

# Carbetocin Versus Oxytocin for Prophylaxis of PPH Used During Caesarean Section: An Open Label Randomized Control Trial

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## Abstract

**Background:** *Postpartum hemorrhage is the leading cause of maternal mortality; uterine atony is the most important cause. Uterotonics are used to prevent uterine atony. Carbetocin, a synthetic analogue of oxytocin seems to be an effective and safe new drug for prevention of PPH after caesarean*

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

**Patients and Methods:** *A randomized-controlled trial was conducted in the Dept. of Obs & Gyane, Rangpur Medical College and Hospital, Rangpur, Bangladesh over a period of twelve months from June 2016 to June 2017. One hundred admitted patients undergoing cesarean section at term were randomized into two groups receiving either 10 IU oxytocin or 100 µg carbetocin after caesarean section. 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:** *Massive blood loss occurred in 6% patients, blood transfusion needed in 20% patients and additional uterotonic needed for 36% patients in Oxytocin group but in Carbetocin group no massive blood loss occurred, only 2% patients needed immediate blood transfusion and 4% patients were required additional uterotonics. There were no major adverse effects observed in both the groups. No patients had developed PPH in carbetocin group. But 8%(4) patients had developed PPH in oxytocin group.*

**Conclusion:** *Carbetocin appears to be an effective new drug than Oxytocin for the prevention of postpartum hemorrhage following caesarean section.*

**Key Words:** *Carbetocin, Oxytocin, Postpartum hemorrhage.*

## Introduction:

PPH complicates 11 % of deliveries worldwide and is annually responsible for 1,32,000 maternal deaths<sup>1</sup>. In low income setting, PPH accounting for 30% of maternal death<sup>2</sup>, while in Bangladesh it is

31%<sup>3</sup>. All pregnant women are at risk of complications during the 3<sup>rd</sup> stage of labor<sup>4</sup>. For women undergoing delivery by cesarean section, there is an increased risk of postpartum hemorrhage compared to vaginal delivery<sup>5</sup>. Primary PPH is the most common obstetric

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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 delivery<sup>6</sup>. If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, haemostatic failure from disseminated intravascular coagulation and ultimately death<sup>7</sup>. So, use of an effective uterotonic drug for prevention of uterine atony is highly recommended. Conventional uterotonics like oxytocin has been used for preventing PPH but it has some limitations like shorter half-life<sup>8</sup>, less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema. On the other hand the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension<sup>9</sup>. Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability<sup>10</sup>.

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 agent<sup>11</sup>. Till now it is recommended that oxytocin should be used as uterotonic agent either in the form of intramuscular injection or intravenous infusion.

Carbetocin has prolonged duration of action (approximately 1 hour) which ensures more contraction time and less adverse effect<sup>12,13</sup>. 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 tone<sup>10</sup>. 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 section<sup>12</sup>. Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain, and pruritus<sup>9</sup>. Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum hemorrhage<sup>14</sup>. We had conducted this clinical study to evaluate the efficacy and safety of Carbetocin for the prevention of PPH during caesarian section.

## Materials and Methods

This randomized control trial was conducted on 100 admitted pregnant women from June 2016 to June 2017 in the Department of Gynecology and Obstetrics, Rangpur Medical College Hospital, Rangpur, Bangladesh. 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 Rangpur Medical College Hospital, Rangpur, Bangladesh.

Inclusion criteria were women with a single pregnancy undergoing caesarean delivery. 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 50 women were enrolled who received Carbetocin 100 µg I/V as a single dose and 50 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.

## Statistical Analysis:

Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 23. Quantitative data were expressed as means ±SD. 95% confidence interval was calculated and p value of <0.05 was considered as significant.

## Result:

A total of 111 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 anemic). Thus 100 women formed the final study group and were included in the final analysis. Mean age of study population were  $25.2 \pm 3.9$  in carbetocin group and  $24.9 \pm 5.3$  in oxytocin group (Table I). Among the study patients 88% (44) had mild anemia in Carbetocin group and 84% (42) had mild anemia in oxytocin group. Mean systolic BP of patients were  $116 \pm 9.5$  mm of Hg and Diastolic BP were  $75 \pm 1.8$  mm of Hg in Carbetocin group and mean systolic BP were  $118 \pm 1.3$  mm of Hg and Diastolic BP were  $77.7 \pm 1.3$  mm of Hg in Oxytocin group. Mean gestational age at delivery were  $36.9 \pm 5.4$  in Carbetocin group and  $38 \pm 5.4$  in Oxytocin group (Table-I). Massive blood loss occurred in 6% patients, blood transfusion needed in 20% patients and additional uterotonic needed for 36% patients in Oxytocin group but in Carbetocin group no massive blood loss occurred, only 2% patients needed

immediate blood transfusion and 4% patients were required additional uterotonics (Table-II). There were no major adverse effects observed in both the groups (Table-III). No patients had developed PPH in carbetocin group. But 8% (4) patients had developed PPH in oxytocin group. (Table-IV)

Table-2. Shows that massive blood loss occurred in 6.0% patients, blood transfusion needed for 20% patients and additional uterotonic drug needed for 36.0% patients in Oxytocin group but in carbetocin group no massive blood loss occurred and blood transfusion needed only 2.0% patients and 4.0% patient was required additional uterotonics. The mean differences were statistically significant ( $P < 0.05$ ).

