EFFECTS OF THREE DOSES OF OXYTOCIN (3, 5 AND 10 IU) ON HAEMODYNAMIC PARAMETERS, UTERINE TONE AND BLOOD LOSS IN ELECTIVE CAESAREAN SECTION UNDER SPINAL ANAESTHESIA- A PROSPECTIVE, RANDOMISED, DOUBLE-BLIND STUDY

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ABSTRACT

BACKGROUND

Obstetric haemorrhage due to uterine atony has been the major complication during elective caesarean section. Oxytocin either bolus and/ or infusion has been the drug of choice to reduce the incidence of peripartum haemorrhage because of less side-effects compared to other uterotonic drugs like methylergometrine. On literature search, we found that different doses of oxytocin ranging from 0.3 to 20 IU have been used by various researchers. Low doses were associated with inadequate uterotonic effect, whereas higher doses were found to be associated with serious haemodynamic side effects. Hence, we decided to find out minimal dose of oxytocin required to produce adequate uterine tone and stable haemodynamic parameters in women undergoing elective caesarean section.

The aim of this study is to compare the effects of three doses of oxytocin (3, 5 and 10 IU) on haemodynamic parameters, uterine tone and blood loss in elective caesarean section under spinal anaesthesia.

MATERIALS AND METHODS

This randomised, double-blind study was conducted in one hundred and fifty full-term pregnant women undergoing elective caesarean section under spinal anaesthesia. All patients received intravenous infusion of either 3 (O_3), 5 (O_5) or 10 (O_{10}) IU of oxytocin after foeto-placental delivery. Uterine Tone (UT) was assessed by obstetrician who was not aware of the drug doses as either adequate or inadequate using a five-point scale, where 1= atonic, 2= partial and inadequate, 3= adequate contraction, 4= well contracted and 5= very well contracted at 2, 4, 6 and 10 mins after oxytocin infusion. Oxytocin related side-effects (including hypotension) were recorded. Minimum effective doses of oxytocin were analysed according to effect on various circulatory parameters, uterine tone and blood loss during surgery.

RESULTS

Uterine Tone (UT) was significant in Groups O_3, O_5 and O_{10} ($p= 0.00$). Lower dose of oxytocin ($O_3 > O_5 > O_{10}$) was associated with less uterine tone and more blood loss ($p < 0.05$). The fall in SBP, DBP and MAP was statistically significant in Group O_{10} ($O_{10}>O_5>O_3$). Any other side effects if occurred were recorded.

CONCLUSION

Administration of 5 IU oxytocin as intravenous infusion in elective caesarean section resulted in adequate uterine tone, stable haemodynamic parameters, lesser blood loss and self-limiting side-effects as compared to 3 and 10 IU.

KEY WORDS

Blood Loss, Caesarean Section, Oxytocin, Post-Partum Haemorrhage, Uterine Tone.

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BACKGROUND

Uterine atony has been the main cause (30%) of obstetric haemorrhage in patients undergoing caesarean delivery**.** Use of uterotonic agents decreases the incidence of PPH by approximately 40% when compared with placebo.[1] Oxytocin, a naturally occurring peptide hormone produced by the posterior pituitary gland, is the most frequently and routinely administered drug after delivery by bolus and/ or infusion in both spontaneous or operative to initiate and maintain adequate uterine contractility, to minimise blood loss and prevent Postpartum Haemorrhage (PPH). Doses ranging from

0.3 to 20 units have been proposed for oxytocin administration during Caesarean Delivery (CD) by various authors.[2-5]

However, the administration of oxytocin has been associated with significant adverse events like nausea, vomiting, headache, hypotension, tachycardia, flushing, chest pain and ST/ T-wave abnormalities in ECG.[2,4.6,7] Even death has been reported after 10 IU bolus oxtocin.[8] In our hospital we have been using 10 units of oxytocin in 100 mL running drip, but we often come across side effects as observed by various authors. Hence, we decided to find out a minimal dose of oxytocin required to produce adequate uterine tone, minimal blood loss, stable haemodynamic parameters with minimal side effects in women undergoing elective caesarean section in an effort to improve patient's safety.

