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Oxytocin versus Carbetocin in the prevention of primary post-partum haemorrhage in hypertensive disorders of pregnancy

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Abstract
Objective: To compare the effectiveness of oxytocin and carbetocin to prevent primary PPH in hypertensive disorder of pregnancy.
Methods: It was a randomized single blind controlled clinical trial, which includes 100 women with hypertensive disorders of pregnancy according to inclusion and exclusion criteria who admited in the Department of Obstetrics and Gynaecology, Institute of Child and Mother Health, (ICMH), Matuail from March 2015 to February 2016. There were two groups by randomization by computer generated code number. Fifty cases were included in each group. Group I received oxytocin and group II received carbetocin for active management of 3rd stage of labour. Main outcome measures estimated were blood loss, change in hemoglobin level before and after delivery, occurrence of PPH. Data were analyzed by computer based software SPSS windows 20.0 version.
Results: This study shows majority of the patients belonged to 21-25 years age group. In management of 3rd stage of labour four (8%) of patients of carbetocin group were required additional uterotonic but in oxytocin group additional uterotonics were required for 82% patients. Fourteen percent needed for blood transfusion in oxytocin group but no need for blood transfusion in carbetocin group. Average blood loss were higher in oxcytocin group than carbetocin group which was 592 ml vs 348 ml. In very few patients had developed side effects like nausea in 4% and abdominal pain in 6% of carbetocin group also nausea in 4%, headache in 2% and abdominal pain in 8% in oxytocin group.
Conclusion: This study showed primary postpartum haemorrhage was less and very few patients needed additional uterotonics in carbetocin group. But majority patients needed additional uterotonics in oxytocin group. There was higher blood loss in oxcytocin group than carbetocin group. So carbetocin is an appropriate alternative to oxytocin for the prevention of primary PPH in hypertensive disorder of pregnancy.

Keywords: Oxytocin, Versus Carbetocin, Post-Partum Haemorrhage, Pregnancy

Introduction
Haemorrhage and hypertensive disorder are the greatest contributors to maternal death in developing countries accounting for more than 30% of direct cause. Postpartum haemorrhage (PPH) is one of the major contributors of maternal mortality and morbidity worldwide. It accounts for 25-35% of all maternal deaths worldwide. World Health organization (WHO) defines primary postpartum haemorrhage (PPH) as blood loss from genital tract of 500 ml or more in the first 24 hours after delivery of the baby The global prevalence of PPH is approximately 6% of all deliveries, whereas in low income countries the prevalence varies from 8.6 to 18.7%, while in Bangladesh it is 31%. Another major contributor to maternal death and morbidity is pre-eclampsia complicating 8% of pregnancies worldwide and 2-5% in developing countries. Preeclampsia also increase the risk of PPH. The lower maternal mortality rate (MMR) attributed to PPH in developed countries suggests that medical interventions utilized for prevention and treatment of PPH contributes significantly to survival of this obstetrical emergency [1]. The Government of Bangladesh is committed to achieve Millennium Development Goal 5. The Maternal Mortality Ratio (MMR) has declined significantly by around 40.0% from 322 to 194 between Bangladesh Maternal Mortality and Health Care Survey (BMMS) 2001 and BMMS 2010 and the goal is to reduce

MMR to 143 deaths per 100,000 live births by 2015. PPH mostly occurs during the third stage of labor after delivery of the baby and before delivery of the placenta, when the uterus may suddenly lose its ability to contract. Around 80% of case of postpartum haemorrhage caused due to uterine atony. So higher awareness is indicated during the 3rd stage of labour in a women with pre-eclampsia. For the prevention of PPH and successful management of 3rd stage of labour we need effective uterotonic drugs. Oxytocin is the most widely available and used uterotonic agent. It binds to the myometrial oxytocin receptors and stimulates contraction of the uterine muscle by increasing the intracellular concentration of calcium. Oxytocin has a short half- life of 3-17 minutes, and a continuous intra venous (IV) infusion is necessary to achieve sustained uterotonic activity. Moreover, large doses or boluses of oxytocin are associated with adverse effects in the form of hypotension, nausea, vomiting, dysrhythmias, ST-T changes, pulmonary edema and severe water intoxication with convulsions. The deamination protects carbetocin from aminopeptidase cleavage, and the replacement of the disulfide bond by CH_2S protects the analogue from disulfidase cleavage. This is the suggested explanation for the protracted half-life of carbetocin in plasma. Another suggested explanation for the prolonged activity of carbetocin is its higher lipophilicity that can alter its tissue distribution. Atke *et al.* [2] suggested that this increased lipophilicity was responsible for an increased half-life in the receptor compartment. The use of carbetocin as uterotonic drug is started very recently in our country but there is yet very few study in our country about the effectiveness of this carbetocin for prevention of PPH in hypertensive disorders of pregnancy. The safe motherhood initiative is a global effort to reduce maternal mortality and morbidity. The aim of modern obstetrical practice is to achieve a healthy mother and healthy baby by proper management of obstetrical problems. Any potential for the improvement in management of PPH and hypertensive disorders of pregnancy should be investigated.

