Haemodynamic effects of intravenous bolus of carbetocin and oxytocin on women undergoing caesarean section

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Abstract

Background: Postpartum hemorrhage (PPH) is still the leading cause of maternal mortality in poor countries. There are many pharmacological options for the management of postpartum hemorrhage, oxytocin being the first line of treatment. There is as yet no evidence about the safety and efficacy of using carbetocin, an oxytocin agonist, in patients with PPH.

Objective: The objective of this study is to compare the haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean section.

Methods: This randomized control trial was conducted on 60 women more scheduled for Cesarean delivery in a selected teaching hospital. Patients were selected according to inclusion criteria. They were divided equally into two groups where Group-A (n1 = 30) patients received i.v. oxytocin 10 U/ml (0.5 ml) + 4.5 ml saline and Group-B (n2 = 30), received i.v. carbetocin 100 µg/ml (1 ml) + 4 ml saline. Then haemodynamic parameters were compared. Main outcome variables were Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean blood pressure (MAP), Heart rate (HR).

Results: The haemodynamic parameters at baseline were almost alike between two groups. After giving test drugs, haemodynamic parameters compared among 1 minute to 15 minutes and also observed similar result between two groups. No PPH found in carbetocin group. PPH ignored bleeding up to 800-1000ml in both groups. 3 cases of PPH found in oxytocin group, which was not statistically significant.

Conclusion: No significant difference in haemodynamic changes found in using carbetocin and oxytocin intravenously after caesarian section.

Keywords: Haemodynamic effects Carbetocin, Oxytocin, Postpartum haemorrhage, Caesarian section.

Introduction:

Oxytocin is the most commonly used uterotonic agent in obstetrics. It is routinely administered after both normal and operative delivery to initiate and maintain adequate uterine contractility for minimizing blood loss and preventing postpartum hemorrhage.[1, 2] Oxytocin injection (synthetic) acts on the smooth muscle of the uterus to stimulate contractions; response depends on the uterine threshold of excitability. It exerts a selective action on the smooth musculature of the uterus, particularly toward the end of pregnancy, during labor and immediately following delivery. Oxytocin stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions and raises the tone of the uterine musculature. It has a very short half-life of 4 to 10 minutes.[3, 4] Carbetocin is a long-acting synthetic oxytocin analogue,[5, 6, 7] 1-deamino-1-monocarbo-(2-O-Methyltyrosine)-oxytocin, firstly described in 1987. It has a half-life of 40 minutes (around 4–10 times longer than oxytocin) and uterine contractions occur in intravenous.

Administration of optimal dosage of 100 µg.[8] A single dose of carbetocin has been hypothesized to act as a 16 hours' intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section. Carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions, and increased uterine tone. The oxytocin receptor content of the uterus is very low in the non-pregnant state, and increases during pregnancy,

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reaching a peak at the time of delivery. J. S. Thomas[9] et al found marked cardiovascular changes occurred in the bolus dose oxytocin; the heart rate increased. The mean arterial pressure decreased. Giovanni Larciprete[10] et al recorded that regarding the haemodynamic effects, both drugs have a hypotensive effect, but a greater reduction in blood pressure within the oxytocin group. This study is undertaken to evaluate the impact of carbetocin versus oxytocin for relevant maternal haemodynamic parameters in a non-invasive set-up during caesarean delivery in a randomized control trial.

Materials & Methods:

This was a prospective randomized control study to compare haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean section in inpatients department of Gynaecology and Obstetrics of Bangladesh Medical College Hospital, Dhaka, during the period of 1st January 2016 to 30th June 2016. Ethical clearance was taken from the concerned authority. A total number of 60 patients were included in this study. These patients were divided into two groups consisting of 30 patients each, allocated randomly. Thirty patients received i.v. oxytocin 10 U/ml (0.5 ml) + 4.5 ml saline was considered as Group-A and rest 30 patients received I.V. carbetocin 100 µg/ml (1 ml) + 4 ml saline was considered as Group-B. Inclusion criteria were ASA grading I & II, age between 18-35 years, undergoing elective caesarean section under Sub arachnoid block & gestational age 36 weeks or more. Exclusion criteria were- ASA grading III & lV, emergency caesarean section, reported adverse reactions to any of the drugs included in the study, known hypertension (pregnancy induced hypertension), preeclampsia and eclampsia, placenta previa, placenta accrete, preoperative systolic blood pressure less than 90 mm of Hg, if required general anaesthesia due to failure of spinal anaesthesia, patient refusal, patients receiving sympathomimetic or sympatholytic drugs. Main outcome variables were Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean blood pressure (MAP), Heart rate (HR) were recorded just before giving the spinal anesthesia with the patient in a left lateral position. With the woman in a sitting position, spinal anesthesia was induced in the L3–L4 intervertebral space, and bupivacaine 12.5 mg were injected through a 27-Gauge spinal needle concomitantly i.v. infusion of Hartmann's solution (37°C, 10 ml/kg) were started. During surgery, the patient was supine with an operating wedge under her right hip (19°). The level of anesthesia was tested by cold sensation 5 minutes after spinal anesthesia as well as by pinching with surgical tweezers before skin incision. Either the study or control drug accordingly to injected slowly, over the course of 60 seconds, starting when the baby's head and shoulders were delivered. Systolic blood pressure, Diastolic blood pressure, Mean blood pressure and Heart rate were monitored before injection control or study drug and 1, 3, 5, 7, 9,11,13 and 15 minutes after injection. Patients were in close monitoring up to 24 hours after caesarean section. Hypotension was treated with i.v. Ephedrine and intravenous fluid infusion.