MATERIALS AND METHODS

It is a prospective, randomised, double-blind study. After obtaining approval from the Hospital Ethics Committee and written informed consent, this study was undertaken between July 2014 and July 2015.

We decided to restrict the group to 50 in each group as per the society 150 ASA grade I or II pregnant females between 18 and 35 years with singleton pregnancies posted for elective Lower Segment Caesarean Section (LSCS) deliveries were enrolled in the study. Patients with active labour, ruptured membranes, known drug allergy to oxytocin, multiple gestations, pregnancy-induced hypertension/ pre-eclampsia, high-risk cases for PPH, inherited or acquired coagulation disorder and thrombocytopenia (platelet count < 100×10^9) and significant cardiorespiratory diseases were excluded from the study.

All the 150 patients were examined a day before surgery for any other incidental finding, to obtain written consent and for randomisation by sealed envelope technique, thus making it 50 in each group was taken for convenience. According to the computer-generated codes (random numbers). Allocation concealment was achieved by placing the randomisation sequence for each technique (random numbers) in sequentially numbered, sealed, opaque envelopes. Drug administrator and monitoring observer along with obstetrician were kept blinded to both drug and the patient thus avoiding observer's bias. The anaesthesiologist who infused the study drug took no further part in the study.

Selected patients were randomly allocated into three groups by sealed envelope technique, (n= 50 each) depending upon the dose of oxytocin given after foeto-placental delivery as below:

Group–O_3 (n= 50)	3 IU of oxytocin mixed with 100 mL NS infused over a period of 2 - 4 minutes after foeto-placental delivery
Group–O_5 (n= 50)	5 IU of oxytocin mixed with 100 mL NS infused over a period of 2 - 4 minutes after foeto-placental delivery
Group–O_{10} (n= 50)	10 IU of oxytocin mixed with 100 mL NS infused over a period of 2 - 4 minutes after foeto-placental delivery

All the patients were kept nil orally for 6 hours before procedure. Upon arrival of the patient in the operation theatre, intravenous access with two 18-G cannula was established and preloading was done with ringer lactate @ 10-15 mL/kg body wt. within 20 mins before spinal anaesthesia from one intravenous cannula. Multipara monitor (Mindray BeneView T5 CM 23123727) was connected to observe and record basal (B0) electrocardiogram, heart rate (HR) and blood pressure (SBP, DBP and MAP) and SpO2.

Premedication

In operating room, all the patients were uniformly premedicated with Inj. Ranitidine 50 mg + Inj. Metoclopramide 10 mg + Inj. Ondansetron 4 mg IV before induction of anaesthesia.

Anaesthesia Procedure and Recording

With all aseptic precautions, Spinal Anaesthesia (SA) was performed in left lateral position by a 25-G Quincke type lumbar puncture needle and hyperbaric bupivacaine 2 - 2.2 mL was injected in subarachnoid L3-L4 space. Immediately, patient was moved to the supine position and left lateral uterine displacement of uterus was done with a wedge. Surgery was allowed to proceed after achieving a T6 sensory level to pinprick. After delivery of foetus and placenta, the study dose of Oxytocin prepared in 100 mL was administered as an IV infusion over a time period of 2 - 4 mins by an anaesthesiologist who took no further part in the study. HR, SBP, DBP and MAP were recorded as before spinal anaesthesia (S0) at 3 mins interval from spinal injection of LA till delivery of foetus (S0, S3, S6), thereafter at 2 mins intervals from the time of study drug administration till 6 mins and again at 10 mins (AD0, AD2, AD4, AD6 and AD10).

Any changes in haemodynamic values (±20% of basal value) were recorded and treated accordingly. Each episode of hypotension was treated with an IV bolus of 6 mg Mephentermine and increasing the rate of crystalloid infusion. Bradycardia was treated with Inj. Atropine sulphate 0.3 mg IV.

