin prick in mid-line and modified bromage scale by Breen TW, Shapiro T and colleagues¹⁸ at 3 and 8 minutes. Vitals (pulse and blood pressure) were noted before and after spinal anesthesia. Block was assessed till fourth thoracic sensory level achievement before surgery began. Also noted was hypotension, tachycardia, vasopressor or atropine need, epigastric discomfort and APGAR score.¹⁹ Hypotension was defined as a decrease in mean blood pressure =20% of the baseline value (or < 90mmHg)²⁰ and each episode of hypotension was treated with intra-venous bolus of 50-100 µg phenylephrine.^{12,13} Increased sympathetic drive in noted in parturient and tachycardia was defined as a maternal heart rate =120 beats / min.²⁰ After delivery of baby; group A, B, C, D and E patients were given 0.5, 1, 3, 5 and 10 units of injection oxytocin as bolus respectively given by consultant anesthesiologist using hidden tagged syringe provided by fellow consultant anesthesiologist and both were part of study team with fixed roles. All patients also received oxytocin infusion of 30 units after bolus injection. Vitals were also noted before and after oxytocin bolus at 1, 2, 3, 6 and 9 minutes interval. Uterine contraction was assessed by attending obstetrician not part of study (with at least four-year experience in obstetrics and were blinded to dose of oxytocin) two min after bolus oxytocin by manual palpation of uterus. In case of inadequate uterine contraction (score of ≤ 8) 'rescue' top-up of oxytocin in aliquot of 2 units was given and repeated once if needed. In case of persistent inadequate uterine tone there-after 10 units of oxytocin were added to on-going infusion. The primary study outcome measure was the assessment of either adequate or inadequate uterine tone at 2 minutes after administration of the initial oxytocin bolus dose. Any episode of secondary outcome variables e.g., shortness of breath, chest discomfort, arrhythmia, hypotension, flushing or epigastric discomfort along with side-effects associated with oxytocin (tachycardia, hypotension, epigastric discomfort) were noted. The hematocrit/ hemoglobin values were measured a day before planned procedure and 24 hours after surgery, as intra-operative blood loss estimation, as done by Anya SU and

colleagues²¹ in their study. Secondly (blood loss is often dispersed and mixed with amniotic fluid) in cesarean section is poorly reproducible and also typically an under estimate whereas comparison of surgical blood loss from one institution to another or from one obstetrician to another is a problematic task, adequacy of uterine contraction by using oxytocin helps in reducing blood loss.²² Also noted were rescue doses of oxytocin. Sample size was calculated using World Health Organization calculator and with statistical assumptions taking confidence interval of 95% and alpha error of 5% (authenticated complication of nausea and vomiting in 2 units group syntocinon = 5% and complication of nausea and vomiting in 5units group syntocinon = 32.5% respectively). The sample size was calculated to be 31 cases in each group (A-E).²³ SPSS analysis was done with version 16. P-value <0.05 was considered as statistically significant.

RESULTS:

The mean age of study population was 28+/- 4.7 years with range from 16-41 years. The mean hemoglobin pre-operatively and post-operatively of all cases in study (n=155) being 11.2 and 10.8 gm/dl respectively, while similar period mean hematocrit values were 34.2% and 32.8% respectively. Prophylactic atropine was used in 2 cases (1.3 %), after sympathetic block atropine was given in 66 cases (42.6%), both pre- and intra-operatively atropine was administered in 3 cases (1.9%) and no atropine was needed in 84 cases (54.2%) of patients in the study. After spinal anesthesia in 48 cases (30.96 %) of study population hypotension was observed treated by injection phenylephrine 100µg bolus.^{12,13} while in 107 cases (69 %) no hypotension was noted. The mean APGAR Score¹⁹ was 7.73(SD of .92) at time of delivery of baby and 9.56(SD of .98) at an interval of 5 minutes (this variation in score was due to intra-uterine death of 2 babies). The mean pulse rate /minute following sympathetic block in study was 101.49(SD of 33.85). The mean systolic and diastolic blood pressure (in mm Hg) following spinal anesthesia being 116.33(SD of 19.79) and 67.67(SD of 16.03) respectively. As we analyzed the data, the frequency of adequate uterine contraction was highest in group D(5