Table- IV. Showed no patients had developed PPH in carbetocin group. But 8% (4) patients had developed PPH in oxytocin group. The mean differences were statistically significant ( $P < 0.05$ ).

**Table-I***Distribution of study subjects according to Baseline characteristics (n=100)*

	Carbetocin Group (50)	Oxytocin Group (50)	P value
Age	$25.2 \pm 3.9$	$24.9 \pm 5.3$	0.31
Mild Anemia	88% (44)	84% (42)	0.31
Systolic BP	$116 \pm 9.5$ mm of Hg	$118 \pm 1.3$	0.21
Diastolic BP	$75 \pm 1.8$ mm of Hg	$77.9 \pm 1.3$ mm of Hg	0.50
Gestational Age	$36.9 \pm 5.4$ weeks	$38 \pm 5.4$ weeks	0.79

(Students "t" test)

**Table-II***Distribution of study subjects according to Outcome of Labour (n = 100)*

Outcome during Labour	Carbetocin	Group (50)	Oxytocin	Group(50)	P value
	Yes (%)	No (%)	Yes (%)	No (%)	
Massive blood loss	00%	100%	6.0% (3)	94.0%(47)	0.001
Blood transfusion	2.0%(1)	98.0%(49)	20% (10)	80.0% (40)	0.001
Need for additional uterotonics	4.0%(2)	96%(48)	36.0%(18)	64.0%(32)	0.001

(Students "t" test)

**Table-III***Distribution of study subjects according to Adverse effects (n = 100)*

Side effects	Carbetocin (n=50) n (%)	Oxytocin (n=50) n (%)	P value
Nausea	2.0%(1)	4.0%(2)	0.25
Vomiting	2.0%(1)	6.0%(3)	0.75
Fever	00%(0)	6.0%(3)	0.33
Arrhythmia	00%(0)	2.0%(0)	0.30
Pulmonary edema	00%(0)	00%(0)	0.50
Abdominal Pain	00%(0)	6.0%(3)	0.33
Headache	00%(0)	6.0%(3)	0.33
Tremor	00%(0)	00%(0)	0.50
Hypotension	00%(0)	00%(0)	0.50
Pruritus	00%(0)	00%(0)	0.50

**Table-IV***Distribution of study subjects according to Outcome of the patient: Primary PPH (n = 100)*

Outcome ( Primary PPH)	Carbetocin group (50)	Oxytocin group (50)	P Value
Yes	0(0.0)	8.0%(4)	0.001
No	50(100)	92.0%(46)	

**Discussion:**

The results of this study had shown that carbetocin is superior in comparison to oxytocin for the prevention of PPH following caesarian section. 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.<sup>15</sup> showed that mean age of study patient in carbetocin group were 26.5 years and 26.7 years in oxytocin group. In this study mean age of study patients were 25.2 years in carbetocin group and 24.9 years in oxytocin group. Debbie-lynuy and Nelindacatherinep et al.<sup>16</sup> showed 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 group. In this study, mean preoperative systolic BP of patients were 116±9.5 mm of Hg and diastolic BP were 75 ±1.8 mm of Hg in carbetocin group and mean systolic BP were 118±1.3mm of Hg and diastolic BP were 77.9±1.3 mm of Hg in oxytocin group. All patients of both the groups were with normal blood pressure.

Reyes OA and Gonzalez GM et al.<sup>15</sup> also showed that the mean gestational age of study patient in carbetocin group were 37.44 weeks and 36.93 weeks in oxytocin group which is almost similar to this study; 36.9±5.4 weeks in Carbetocin group and 38±5.4 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 this study, there were no major adverse effects observed in both the groups.

Manal M. E Behery et al.<sup>17</sup> showed that none of women in carbetocin group required blood

transfusion, while 15.5% in oxytocin group required blood transfusion. In this study, only 2%(1) patient in carbetocin group was needed blood transfusion but in oxytocin group blood transfusion were required for 20% patients.

Sergio Rosales-Ortiz, Rogelio Perez Aguado et al.<sup>18</sup> showed that only 1.5% patients need additional uterotonics in carbetocin group and 5.8% patients in oxytocin group. Manal M. E Behery et al.<sup>17</sup> showed that none of the patient in carbetocin group required additional uterotonics while as high as 71.5% of women in oxytocin group needed additional oxytocin to ensure adequate uterine contraction for long period. CAG. Holleboom, J. van Eyck et al.<sup>19</sup> 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.<sup>16</sup> showed that only 5.7% patients were need for additional uterotonics in carbetocin group and 34.3% patients in oxytocin group. In this study, 4% patients of carbetocin group were required additional uterotonic but in oxytocin group additional uterotonics were required for 36% patients.

Ahmed Mohamed Maged et al.<sup>20</sup> also showed the occurrence of PPH were 4% in carbetocin group and 16% in oxytocin group. In this study, occurrence of PPH in oxytocin group was 8% patients but in carbetocin group none of patients had developed PPH.

Primary postpartum hemorrhage (PPH) is the most common form of major obstetric hemorrhage<sup>21</sup>. It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide<sup>22,23</sup>. The most common point at which PPH occurs is during the third stage of labour, when the uterus may suddenly loss its ability to contract. Around 80% of cases of postpartum hemorrhage occur due to uterine atony<sup>24</sup>. Bleeding due to uterine atony, can be prevented by an effective uterotonic drug<sup>25</sup>. 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 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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