

Efficacy and Safety of Carbetocin for the Prevention of Primary PPH During Caesarean Section: An Open Label Single Arm Study

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Abstract

Background: The risk of postpartum haemorrhage is much higher for women undergoing caesarean section, particularly in developing countries where the majority of operations are carried out as an emergency procedure. Postpartum haemorrhage is the leading cause of maternal mortality worldwide. Around 67–80% of cases are caused by uterine atony. Preventive measures include prophylactic drugs use to aid uterine contraction after delivery, thus avoiding severe blood loss and reducing maternal morbidity and mortality. Carbetocin a synthetic analogue of oxytocin is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anaesthesia.

The Aim of Study: To see the efficacy and safety of Carbetocin for the prophylaxis of PPH during caesarean section.

Patients and Methods: An open label single arm clinical trial was conducted in the Bagerhat Sadar Hospital, Bangladesh over a period of six months from May 2017 to October 2017. Ninety patients who had got admitted in Bagerhat Sadar Hospital, undergoing cesarean section at term were selected. 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, blood loss was observed and measured by weighing sanitary napkin observed for six hours. Need for additional uterotonic drug, additional blood transfusion as well as adverse effects were all documented.

Results: Massive blood loss occurred only in 3.3% patients. Among the study population 96.7% patients did not need any additional uterotonics. No patient had developed fever, arrhythmia, pulmonary edema, tremor, abdominal pain and pruritus. Only 2.2% had nausea, only 3.3% had hypotension, only 3.3% had vomiting and only 2.2% had headache which was not statistically significant. Only 4.4% patients developed PPH.

Conclusion: Carbetocin appears to be an effective new drug for the prophylaxis of postpartum hemorrhage in cesarean section.

Key Words: Carbetocin, Primary PPH.

Introduction:

Postpartum haemorrhage (PPH) is one of the major contributors to maternal mortality and morbidity worldwide. If a woman bleeds after childbirth and does not receive immediate medical care, she may die within two hours. So the biggest killer is obstetric

hemorrhage and the most frequent cause is uterine atony with an estimated mortality rate of 140,000 per year or 1 maternal death every 4 minutes.¹ PPH complicates 11 % of deliveries worldwide and is annually responsible for 1,32,000 maternal deaths². In developing countries, mortality from PPH remains

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high³. In low income setting, PPH accounting for 30% of maternal death⁴, while in Bangladesh it is 31%⁵. All pregnant women are at risk of complications during the 3rd stage of labor⁶. Maternal risk factors contribute to the development of postpartum hemorrhage⁷. For women undergoing delivery by cesarean section, there is an increased risk of postpartum hemorrhage compared to vaginal delivery⁸. 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 delivery.⁹ .If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation and ultimately death¹⁰. So use of an effective uterotonic drug for prevention of uterine atony as well as PPH is highly recommended .

Conventional uterotonics like oxytocin is 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 acts 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 postpartum haemorrhage¹⁹.

We had conducted this clinical study to evaluate the efficacy and safety of Carbetocin for the prophylaxis of PPH during caesarian section.

Materials and Methods:

An open label single arm clinical trial was done from May'2017 to October'2017 in the Department of Gynecology and Obstetrics, Bagerhat Sadar Hospital, Bagerhat, Bangladesh. Ninety pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion criteria. A written informed consent was taken from eligible women on admission. Inclusion criteria were women with a single pregnancy undergoing caesarean delivery. Indication of cesarean section were cephalopelvic disproportion, malpresentation-eg, breech, transverse lie, previous history of cesarean section, fetal distress, very low birth weight and failed induction of labour. 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. Study medication was a single dose of 100 microgram carbetocin intravenously by anesthetists during cesarean section, immediately after the delivery of the baby and prior to the delivery of the placenta.