units bolus) however statistically there was no significant difference among all groups(p value=0.314).When we compared group B(1-unit bolus) with least observed adequate uterine contraction, with group D(5 units bolus) the best uterine contraction, a P-value of 0.04 shows that the difference between group B and D was statistically significant. Since in routine practice and as per mentioned in text books a 10 units bolus of oxytocin is stated so we have compared our results between the group D(5 units) and group E(10 units)²⁴. In comparing group D and E(5 and 10 units oxytocin bolus) group-D showed most optimal uterine contraction 61.3% cases in comparison to commonly used 10 units bolus dose (group-E) 48.4% cases, with minimal side effects like, less tachycardia(12.9% versus 72.9%) and hypotension (12.9% versus 32.3%), while no top-up bolus doses were needed in 54.8% cases(group-D) and 48.8%(group-E) cases and no complain of epigastric discomfort observed in group-D, whereas in group-E epigastric discomfort was noted in 3.2% of cases respectively. The systolic and diastolic blood pressure in relation to oxytocin bolus dose mean (Std. deviation), heart rate from 1-10 minutes of syntocinon bolus, is shown in table-1 and 2 respectively. The heart rate variability in reference to baseline on administering bolus oxytocin dose is graphically shown for the initial two minutes in graph-1. In detail study parameters noted in different groups are depicted in table-3. In this study no top-up was needed in the ongoing oxytocin infusion in all cases.

DISCUSSION:

Oxytocin has been widely used since decades in caesarean sections for promoting uterine contraction and to prevent post-partum hemorrhage. Oxytocin is a naturally occurring peptide hormone that is synthesized in the para ventricular nuclei of the hypothalamus and from here it is transported in secretory granules to the posterior pituitary and then it is released as per requirement of body. It has two main effects: uterine contraction and milk ejection from the lactating mammary gland.²⁵Review of literature show numerous doses finding studies regarding use of oxytocin in caesarean section. Butwick AJ and colleagues compared oxytocin in

Table-1: Hemodynamic variables after oxytocin bolus. (n=155)

Systolic / diastolic blood pressure (mmHg) Related to oxytocin intra-venous bolus						
Time interval	Baseline	1 minute	2 minutes	3 minutes	6 minutes	10 minutes
Mean	113.52 / 64.83	107.00 / 58.96	109.99 / 60.53	110.36 / 60.74	110.08 / 59.63	110.28 / 60.35
Std. deviation	16.708 / 14.519	17.81 / 15.91	16.58 / 12.83	14.22 / 13.40	14.44 / 13.26	13.54 / 12.91

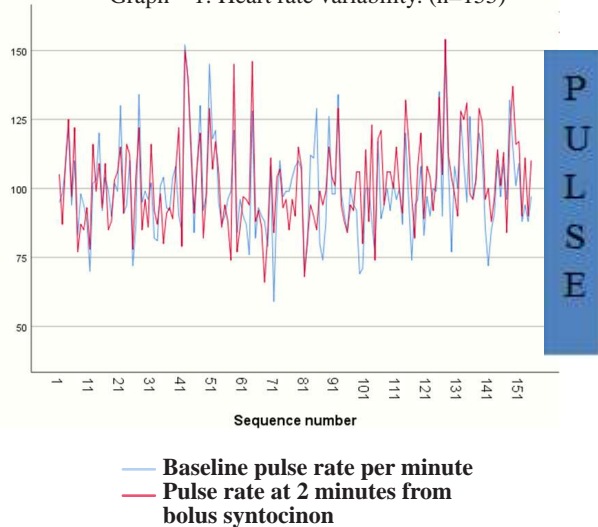
Table-2: Heart rate parameters after oxytocin bolus. (n=155)