Materials and Methods

Type of study: It was a randomized single blind controlled clinical trial.

Place of study: The study was carried out in the Department of Obstetrics and Gynaecology, Institute of Child and Mother health, Matuail, Dhaka, Bangladesh.

Duration of study: The study was carried out from March 2015 to February 2016.

Study population: Term pregnancy with hypertensive disorder who were admitted in the Department of Obstetrics and Gynecology in Institute of Child and Mother health, Matuail (ICMH) were study participants.

Sample size: There were two groups by randomization by computer generated code number. Fifty cases were included in each group. Group I received oxytocin and group II received carbetocin for active management of 3rd stage of labour.

Inclusion criteria

1. Term pregnancy with mild pre-eclampsia.

Exclusion criteria

1. Placenta praevia
2. Placental abruption
3. Severe Pre eclampsia
4. Eclampsia
5. Cardiac, renal or liver disease
6. Epilepsy
7. Cervical or any other perineal tear
8. Women with history of hypersensitivity to carbetocin and oxytocin.

Study procedure: It was a randomized single blind controlled clinical trial. It was done from March 2015 to February 2016 in the department of obstetrics and gynaecology in Institute of Child and Mother Health, Matuail, Dhaka. 100 term pregnant women with mild preeclampsia who were admitted in the hospital were enrolled for the study. The participates were selected after fulfilling the inclusion and exclusion criteria. Randomization was done by computer generated code number. Inclusion criteria was term pregnancy about 37 to 42 weeks with mild preeclampsia with diastolic blood pressure more than 90 but less than 110 mm of Hg and systolic blood pressure more than 140 but less than 160 mm of Hg were selected. Severe preeclampsia where BP more than 160/110 mm Hg. was excluded from the study because of alarming high rise of blood pressure in pregnancy may have an uneventful outcome like convulsion, HELLP syndrome, low platelet count, IUGR which causes chance of drop out of the patient from the study. Beside these we only select haemodynamically stable patient both mother and foetus. Once the decision to interrupt the pregnancy was made or if the patient went into labour spontaneously, written informed consent was obtained at an early stage of labour by one of the investigators. After taking informed consent detailed, relevant history and examination findings was assessed. All patients were in stable condition. There was no evidence of maternal hemodynamic instability or fetal distress before randomization. The patients were randomized to receive a single dose of either carbetocin (100 pgm) intravenously or injection oxytocin 2 ampule (10 Unit) intramuscularly after the delivery of baby (Following either vaginal birth or Caesarean section) before delivery of placenta. The randomization protocol required a designated member of the staff to open a sealed, opaque envelope containing a computer generated code randomizing the patient into one of the two groups. This code was used to identify the patient and the patient did not know which drugs were used.

To estimate the amount of blood loss a standardized delivery mat (Quaiyum's mat) was used at delivery table and five (05) pre-weighed standard sanitary pads were given for patients use after delivery upto 24hrs. The amount of blood loss in NVD was estimated by weighing the soaked mat and soaked pad and determining the difference between the soaked and unsoaked materials. Method of measurement of blood loss during C/S was done by using pre- weighed dry mobs during operation. No sucker was used for blood sucking. Blood loss during operation after the delivery of baby was taken by the pre- weighted dry mobs. Weight of mobs were measured before and after soaking with blood. Women were advised to preserve the soaked mat and all soaked pads in a sealable container that was provided by the study staff members. The primary outcome was measure by amount of blood loss within 24 hours after delivery. Primary PPH was diagnosed

