

Efficacy and Safety of Carbetocin in Comparison to Oxytocin for the Prevention of Primary PPH during Caesarean Section: An Open Label Randomized Control Trial

N KABIR^a, BHARA^b, D AKTER^c, TADAISY^d, S JESMIN^e, M RAZZAK^f, H BEGUM^g, GMR ISLAM^h

Summary:

Background: Postpartum hemorrhage (PPH) is a potentially life-threatening complication of both vaginal and caesarean delivery. The most frequent cause of postpartum hemorrhage is uterine atony, when the uterus fails to contract fully after delivery of the placenta. For the prevention of this uterine atony we need an effective uterotonic drug. Till now oxytocin is used for enhancing uterine contraction after delivery. But oxytocin has some limitations like shorter half-life, less contraction time and more side effects, whereas carbetocin has prolonged duration of action which ensures more contraction time and less adverse effects. So, carbetocin considered as a good alternative over oxytocin for the prevention of primary PPH in caesarean section.

The Aim of Study: To see the efficacy and safety of carbetocin over oxytocin for the prevention of primary PPH during caesarean section.

Patients and Methods: A randomized-controlled trial was conducted in the Institute of Child and Mother Health (ICMH), Dhaka, Bangladesh over a period of nine months from January to September 2016. Ninety-four patients who had got admitted in ICMH undergoing caesarean section at term were randomized into two groups receiving either 10IU oxytocin or 100µg carbetocin, after the operation.

Outcome measures such as primary PPH, massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects were all documented.

Results: This study had shown that carbetocin is superior in comparison to oxytocin for the prevention of primary PPH following caesarean section. Each patient obtained either a single dose of 100 microgram carbetocin intravenously or 10 IU of oxytocin during caesarean section. Massive blood loss occurred in 6.4% patients, blood transfusion needed in 17% patients and additional uterotonic needed for 25.5% patients in oxytocin group but in carbetocin group no massive blood loss occurred, only 2.1% patient needed immediate blood transfusion and no patient was required additional uterotonics. There were no major adverse effects observed in both the groups. No patients had developed PPH in carbetocin group. But 12.8% patients had developed primary PPH in oxytocin group.

Conclusion: Carbetocin appears to be an effective new drug than oxytocin for the prevention of primary postpartum hemorrhage in caesarean section.

Key Words: Carbetocin, Oxytocin, Postpartum hemorrhage.

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- a. Prof. Nazneen Kabir, Ex. Executive Director & Head of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka.
- b. Prof. Dr. Begum Hosne Ara, Executive Director & Head of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka.
- c. Dr. Dilruba Akter, Professor, Department of Obstetrics and Gynecology, ICMH, Matuail, Dhaka.
- d. Dr. Tahmina Afrin Daisy, Associate Professor, Dept. of Obstetrics and Gynecology ICMH, Matuail, Dhaka.
- e. Dr. Sonia Jesmin, Assistant Professor, Department of Obstetrics and Gynecology, ICMH, Matuail, Dhaka.
- f. Dr. Mollika Razzak, Assistant Professor, Department of Obstetrics and Gynecology, ICMH, Matuail, Dhaka.
- g. Dr. Hasina Begum, Assistant Professor, Department of Obstetrics and Gynecology, ICMH, Matuail, Dhaka.
- h. Dr. G. M. Raihanul Islam, Senior Manager, MSD, Beacon Pharmaceuticals Ltd.

Address of Correspondence: Prof. Nazneen Kabir, Ex. Executive Director & Head of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka. Mobile: 01711563876, E-mail : edrafed@gmail.com

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Introduction:

Postpartum Hemorrhage (PPH) is a potentially life-threatening complication of both vaginal and cesarean delivery. PPH complicates 11 % of deliveries worldwide, and is annually responsible for 1, 32, 000 maternal deaths¹. In developing countries, mortality from PPH remains high². In low income setting, PPH accounting for 30% of maternal death³, while in Bangladesh it is 31%⁴. The target of MDG-2015 was 143 deaths per 100,000 live births^{5,6}. We have already achieved this target. The key contribution to this decrease was a drop-in mortality risk mainly due to improved access and use of health facilities. Now, building on the momentum generated by MDG-5, the sustainable development goals (SDGs) establish a transformative new agenda for maternal health towards ending preventable maternal mortality. Target of SDG

3 is to reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030⁷.

Use of an effective uterotonic drug for prevention of uterine atony as well as PPH is highly recommended. Primary PPH is the most common obstetric hemorrhage and is defined by the World Health Organization as the loss of blood estimated to be >1000ml from the genital tract after caesarean section within 24 hours of delivery⁸.