Statistical data analysis

All data presented as (mean±SD). Analysis of data was done by unpaired t-test & chi-square test. A p value <0.05 accepted as statistically significant. Statistical analysis was done by Statistical Package for Social Science (SPSS) for Windows version 20.0

Results:

Table 1: Demographic characteristics of patients (N=60)

	Group-A (Mean±SD)	Group-B (Mean±SD)
Age (Year)	26.5±4.5	27.2±4.8
Gestational age (weeks)	38.6±1.6	38.9±1.6
Weight (Kg)	59.3±3.0	59.9±2.3

Table 1 shows demographic characteristics of the study patients, it was observed that mean age was found in 26.5±4.9 years in Group-A and 27.2±4.8 years in Group-B. The mean gestational age was found 38.6±1.6 weeks in Group-A and 38.9±1.6 weeks in Group-B. The mean (SD) weight of the study patients were 59.3 ± 3.0 Kg in Group-A and 59.9 ± 2.3 Kg in Group-B, majority patients were in 55-60 kg weight group. The difference was not found statistically significant (p>0.05).

Table 2: Pre-operative assessment of patient

	Group-A No (%)	Group-B No (%)
Gravida-Multi	20 (66.7)	22 (73.3)
ASA G-I	18 (60)	21 (70)
ASA G-II	12 (40)	9 (30)

Table 2 shows Pre-operative assessment of the study patients. Majority 20(66.7%) patients were multi gravida in Group-A and 22 (73.3%) in Group-B. The ASA Grade I was 18(60%) in Group-A and 21(70%) in Group-B. The ASA Grade II was 12(40%) in Group-A and 9(30%) in Group-B. The difference was not statistically significant (p>0.05) between two groups. That is the groups were homogenous.

Table 3: Haemodynamic mean parameters comparison at different time after injection of drugs

	Baseline	1 min	3 min	5 min	7 min	9 min	11 min	13 min	15 min
Group-A									
SBP	117.3±7.8	116.7±7.5	111.5±11.7	109.±7.36	107.5±5.4	106.5±4.5	107.3±4.5	105.0±8.1	104.0±11.1
DBP	76.3±5.6	75.7±6.8	72.8±8.6	54.5±3.8	74.0±7.9	74.8±3.6	71.3±3.6	70.1±4.3	65.30±9.1
MAP	81.3±5.6	88.9±7.0	86.4±5.8	73.3±5.4	74.2±6.2	73.3±5.8	74.7±4.2	69.9±5.3	67.9±5.3
HR	85.7±3.92	89.5±8.4	92.3±10.6	98.0±2.8	91.8±5.5	88.1±7.5	91.8±5.2	93.2±2.3	92.5±3.0
Group-B									
SBP	120.0±6.9	119.7±6.7	113.2±10.	108.±6.9	108.7±4.3	107.6±3.6	106.9±3.6	105.±7.4	108.5±11.4
DBP	78.7±4.3	77.8±4.9	73.5±8.9	73.7±8.1	55.0±3.6	73.3±4.9	72.3±4.9	74.9±4.8	67.5±8.4
MAP	81.7±4.1	86.4±4.4	86.3±6.2	72.0±6.0	74.7±7.3	73.4±6.2	74.3±5.3	74.8±6.4	70.8±6.4
HR	87.7±5.2	86.9±9.5	91.3±11.5	97.6±2.2	99.4±4.4	87.5±6.6	90.1±2.1	90.4±3.5	89.3±2.60

Table 3 shows, in Group-A: SBP decreases from baseline to 15 min gradually. DBP also follows the same pattern, but it shows a drop at 5 min reading, then again rises, and after that gradually decreases to 15 min reading. MAP rises from baseline to 1min reading, then gradually decreases to 15 min reading. HR rises from baseline to 5 min reading, then gradually decreases to 15 min reading with a drop at 9 min reading.