when blood loss ≥ 500 ml within 24 h of delivery in both group. Within the defined period research team consider one full-soaked mat (448 ml) and nine full soaked sanitary pads (540ml) as cut of marker for severe PPH (1048 ml).
Secondary outcome like intensity of uterine contraction was assessed by abdominal examination of uterus, need of additional uterotonics during the first 24 hours. Uterine atony (Determined by physical examination and continuous postpartum bleeding) was considered a therapeutic failure and additional uterotonics were used (Oxytocin and/or prostaglandin, ergometrin and the decision of the attending physician). Any requirement for blood transfusion also recorded. Hemoglobin estimation was done from venous blood by autoanalyzer. Antepartum and postpartum Hb gm/dl difference was recorded. Vital signs (Blood pressure, heart rate, respiratory rate) and urine output were measured according to standard protocol.

Data analysis: Statistical analyses were carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The qualitative observations were indicated by frequencies and percentages. Noncontinuous variables were analyzed using the Chi-Square test. Student t-test were used for continuous variables if applicable. P values <0.05 were considered as statistically significant.

Results

Table-1 shows maximum patients were 21-25 years in age group between two groups. Also majority were house wives in both groups and belong to middle class status. Mode of clinical trial was not significantly associated with occupation and socio-economic status. Table shows age was 25.54±4.50 years in carbetocin group and 26.62±4.04 years oxytocin group. The BMI was 24.6±1.3 kg/m² in carbetocin group and 24.3±1.6 in oxytocin group. The mean preoperative systolic BP of patients were 145.60±26.66 mm of Hg and diastolic BP were 98.40 ±17.30 mm of Hg in carbetocin group and mean systolic BP were 148.00±17.37 mm of Hg and diastolic BP were 98±7.55 mm of Hg in oxytocin group. The difference was statistically not significant in respect of age, BMI and BP between two groups.

Table 1: Baseline and socio-demographic characteristics of study subjects (n=100)

Age in years	Carbetocin (n=50)		Oxytocin (n=50)		P value
	n	%	n	%	
≤20	7	14	3	6	
21-25	22	44	20	40	
26-30	14	28	17	34	
31-35	7	14	10	20	
Age (Mean± SD)	25.54±4.50		26.62±4.04		0.210
Occupation					
House wife	42	84	46	92	0.469
Service holder	2	4	1	2	
Garments worker	6	12	3	6	
Socio-economic					
Middle	28	56	32	64	0.414
Lower	22	44	18	36	
BMI(Mean± SD)	24.6±1.3		24.3±1.6		0.86
Systolic BP(Mean± SD)	145.60±26.66		148.00±17.37		0.595
Diastolic BP(Mean± SD)	98.40±17.30		98.00±7.55		0.881

Data were analysed using chi-square test

Table 2: Association of Gravida and mode of delivery with type of treatment (n=100)

Obstetrical characteristics	Carbetocin (n=50)		Oxytocin (n=50)		P value
	n	%	n	%	
Gravida					
Primi	29	58	28	56	0.840
Multi	21	42	22	44	
Mode of delivery					
Normal	28	56	19	38	0.109
C/S	22	44	31	62	

Data were analysed using chi-square test

Table-2 shows 58% were primi and 42% were multi in carbetocin group. On the other hand 56% were primi and 44% were multi in oxytocin group. Regarding mode of delivery 56% were normal and 44% were caesarean section in carebtocin group. On the other hand 19% were normal and 62% were caesarean section in oxytocin group. Analysis revealed that mode of clinical trial had no association with Gravida and mode of delivery.

Table 3: Distribution of study subjects according to outcome of clinical trial with carbetocin and oxytocin (n=100)

	Carbetocin (n=50)		Oxytocin (n=50)	
	n	%	n	%
Uterine tonicity				
Flabby	4	8	41	82
Contracted	46	92	9	18
Need for additional uterotonics				
Yes	4	8	41	82
No	46	92	9	18
Occurrence of primary PPH				
Yes	1	2	7	14
No	49	98	43	86
Need for blood transfusion				
Yes	0	00	7	14
No	50	100	43	86

Table 4: Association between mode of clinical trial and unterine tonicity, need for additional uterotonics and need for blood transfusion (n=100)

Uterine tonicity	Carbetocin (n=50)	Oxytocin (n=50)	P value
Flabby	4	41	0.001
Contracted	46	7	
Need for additional uterotonics			
Yes	4	41	0.001
No	46	9	
Need for blood transfusion			
Yes	0	7	0.001
No	50	43	

Data were analysed using chi-square test

Table-3 shows 8% had flabby uterus in carbetocin group and 82% had flabby uterus in oxytocin group. Significantly higher contracted uterus found with carbetocin than oxytocin (p<0.01).