Primary PPH is the most common one and up to 80% cases it occurs due to uterine atony⁵, when the uterus fails to contract fully after delivery of the placenta. There are numerous reasons for the uterus failing to contract effectively; including exhaustion, sepsis etc. Other causes of PPH are suspected or proven placental abruption, known placenta previa, multiple pregnancy, preeclampsia, gestational hypertension, previous PPH, Asian ethnicity, obesity (BMI >35) and anaemia (<9g/dl). Intrapartum risks include: Delivery by emergency or elective caesarean section, induction of labour, retained placenta, mediolateral episiotomy, operative vaginal delivery, prolonged labour (> 12 hours), big baby (>4kg), pyrexia in labour, and age >40 years⁹.

If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation, and ultimately death¹⁰.

Conventional uterotonics like oxytocin has used for preventing PPH but it has some limitations like shorter half-life¹¹, less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema. In addition, the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension¹². Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability¹³. In our country cold chain is not properly maintained for oxytocin. So, there is a chance of its effectiveness and stability problems. As a result, treatment failure may occur, bleeding due to uterine atony, can be prevented by an effective uterotonic agent¹⁴. Till now it is recommended that oxytocin should be used as uterotonic agent either in the form of intramuscular injection or intravenous infusion.

Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties^{15,16}. Carbetocin has

prolonged duration of action (approximately 1 hour) which ensures more contraction time and less adverse effect^{17,18}. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. 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 tone¹³. A single dose of carbetocin has been hypothesized to act up to 16 hours in comparison to intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in caesarean section¹². Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain, and pruritus¹³. Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum hemorrhage¹⁹. We had conducted this clinical study to evaluate the efficacy and safety of Carbetocin for the prevention of primary PPH during caesarean section. **Materials and Methods**

This randomized control trial was done from January 2016 to September 2016 in the Department of Obstetrics and Gynecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh. About ninety-four pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion criteria. According to computer generated randomization sequential number was allocated for the cases. A written informed consent was taken from eligible women on admission. The study protocol was approved by the ethical committee of Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh.

Inclusion criteria were women with a single pregnancy undergoing caesarean delivery above 36 weeks or greater (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report). Exclusion criteria were placenta previa, multiple gestation, placental abruption (determined by history and ultrasound report) hypertensive disorders in pregnancy, preeclampsia, and known case of cardiac, renal, liver diseases, epilepsy, moderate anemia and unwilling to participate in the study.

During the study period 47 women were enrolled who received Carbetocin 100 µg I/V as a single dose and

47 women who received 10 IU of oxytocin after caesarean section. The primary outcome was measured by the amount of blood loss within 24 hours after delivery. Blood loss was estimated by the surgeon in the usual way (visual estimation, number of used sanitary pad and amount of aspirated blood). The secondary outcomes were massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation and administration of additional uterotonics was the decision of the investigator.

Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were expressed as means \pm SD. 95% confidence interval was calculated and p value of <0.05 was considered as significance.

Result:

A total of 105 pregnant women with a single pregnancy were initially recruited for inclusion in this study. 11 cases were excluded (4 had pre-eclampsia, 2 eclampsia, 3 multiple gestation, 2 severely anaemic). Thus 94 women formed the final study group and were included in the final analysis. Mean age of study population were 23.7 ± 3.7 in carbetocin group and 24.7 ± 4.3 in oxytocin group (Table I). Among the study

patients 38.3% (18) had mild anemia in Carbetocin group and 40.4% (19) had mild anemia in oxytocin group. Mean systolic BP of women were 108 ± 8.6 mm of Hg and Diastolic BP were 71 ± 5.4 mm of Hg in Carbetocin group and mean systolic BP were 105 ± 7.2 mm of Hg and Diastolic BP were 70 ± 6.2 mm of Hg in Oxytocin group. Mean gestational age at delivery were 38.8 ± 1.3 in Carbetocin group and 39 ± 1.5 in Oxytocin group (Table-1). Massive blood loss occurred in 6.4% cases, blood transfusion needed in 17% cases and additional uterotonic drug needed for 25.5% women in oxytocin group but in carbetocin group no massive blood loss, only 2.1% needed immediate blood transfusion and no patient was required additional uterotonics (Table-2). There were no major adverse effects observed in both the groups (Table-3). No patients had developed PPH in carbetocin group. But 12.8% (6) patients had developed PPH in oxytocin group (Table-4).