After the delivery of the foetus and placenta, the obstetrician who too was unaware of study drug doses assessed the UT by manual palpation of the uterus using the 5-point scale[9] at 2, 3, 6 and 10 minutes where 1= atonic, 2= partial but inadequate contraction, 3= adequate contraction, 4= well contracted and 5= very well contracted.

If UT was inadequate after 6 minutes of study dose, the rescue dose of 2.5 units of Oxytocin was given on the request of operating surgeon.

Approximate blood loss during surgery was estimated by swab weight, blood in suction bottle and visual appearance at operative site. 5 IU of oxytocin in 500 mL of NS was given as slow infusion over 8 hours in the post-operative ward as per hospital protocol. Oxytocin related side effects including hypotension, tachycardia, nausea, vomiting, flushing, headache, chest pain or cardiac arrhythmias if occurred were recorded.

The observations recorded in all the groups were tabulated and statistical analysis was carried out by using One-Way Analysis of Variance (ANOVA) followed by post-hoc Tukey test for comparing mean values of different groups (Intergroup Comparison). Repeated measure two-way ANOVA can be used for haemodynamic changes for 3 groups in comparison.

However, we have used One-Way ANOVA for 3 group comparison at every point of time to show significant difference between groups and for changes within group.

Paired t-test was used to know changes in parameter within each group from pre-value to different post values. These are also appropriate selection of statistical methods as per requirement. Fisher's test is used for intragroup comparison to compare the changes in pre- and post-values of variables.

Association between groups and parameter was analysed by Chi-square test. MS Excel and SPSS software version 17 was used to carry out all the statistical calculations. P-value >0.05 was taken to be statistically insignificant and p-value <0.05 was taken as statistically significant, whereas p-value <0.01 was taken to be statistically highly significant.

RESULTS

All the three study groups were comparable as regards to demographic data (Table 1) and baseline haemodynamic variables (Table 2).

A clinically as well as statistically significant increase in the HR was observed at all the stages (maximum at six minutes after administration of Oxytocin. An increase of 52.18% from baseline heart rate was observed in group O_{10} (Table 2).

All the three variables of blood pressure (SBP, DBP and MAP) showed a fall at all the stages of the study. Fall in SBP and MAP was maximum at 10 minutes after Oxytocin, whereas maximum fall in DBP was observed at six minutes of oxytocin administration (Table 2).

3 IU of Oxytocin appeared to be insufficient, as 94% patients had inadequate contraction of uterus (grade 2) at 4 minutes stage after Oxytocin, but obtained adequate contraction (grade 3) after 10 mins in 94% cases; 22% cases in this group required rescue dose of 2.5 IU of oxytocin as per study plan. None of the patients had grade 5 uterine contraction in this group. In oxytocin group O_{10}, at 10 minutes interval highest number of patients had grade 5 uterine tone as compared to group O_5 (84% vs. 46% respectively) (Table 3).

Blood loss during surgery was maximum in group O_3 as compared to group O_5 and O10 (878.00 ± 146.09, 806 ± 44.76 and 754 ± 60.47 mL respectively).

As shown in Table 4, hypotension and tachycardia was observed in 100% patients in group O_{10}. Similarly, group O_{10} had highest number of incidence of chest pain and nausea/ vomiting as compared to group O_3 and O_5.

Data	Group O_3	Group O_5	Group O_{10}
Age (Years)	25.56±2.72	25.06±2.96	24.62±2.67
Weight (kgs)	57.3±4.5	55±6.0	56±6.2

Table 1. Demographic Data (Mean ± SD)

[Values are mean ± SD, O_3 - Group receiving 3 units of oxytocin, O_5 - Group receiving 5 units of oxytocin, O_{10} - Group receiving 10 units], whereas p-value < 0.01 taken to be statistically highly significant.