In Group-B: SBP decreases from baseline to 15 min gradually. DBP also follows the same pattern, but it shows a drop at 7 min reading, then again rises, and after that gradually decreases to 15 min reading. MAP rises from baseline to 1min reading, then gradually decreases to 15 min reading. HR rises from baseline to 7 min reading, then gradually decreases to 15 min reading with a drop at 9 min reading.

The mean difference of all haemodynamic parameters were not statistically significant (p>0.05) in unpaired t-test.

Table 4: Mean and Range of SBP and DBP of Group-A and Group-B.

	Group A		Group B	
	Mean	**Range**	**Mean**	**Range**
SBP	109.4 mm Hg	125.1-92.9 mm Hg	110.8 mm Hg	126.9-97.1 mm Hg
DBP	70.5 mm Hg	50.7-81.9 mm Hg	71.8 mm Hg	51.4-83 mm Hg

Mean SBP in Gr-A and Gr-B is 109.4 mm Hg and 110.8 mm Hg; mean DBP is 70.5 mm Hg and 71.8 mm Hg in in both groups respectively.

Table 5: Changes in MAP

MAP	Group-A	Group-B
Decrease in MAP	24 mmHg	12 mmHg
Range of Decrease in MAP	19-32 mmHg	8-18 mmHg

Decrease in MAP in group A and group B is 24 mmHg and 12 mmHg respectively. In group A and in group B range of decrease is 19-32 mmHg and 8-18 mmHg.

Table 6: PPH between Group-A and Group-B

Status of PPH	Group-A	Group-B
PPH	3 cases (10%)	00

PPH ignored bleeding up to 800-1000ml in both groups. three cases of PPH found in oxytocin group, which was not statistically significant. PPH was 10% in Group-A (Table 6).

Discussion:

This prospective randomized control study was carried with an objective to compare the haemodynamic effects in blood pressure and heart rate in carbetocin and oxytocin group after caesarean section.

In this current study in Table-1, it was observed that mean age was found in Group-A 26.5±4.9 years and 27.2±4.8 years in Group-B. No significant differences were found between group A and group B. Similarly, Mohamed et al.[11] found non-significant difference between oxytocin group and carbetocin group as regards age, where mean of group A was 26.97 years and 26.09 years in group B. Fahmy et al.[12] observed that the mean age was found 25.4 ±4 years in group A and 24.5 ±3 years in Group-B, which are closely resembled with the present study. On the other hand, Holleboom et al.[13] had observed the mean age was 33.3±4.6 years in Oxytocin group and 33.0±4.6 years in Carbetocin group. Similarly, Uy et al.[14] observed at baseline, there was no significant difference between oxytocin and carbetocin in terms of mean age, where mean was 31 years and 30 years respectively. The higher mean age may be due to geographical variations, racial, ethnic differences, genetic causes, different lifestyle and increased life expectancy may have significant influence in their study patients.

In this present study it was observed that the mean gestational age was found 38.6±1.6 weeks in Group-A and 38.9±1.6 weeks in Group-B. The mean gestational age was not statistically significant (p>0.05) between two groups, which is consistent with Uy et al.[14] study, where the investigators found there was no significant difference between oxytocin and carbetocin in terms of mean gestational weeks (P>0.05). Holleboom et al. [13] found that the mean gestational age was found 38.8±1.0 weeks in Oxytocin group and 38.9±1.0 weeks in carbetocin group. The difference was not statistically significant (p>0.05) between two groups, which is consistent with the present study. Similarly, Larciprete et al.[10] and Reyes et al.[15] had observed the identical mean gestational age of their studied patients, thus support the present study.

In this current study, it was observed that the mean (SD) weight of the study patients were 59.3 ± 3.0 Kg in group-A and 59.9 ± 2.3 Kg in group-B, majority patients were in 55-60 kg weight group. No significant differences were found between Group-A and Group-B, which is similar with Kim et al. [16] study.