Heart rate (per minute); related to oxytocin intra-venous bolus					
Time interval	Baseline	1 minute	3 minutes	6 minutes	10 minutes
Mean	99.48	105.74	99.24	98.72	98.66
Std. deviation	16.51	17.03	16.43	16.18	15.97

Table-3: Parameters noted in different groups. (n=155)

Bolus of oxytocin	Group-A (0.5 IU)	Group-B (1 IU)	Group-C (3 IU)	Group-D (5 IU)	Group-E (10 IU)	P-value
Mean age(years)	28.4	29.6	28.7	27.4	28.6	
Adequate uterine contraction	54.8%	35.5%	54.8%	61.3%	48.4%	0.314
Tachycardia after bolus	3.2%	6.5%	3.2%	12.9%	72.9%	0.38
Hypotension after bolus	9.7%	12.9%	19.4%	12.9%	32.3%	0.136
Epigastric discomfort after oxytocin bolus	0%	0%	6.5%	0%	3.2%	0.245
Top ups of oxytocin (once only)	51.6%	35.5%	29%	22.6%	35.5%	0.687
Top ups of oxytocin (more than once)	6.4%	22.6%	16.1%	10%	16.1%	
No top-up required	42%	41.9%	54.8%	54.8%	48.4%	

Graph – 1: Heart rate variability. (n=155)



boluses of zero (placebo group), 1, 3, 5 IU soon after delivery of baby followed by infusion of 5 IU /hour and at two minutes uterine tone was assessed that was same in all groups and 66 % in placebo group, however half of the patients in placebo group needed rescue oxytocin. None of the patients in 3 and 5 IU group required rescue oxytocin probably because uterine massage was also done in this study. The estimated blood loss was similar in all groups of this study which depicted that adequate uterine tone can be achieved with low doses of oxytocin.²⁶

Qian XW, et al. did a dose (ED 95) finding study of oxytocin infusion in 150 patients. All patients received oxytocin bolus of 1 unit soon after delivery of baby followed by infusion of 0,1,2,3,5, or 8 IU /hour as per category of patient. Uterine tone was assessed by gynecologist as adequate or inadequate requiring top up bolus of oxytocin. In this study ED 95 was estimate to be 7.72 IU. No difference was noted regarding oxytocin dose related side effects. This study suggested that dose of oxytocin required in post-partum period can be reduced if given as an infusion followed after bolus.²⁷ This regimen was adopted in our study.

Beiranvand S and colleagues in study stated that minimum

effective dose of oxytocin in non-laboring patients was 1 unit and in laboring patients it was 1.5 unit.²⁸ A study by Shashikiran and colleagues to determine minimum effective dose of oxytocin during cesarean delivery in high risk cases of uterine atony concluded that 0.405IU / min infusion of oxytocin was adequate and higher doses did not result in further improvement of uterine tone.²⁹ In study by Keikhaie KR and colleagues³⁰ stated in their study that high dose oxytocin infusion is needed to prevent atony and post-cesarean bleeding with no major side-effects.

Few limitations in our study were that variations in response to oxytocin that might be present with respect to history of previous caesarean sections and multi gravidity. The rescue bolus doses of oxytocin were incorporated in our study design to reduce the risk of uterine atony or bleeding for patients with in-adequate uterine tone as intra-venous bolus oxytocin has a short half-life of 4-10 minutes. We recognize that uterine tone assessment in our study was affected by use of rescue bolus doses. The subjective nature of uterine tone assessment by obstetrician in our study though a limitation but this assessment is in line with current obstetric practice until a more accurate tool is available for assessing uterine tone.

CONCLUSION:

It was concluded that low doses of oxytocin are as effective as high doses in terms of uterine contraction with minimal side effects

Author Contribution:
 Muhammad Salman Maqbool: Concept, Study Design, Planning, Experimentation, Study conduction, Drafting, Manuscript Writing, Data Analysis, Interpretation, Discussion, Critical Review, Final Approval of version
 Ayesha: Concept, Study Design, Planning, Experimentation, Study conduction, Drafting, Manuscript Writing, Data Analysis, Interpretation, Discussion, Critical Review
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