H Var.	Groups	B_0	S_0	S_3	S_6	AD_0	AD_2	AD_4	AD_6	AD_{10}
HR (rate/ min)	O_3	87.04 ± 9.33	85.26± 8.24¥ (-2.045%)	89.36± 7.60 (+2.665%)	87.18± 7.14 (+0.160%)	88.80±8.41 (+2.022%)	91.08± 8.50¥ (+4.641%)	93.72± 8.62* (+7.674%)	114.40± 127.48 (+31.433%)	98.82± 8.34* (+13.534%)
	O_5	87.00± 9.74	82.36± 12.12¥ (-5.333%)	87.12± 11.36¥ (+0.137%)	90.94± 18.85* (+4.528%)	88.98± 11.36 (+2.275%)	92.52± 9.66 (+6.344%)	95.14± 10.47 (+9.356%)	97.96±10.21* (+12.597%)	98.36± 9.58 (+13.057%)
	O_{10}	86.08± 9.48	76.06± 9.65* (-11.640%)	89.56± 8.82 (+4.042%)	91.02± 11.24 (+5.738%)	85.66±14.14 (-0.487%)	119.76±7.42* (+39.126%)	124.66± 6.80* (+44.818%)	131.00± 7.80* (+52.184%)	116.00± 6.99* (+34.758%)
SBP (mmHg)	O_3	126.00± 8.29	120.60±9.50* (-4.285%)	115.68± 10.28* (-8.190%)	116.90± 15.29* (-7.222%)	116.62± 12.84* (-7.444%)	119.08±7.60* (-5.492%)	116.44± 11.11* (-7.587%)	108.88± 9.65* (-13.587%)	94.30± 25.82* (-24.10%)
	O_5	127.64± 5.55	118.54± 11.64* (-7.129%)	114.08± 9.01* (-10.623%)	111.04± 6.60* (-13.005%)	106.94 ±7.92* (-16.217%)	107.26± 4.46* (-15.966%)	104.18± 4.74* (-18.379%)	102.80± 4.76* (-19.460%)	98.96± 3.53* (-22.469%)
	O_{10}	127.68± 6.03	124.24±5.04* (-2.694%)	119.76± 4.69* (-6.203%)	116.04± 4.56* (-9.116%)	112.72± 5.73* (-11.716%)	108.24± 4.51* (-15.225%)	103.92± 4.48* (-18.609%)	110.04± 19.74* (-13.815%)	96.52± 5.88* (-24.804%)
DBP (mmHg)	O_3	80.94±10.11	78.90± 8.82* (-2.520%)	73.82± 11.13 (-8.796%)	76.80± 14.41* (-5.114%)	75.18± 11.90* (-7.116%)	73.64± 13.56* (-9.019%)	72.40± 10.98* (-10.551%)	67.16± 13.16* (-17.024%)	67.68± 6.73* (-6.382%)
	O_5	81.52± 7.54	78.14±10.39* (-3.459%)	75.76±8.11* (-6.399%)	73.68± 8.75* (-8.969%)	71.80± 9.22* (-11.292%)	70.68± 7.22* (-12.676%)	69.34± 4.94* (-14.331%)	66.62± 7.19* (-17.692%)	67.04± 5.21* (-17.173%)
	O_{10}	82.56± 3.08	85.32± 3.06* (3.343%)	82.12± 2.81 (-0.532%)	79.64± 2.96* (-3.536%)	76.04± 4.63* (-7.897%)	71.80± 3.98* (-13.032%)	68.44± 2.92* (-17.102%)	61.76± 3.99* (-25.193%)	70.40± 14.41* (-14.728%)
MAP (mmHg)	O_3	94.74± 8.41	92.04± 8.83 (-2.849%)	86.68± 10.80* (-8.507%)	89.80± 14.15 (-5.214%)	87.62± 12.42* (-7.515%)	87.68 ± 15.30¥ (-7.451%)	85.82± 8.31* (-9.415%)	81.72± 7.21* (-13.742%)	77.18± 5.74* (-18.534%)
	O_5	94.66± 4.93	90.86± 10.19* (-4.014%)	88.30± 8.08* (-6.718%)	85.30± 7.73* (-9.888%)	83.56± 7.93* (-11.726%)	82.36± 5.85* (-12.993%)	80.08± 4.76* (-15.402%)	77.82± 6.46* (-17.789%)	77.32± 4.08* (-18.318%)
	O_{10}	95.36± 3.86	97.90± 3.65* (+2.663%)	94.32± 3.35* (-1.090%)	90.92± 4.11* (-4.656%)	87.94± 4.51* (-7.781%)	83.58± 3.63* (-12.353%)	79.86± 2.99* (-16.254%)	76.46± 16.26* (-20.479%)	72.86± 4.02* (-23.594%)