Table-4 shows 8% had flabby in carbetocin group and 82% had flabby in oxytocin group. In additional uterotonics, 8% need for additional uterotonics in carbetocin group and 82% need for additional uterotonics in oxytocin group. Higher occurrence of primary PPH in oxytocin group than carbetocin group. 14% need for blood transfusion in oxytocin group but no need for blood transfusion in carbetocin group.

Table 5: Relationship between mode of clinical trial and primary PPH (n=100)

Occurrence of primary PPH	Carbetocin (n=50)	Oxytocin (n=50)	P value
	n	%	
Yes	4	7	0.027
No	49	43	

Data were analysed using chi-square test

The table-5 shows that occurrence of primary PPH in carbetocin group is almost negligible (p<0.05).

Table 6: Mean average blood loss according to category of clinical trial & mode of delivery (n=100)

	Carbetocin (n=50)	Oxytocin (n=50)	P value
	(Mean± SD)	(Mean± SD)	
NVD	329±23.31	572±28.75	0.001
CS	366±7.18	612±9.24	0.001
P value	0.001	0.001	

Data were analysed using unpaired and paired 't' test

The table-6 shows that mean blood loss in carbetocin group is less than blood loss in oxytocin group.

Table 7: Hb (gm/dl) status of the study subjects according to mode of clinical trial (n=100)

	Carbetocin (n=50)	Oxytocin (n=50)	P value
	(Mean± SD)	(Mean± SD)	
Antepartum Hb (gm/dl)	10.70±0.30	10.58±0.37	0.083
Postpartum Hb (gm/dl)	9.72±0.24	9.16±0.90	0.001
P value	0.001	0.001	

Data were analysed using unpaired and paired 't' test

Table-7 shows antepartum Hb were 10.70±0.30 mg/dl in carbetocin group and 10.58±0.37 in oxytocin group. In postpartum Hb 9.72±0.24 gm/dl were carbetocin group and 9.16±0.90 were oxytocin group. The difference was statistically significant between two groups (p<0.05).

Table 8: Association of adverse effects with mode of clinical trial (n=100)

Side effect	Carbetocin (n=50)		Oxytocin (n=50)		P value
	n	%	n	%	
Nausea					
Yes	2	4	2	4	1.00
No	48	96	48	96	
Headache					
Yes	0	00	1	2	0.315
No	50	100	49	98	
Abdominal pain					
Yes	3	6	4	8	0.695
No	47	94	46	92	

Data were analysed using chi-square test

Out of 50 cases, 2 patients had developed nausea and only 3 cases had abdominal pain in carbetocin group. On the other hand in oxytocin group 2 patients had developed nausea, 1 patients headache and 4 cases had abdominal pain. The difference was statistically not significant between two groups (p>0.05) (Table-8).

Discussion

Postpartum hemorrhage (PPH) remains a major killer of women worldwide. Carbetocin is well tolerated and the safety profile is similar to that of oxytocin [3]. This study aimed to compare the effectiveness of oxytocin and carbetocin to prevent primary PPH in hypertensive disorder of pregnancy. This study shows the mean age of study patients were 25.54 years in carbetocin group and 26.62 years in oxytocin group. In this study, mean preoperative systolic BP of patients were 145.60±26.66 mm of Hg and diastolic BP were 98.40 ±17.30 mm of Hg in carbetocin group and mean systolic BP were 148.00±17.37 mm of Hg and diastolic BP were 98±7.55 mm of Hg in oxytocin group. Debbie-lynuy *et al*. [4] showed that mean preoperative systolic BP of study patients in carbctocin group were 117±6.8 mm of Hg and diastolic BP were 69 ±7.7 mm of Hg and mean preoperative systolic BP were 118±8.3 mm of Hg and diastolic BP were 73±18.5 mm of Hg in Oxytocin group. Ahmed Mohamed Maged *et al*. [5] have randomized 200 women undergoing vaginal delivery in high risk women the average gestational age were 39.4±1.3 weeks in carbctocin group and 39.2±1.4 weeks in oxytocin group, which almost similar to our study; 39.01±1.1 weeks in Carbetocin group and 3 9.09± 1.7 weeks in oxytocin group. They also showed that there was no significant difference between the two study groups regarding occurrence of adverse effects of both drugs. In the current study, there were no major adverse effects observed in both groups. In this study, none of patients in carbetocin group needed blood transfusion but in oxytocin group blood transfusion were required in 14% patients. Behery *et al*. [6] showed that none