Table-1. Data are presented as mean \pm SD. The mean differences were not statistically significant ($P > 0.05$)

Table-2. Shows that massive blood loss occurred in 6.4% patients, blood transfusion needed for 17% patients and additional uterotonic drug needed for 25.5% patients in Oxytocin group but in carbetocin

Table-I

<i>Baseline characteristics of study patients (n=94)</i>			
	Carbetocin Group (n=47)	Oxytocin Group (n=47)	P value
Age	23.7 ± 3.7	24.7 ± 4.3	0.317
Mild Anemia	18(38.3%)	19(40.4%)	0.317
Systolic BP	108 ± 8.6 mm of Hg	105 ± 7.2	0.210
Diastolic BP	71 ± 5.4 mm of Hg	70 ± 6.2 mm of Hg	0.509
Gestational Age	38.8 ± 1.3 weeks	39 ± 1.5 weeks	0.799

Table-II

<i>Outcome of Third stage of Labour (n = 94)</i>					
Outcome of 3rd stage of Labour	Carbetocin Group (n=47)		Oxytocin Group (n=47)		P value
	Yes (%)	No (%)	Yes (%)	No (%)	
Massive blood loss	0(0%)	47(100%)	3(6.4%)	44(93.6%)	0.001
Blood transfusion	1(2.1%)	46(97.9%)	8(17%)	39(83%)	0.001
Need for additional uterotonics	0(0%)	47(100%)	12(25.5%)	35(74.5%)	0.001

group no massive blood loss occurred and blood transfusion needed only 2.1% patient and none of patient was required additional uterotonic. The mean differences were statistically significant ($P < 0.05$).

Table-3. There were no major adverse effects observed in both groups. The differences were not statistically significant ($P > 0.05$).

Table- 4. Showed no patients had developed PPH in carbetocin group. But 12.8% patients had developed PPH in oxytocin group. The mean differences were statistically significant ($P < 0.05$).

Table-III

Adverse effects (n = 94)

Side effects	Carbetocin	Oxytocin	P value
	(n=47)	(n=47)	
	n (%)	n (%)	
Nausea	1(2.1%)	1(2.1%)	0.50
Vomiting	1(2.1%)	0(0%)	0.30
Fever	0(0%)	0(0%)	0.50
Arrhythmia	0(0%)	0(0%)	0.50
Pulmonary edema	0(0%)	0(0%)	0.50
Abdominal Pain	4(8.5%)	5(10.6%)	0.72
Headache	0(0%)	1(2.1%)	0.30
Tremor	0(0%)	0(0%)	0.50
Hypotension	0(0%)	0(0%)	0.50
Pruritus	0(0%)	0(0%)	0.50

Table-IV

Outcome of the patient: Primary PPH (n = 94)

Outcome	Carbetocin	Oxytocin	P Value
(Primary PPH)	group (47)	group (47)	
Yes	0(0%)	6(12.8%)	0.001
No	47(100%)	41(87.2%)	

Discussion:

In the present study each patient obtained a single dose of 100 microgram carbetocin intravenously during cesarean section, immediately after the delivery of the baby and prior to the delivery of the placenta. Outcome measures such as primary PPH, massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects were documented.

Reyes OA and Gonzalez GM et al showed that mean age of study patient in carbetocin group were 26.5 years and 26.7 years in oxytocin group²⁰. In this study mean age of study patients were 23.7 years in carbetocin group and 24.7 years in oxytocin group. A study from Philippines found that mean preoperative systolic BP of study patients in carbetocin 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±8.5 mm of Hg in Oxytocin group²¹. In this study, mean preoperative systolic BP of patients were 108±8.6 mm of Hg and diastolic BP were 71 ±5.4 mm of Hg in carbetocin group and mean systolic BP were 105±7.2 mm of Hg and diastolic BP were 70±6.2 mm of Hg in oxytocin group which were almost similar with previous study. All patients of both the groups were with normal blood pressure.

A study in Panama showed that the mean gestational age of study women in carbetocin group were 37.44 weeks and 36.93 weeks in oxytocin group²⁰ which is almost similar to this study; 38.8±1.3 weeks weeks in carbetocin group and 39± 1.5 weeks 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 the drugs. In present study, there were no major adverse effects observed in both the groups.

In this study, only 2.1%(1)patient in carbetocin group was needed blood transfusion but in oxytocin group blood transfusion were required for 17%(8) patients which was almost similar to a previous study.²²

Current study showed that, none of patients of carbetocin group were required additional uterotonic but in oxytocin group additional uterotonic were required for 25.5% patients. Similar results were also found in previous study.^{21,22,23}

Occurrence of PPH were less in carbetocin group of this study. This result was similar to a previous prospective double-blinded randomized study conducted in Egypt.²⁵

Primary postpartum hemorrhage (PPH) is the most common form of major obstetric hemorrhage²⁶. It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide^{27,28}. The most common point at which PPH

occurs is during the third stage of labour, when the uterus may suddenly lose its ability to contract. Around 80% of cases of postpartum hemorrhage occur due to uterine atony²⁹. Bleeding due to uterine atony, can be prevented by an effective uterotonic drug³⁰. The promising findings suggested that carbetocin appears to be an effective new drug for the prevention of PPH in caesarian delivery. A single dose of 100 microgram IV carbetocin is more effective than oxytocin for maintaining adequate uterine tone, decreases blood loss and preventing postpartum hemorrhage in women undergoing caesarian delivery. Carbetocin can be considered as a good uterotonic agent over oxytocin for the prevention of primary PPH in caesarian section.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the clinical trial.

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