Table 2. Haemodynamic changes at various time intervals of anaesthesia and after administration of oxytocin

[Values are mean ± SD, Values in brackets are mean percentage change from basal(+) - increase, (-) - decrease, H. Var. - Haemodynamic variables, HR - Heart rate, SBP - Systolic blood pressure, DBP - Diastolic blood pressure, MAP - Mean arterial pressure, O_3 - Group receiving 3 units of oxytocin, O_5 - Group receiving 5 units of oxytocin, O_{10} - Group receiving 10 units of oxytocin, B_0 - Basal value (0 minute), S_0 - Before Spinal, S_3 - 3 mins after Spinal, S_6 - 6 mins after Spinal, AD_0 - at the time of oxytocin administration, AD_2 - 2 mins after giving Oxytocin, AD_4 - 4 mins after giving Oxytocin, AD_6 - 6 mins after giving Oxytocin, AD_{10} - 10 mins after giving Oxytocin, HR - Heart rate, SBP - Systolic blood pressure, DBP - Diastolic blood pressure, MAP - Mean arterial pressure, ¥ - Significant value ($p < 0.05$), * - Highly significant value ($p < 0.01$)].

Grading of Uterine Tone	Time after Oxytocin Administration	Group O_3		Group O_5		Group O_{10}	
		No of Pt.	%	No of Pt.	%	No of Pt.	%
1	AD_2	0	0	0	0	0	0
	AD_4	0	0	0	0	0	0
	AD_6	0	0	0	0	0	0
	AD_{10}	0	0	0	0	0	0
2	AD_2	46	92	0	0	0	0
	AD_4	47	94	0	0	0	0
	AD_6	09	18	0	0	0	0
	AD_{10}	02	4	0	0	0	0
3	AD_2	02	4	17	34	0	0
	AD_4	01	2	05	10	0	0
	AD_6	39	78	04	08	0	0
	AD_{10}	47	94	00	00	0	0
4	AD_2	02	4	31	62	44	88
	AD_4	02	4	37	74	33	66
	AD_6	01	2	34	68	18	36
	AD_{10}	01	2	27	54	08	16
5	AD_2	00	0	2	04	06	12
	AD_4	00	0	08	16	17	34
	AD_6	01	2	12	24	32	64
	AD_{10}	00	0	23	46	42	84

Table 3. Assessment of Uterine Tone with dose of Oxytocin and Time Duration

[Grading of Uterine tone-1 = atonic, 2 = partial but inadequate contraction, 3 = adequate contraction, 4 = well contracted, 5=very well contracted, O_3 - Group receiving 3 units of oxytocin, O_5 - Group receiving 5 units of oxytocin, O_{10} - Group receiving 10 units of oxytocin, AD_2 - 2 mins after giving Oxytocin, AD_4 - 4 mins after giving Oxytocin, AD_6 - 6 mins after giving Oxytocin, AD_{10} - 10 mins after giving Oxytocin].