of women in carbetocin group required blood transfusion, while 15.5% in oxytocin group required blood transfusion. In this study four (8%) of patients of carbetocin group required additional uterotonic drugs but in oxytocin group additional uterotonics drugs were required in 82% patients. Behery *et al*. [6] showed that none of the patient in carbctocin group required additional uterotonics drugs while 71.5% of women in oxytocin group needed additional oxytocin to ensure adequate uterine contraction for long period. Samimi *et al*. [7] also showed the comparison between carbetocin with oxytocin, prophylaxis of uterine atony with carbetocin after an elective caesarean section diminished the need for additional uterotonics by more than 50% in oxytocin group. Debbie-lynuy *et al*. [4] showed that only 5.7% patients were need for additional uterotonics in carbetocin group and 34.3% patients in oxytocin group. In this study average blood loss in carbctocin group was 348 ml and oxytocin group is 592 ml. This fact can be explained by the known longer half-life of carbetocin. As compared to oxytocin, the carbetocin molecule is better protected from the effects of aminopeptidases and disulfidases, prolonging the half-life and decreasing enzymatic degradation. Reyes *et al*. [8] also showed the mean amount of blood loss in carbctocin group was 366 ml and oxytocin group were 400 ml when compared the efficacy of carbetocin with oxytocin. Average 34 ml more blood loss was observed in oxytocin group. Ahmed Mohamed Maged [5] showed the mean amount blood loss in carbetocin group was 337 ml and oxytocin group were 378 ml. Average 41 ml more blood loss was observed in oxytocin group. Elsafty *et al*. [9] showed that amount of blood loss in third stage of labour was an average of 207 ml of blood in the oxytocin group and an average of 87 ml of blood in carbetocin group. Average 120 ml more blood loss was observed in oxytocin group. It was concluded that Carbetocin is effective in preventing postpartum hemorrhage in both high and low risk groups [10]. In this study, occurrence of PPH in oxytocin group 7 (14%) of patients but in carbetocin group only one (2%) of patients had developed PPH. Ahmed Mohamed Maged *et al*. [5] also showed the occurrence of PPH were 4% in carbetocin group and 16% in oxytocin group. No significant side effect observed in this study. Nausea occurred in 4% cases and 6% occurred in abdominal pain in carbetocin group and nausea occurred in 4% cases, 2% headache and 8% occurred in abdominal pain in oxytocin group. Nausea and abdominal pain were common side-effects of carbetocin, as found in previous studies [5, 11, 12]. Yuen *et al*. [13] reported carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties. It has a rapid onset of action and a prolonged duration of action relative to oxytocin. It is administered as a single-dose of 100µg either intravenously or intramuscularly. Irrespective of the route of administration, carbetocin produces tetanic uterine contractions within 2 minutes. However, the tetanic contractions last for 11 minutes followed by rhythmic contractions for 120 minutes after intramuscular injection, which are both twice as long when compared with that following intravenous injection (6 minutes and 60 minutes respectively). However, it was associated with a significantly lower incidence of nausea, vomiting, and hypertension, but a significantly higher incidence of tachycardia.

Conclusion

Higher contracted uterus with less primary PPH were observed among the patients treated with carbetocin. Additional uterotonics was needed only in very few patients in carbetocin as compared to oxytocin treated group. A single dose carbetocin is more effective than oxytocin for maintaining adequate uterine tone, blood loss and preventing postpartum haemorrhage in next 24 hrs. Thus carbetocin appears to be an effective drug in the active management of third stage of labour to prevent primary PPH.

Limitation

- The sample size of the study was small
- The study period was short
- The study was carried out in a single center
- The estimate of blood loss was not perfectly quantitative.

Recommendation

- Further studies are needed to assess the use of carbetocin in women at risk of post-partum haemorrhage and in the rural setting of developing countries.
- Use of carebetocin replacing oxytocin during active management of 3rd stage of labour to prevent primary PPH can be recommended.

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