In this current study it was observed that majority 66.7% patients were multi gravida in Group-A and 73.3% in Group-B (Table -2). The difference was not statistically significant (p>0.05) between two groups. Similarly, Uy et al. [14] found at baseline, there was no significant difference between oxytocin and carbetocin in terms of parity (p>0.05). Holleboom et al. [13] undertook a study and observed multigravida 23.1% and 28.3 in oxytocin and carbetocin group respectively. The difference was not statistically significant (p>0.05) between two groups.

In this current study, it was observed that the ASA Grade was almost two third 60% belonged to grade I in group A and 70% in groups B. The difference was statically not significant (p>0.05) between two group. Bhattacharya et al.[1] observed that 77.50% had ASA grade I and 25.0% ASA grade II in Group-A. In Group-B, 77.5% patients had ASA grade I and 22.5% ASA Grade II, which is consistent with the current study.

In this current study in Table-3, it was observed that the haemodynamic parameters result at baseline and found that the mean (SD) heart rate was 85.73.92 beats/min range from 80 to 90 beats/ min in group-A and 87.75.2 beats/min range from 81 to 92 beats/ min in group-B. The mean (SD) systolic BP was 117.37.8 mmHg in Group-A and 120.06.9 mmHg in Group-B. Similarly, the mean (SD) diastolic BP was 76.35.6 mmHg in Group-A and 78.74.3 mmHg in Group-B. The mean difference of all haemodynamic parameters at preoperative period were not statistically significant (p>0.05) in unpaired t-test.

Fahmy et al.[12] observed the mean heart rate was found 76.2±5.16 (beats/min) in Group-A and 75.9±4.9 (beats/min) in Group-B. In another study Mohamed et al[11]. (2015) observed that the mean systolic blood pressure 110.1 (mm Hg) with the range from 80-130 (mmHg) in oxytocin group and 98.8 (mmHg) with the range from 80-130 (mmHg) in carbetocin group and the mean diastolic blood pressure 71.7 (mmHg) with the range from 50-90 (mmHg) in oxytocin group and 65.4 (mmHg) with the range from 40-80 (mm Hg) in carbetocin group, which are consistent with the current study (Table 4). Similar findings also observed by Larciprete et al[10] after giving test drugs, parameters compared between 1 minute to 15 minute.

The current study (Table 5**)** demonstrated an average decrease in MAP of 24 mmHg ranged from 19 to 32 mmHg in group A, whereas in group B average decrease in MAP of 12 mmHg range from 8 to 18 mmHg. Whilst this magnitude of decrease in MAP may be well tolerated normally. In the present study it was observed that the changes in heart rate were significantly higher in group A with compared to group B. However, the gentler increase of heart rate in group B is preferable clinically. Thomas et al.[9] (2007) found in their study that the decrease in MAP of 8(8.7) mmHg and the small increase in HR are certainly clinically preferable, which is closely resemble with the present study.

Uy et al.[14] found systolic and diastolic BP were not significantly different immediate post intervention between the two groups, immediate post-operative and while recovering between groups were also not significant. Attilakos et al.[5] showed there were significant changes with time for each of systolic blood pressure and diastolic blood pressure respectively but no significant main effect of group, which are similar with the current study.

In this current study (Table 6), it was observed that all patients had bleeding up to 800-1000ml in both groups. Holleboom et al.[13] showed the blood loss were also comparable in both groups. In another study Larciprete et al.[10] reported that there was no significant difference in the amount of estimated blood loss and the incidence of primary post-partum haemorrhage in both groups. In fact, the investigators did not demonstrate any difference in the amount of blood loss after caesarean section. In another study Uy et al.[14] found that the estimated blood loss was significantly lower in the carbetocin group.

In this current study (Table 6**)**, it was observed that 10.0% patients had primary PPH in Group-A and not found in Group-B. PPH was comparatively higher in group A, but the difference was not statistically significant **(**p>0**.**05**)** between two groups**.** Similarly, Holleboom et al.[13] found PPH 8.4% and 7.8%, in oxytocin and carbetocin group respectively. In another study Larciprete et al.[10] reported that there was no significant difference in the amount of estimated blood loss and in the incidence of primary post-partum haemorrhage in both groups.

Conclusion:

This study was undertaken to evaluate the Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean section. Age, parity, gestational age, weight and indication of C/S were almost similar between two groups. All patients had almost stable haemodynamic status in carbetocin group and oxytocin group. Fewer side effects and no primary PPH observed in carbetocin group. Therefore, it can be concluded that both drugs have comparable haemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use. Minimal differences in the recovery phase are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin. Single dose of carbetocin appears to be more effective than oxytocin for several hours on uterine contraction.

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