Sl. No.	Side-Effects and Complications	Group- O_3		Group- O_5		Group- O_{10}	
		(n)	(%)	(n)	(%)	(n)	(%)
1.	Hypotension (< 20%)	1	2%	6	12%	50	100%
2.	Hypertension (> 20%)	_	_	_	_	_	_
3.	Bradycardia (PR < 60 bpm)	_	_	_	_	_	_
4.	Tachycardia (PR > 120 bpm)	1	2%	1	2%	50	100%
5.	PVC/ Arrhythmia	_	_	_	_	_	_
6.	Chest Pain/ Ghabrahat	_	_	1	2%	4	13.33%
7.	Nausea/ Vomiting/ Flushing	_	_	1	2%	13	26%

Table 4. Incidence of Side Effects and Complications

[O_3 - Group receiving 3 units of oxytocin, O_5 - Group receiving 5 units of oxytocin, O_{10} - Group receiving 10 units]

DISCUSSION

Amongst various uterotonic drugs, Oxytocin is the commonest drug used to prevent blood loss after delivery of foetus and placenta. Still use of Oxytocin in caesarean deliveries is empirical and vague, although various societies like British National Formulary, American College of Obstetricians and Gynecologists and Society of Obstetricians and Gynecologists of Canada have issued guidelines for the use of Oxytocin in caesarean deliveries to prevent PPH.[10] We decided to compare the three doses of Oxytocin (3, 5 and 10 IU) by infusion to find out the minimum dose with maximum effect and minimal side effects in elective caesarean deliveries under spinal anaesthesia. Recently, more and more emphasis is given on reducing the speed of injection rather than dose of Oxytocin in view of potential sudden and severe haemodynamic instability following bolus dose.[11-13] Therefore, we decided to use oxytocin infusion instead of bolus dose to avoid potential harmful haemodynamic changes.

Our results shows that 3 units of oxytocin by infusion after foeto-placental removal from uterus resulted in stable haemodynamic variable, but produced lesser degree of uterine tone (grade 3) and high mean blood loss (878.00 ± 146.09 mL), whereas 10 units produced excellent uterine tone (grade 4/5), minimum mean blood loss (754 ± 60.47 mL) but higher degree of hypotension and tachycardia and other side effects in majority of patients, although these

changes were short lasting and self-limiting. Svantrom et al also reported profound tachycardia, hypotension and chest pain with ECG changes with 10 IU of oxytocin, but these changes were short lasting[7] Secher et al also found profound hypotension after 10 IU bolus oxytocin.[14]

Administration of 5 units of oxytocin after foeto-placental removal from uterus produced acceptable haemodynamic stability, adequate uterine tone (grade 4/5) in majority of the patients and mean blood loss of (806 ± 44.76 mL) in majority of the patients along with and minimal side effects. These results are in accordance of Pinder et al[4] and Thomas and Cooper[6] who also recorded rise in HR along with fall in MAP in infusion of oxytocin. Sarna[5] et al observed no further improvement in UT and blood loss if more than 5 IU oxytocin is used in non-labouring women undergoing caesarean delivery. The British National Formulary also recommends 5 IU oxytocin by slow intravenous injection after caesarean delivery.[15] Another survey in 2010 in Great Britain and Ireland also revealed greater reliance on 5 IU bolus.[16] Our results were in contrast to Butwick[3] et al who observed better haemodynamic stability and adequate UT with low doses (0.5 - 3 IU) as compared to % IU. They further stated that 5 IU dose regimen in caesarean deliveries needs to be re-evaluated.

One limitation of our study was that we enrolled only parturient posted for elective caesarean deliveries that had minimum clinical risk PPH due to uterine atony. The requirement of oxytocin may be different in patient with active labour. A significant difference was noted in uterine tone and need for additional uterotonics between labouring and non-labouring patients.[17]

CONCLUSION

Hence, we conclude that 5 IU Oxytocin on intravenous infusion after delivery of foetus and placenta produces good UT, less blood loss and stable haemodynamic parameters with self-limiting side effects.

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