Primary outcome is primary postpartum haemorrhage (PPH) defined as blood loss from genital tract of 1000 ml or more within 24 hours in case of caesarean section. Blood loss was estimated by the surgeon in the usual way such as visual estimation and amount of aspirated blood¹⁶. The secondary outcomes were massive blood loss, defined as blood loss of 50% of circulating blood volume within a 3-hour period, need for additional uterotonic therapy that means when single unit of duratocin did not control of primary PPH we used misoprostol as an additional uterotonics, additional

blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation. 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 23. 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 100 pregnant women with a single ton pregnancy were initially recruited for inclusion in this study; 10 cases were excluded (4 had pre-eclampsia, 2 eclampsia, 1 multiple gestation, 3 severely anaemic). Thus 90 women formed the final study group and were included in the final analysis. Mean age of study population were 24.5 ± 4.48 years (Table I). Among the study patients 96.7% (87) had mild anemia. Mean systolic BP of patients were 110 ± 1.17 mm of Hg and Diastolic BP were 70 ± 8.5 mm of Hg. Mean gestational age at delivery were 38.2 ± 1.12 weeks (Table-I). Massive blood loss occurred in 3.3% patients and additional uterotonic needed for 3.3% patients (Table-II). There were no major adverse effects observed in this study (Table III). Only 4.4%(4) patients had developed PPH.(Table-IV)

Table-I

Baseline characteristics of study patients (n=90)

Age	24.5 ± 4.48
Mild Anemia	96.7% (87)
Systolic BP	110 ± 1.17 mm of Hg
Diastolic BP	70 ± 8.5 mm of Hg
Gestational Age	38.2 ± 1.12 weeks
Primigravida	44.4%(40)
Multi-gravida	55.5%(50)

Table-I. Data were presented as mean \pm SD. Here Mean age 24.5 ± 4.48 years, Mild anemia 96.7%, Mean systolic BP 110 ± 1.17 mm of Hg, Diastolic BP 70 ± 8.5 mm of Hg, Gestational age 38.2 ± 1.12 weeks, primigravida 44.4% and multi-gravida 55.5%.

Table-II

Outcome during Labour (n = 90)

	Yes (%)	No (%)	P value
Massive blood loss	3.3%(3)	96.7%(87)	0.41
Need for additional uterotonics	3.3%(3)	96.7%(87)	0.41

Table-II. Showed that massive blood loss occurred in 3.3% patients and additional uterotonic drug needed for 3.3% patients. The difference were not statistically significance. ($P > 0.05$)

Table-III

Adverse effects (n = 90)

Side effects	(n=90) n (%)	P value
Nausea	2.2%(3)	0.42
Vomiting	3.3%(3)	0.41
Fever	00%(0)	0.50
Arrhythmia	00%(0)	0.50
Pulmonary edema	00%(0)	0.50
Abdominal Pain	00%(0)	0.50
Headache	2.2%(3)	0.42
Tremor	00%(0)	0.50
Hypotension	3.3%(3)	0.41
Pruritus	00%(0)	0.50

Table-III. There were no major adverse effects observed in the study population. The differences were not statistically significant. ($P > 0.05$)

Table-IV

Outcome of the patient: Primary PPH (n =90)

Outcome (Primary PPH)	(n=90),n(%)	P value
Yes	4.4%(4)	0.06
No	95.6%(86)	

Table-IV Showed only 4.4% patients developed PPH. P value > 0.05 , So it is not statistically significant.

Discussion:

The results of this study had shown that carbetocin is effective for the prevention of primary PPH following cesarian 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.²⁰ showed that mean age of study patient were 26.5 years. In this study mean age of study patients were 24.5 ± 4.48 years. Debbie-lynuy and Nelindac atherinep et al.²¹ showed that mean preoperative systolic BP of study patients were 117 ± 6.8 mm of Hg and diastolic BP

were 69 ± 7.7 mm of Hg. In this study, mean preoperative systolic BP of patients were 110 ± 1.17 mm of Hg and diastolic BP were 70 ± 8.5 mm of Hg. All patients were with normal blood pressure.

Reyes OA and Gonzalez GM et al²⁰ also showed that the mean gestational age of study patient were 37.44 weeks which is almost similar to this study; 38.2 ± 1.12 weeks. They also showed that there was no significant adverse effects of the drug. In this study, there was no major adverse effects.

Sergio Rosales-Ortiz, Rogelio Perez Aguado et al.²² showed that only 1.5% patients need additional uterotonics. Manal M. E Behery et al.²³ showed that none of the patient in carbetocin group required additional uterotonics. CAG. Holleboom, J. van Eyck et al.²⁴ 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.²¹ showed that only 5.7% patients were need for additional uterotonics in carbetocin group. In this study, 3.3%(3) patients were required additional uterotonic.

Ahmed Mohamed Maged et al.²⁵ also showed the occurrence of PPH were 4% in their study. In our study, occurrence of PPH was only in 4.4%(4) patients.

Primary postpartum haemorrhage (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 loss 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 drug^{30,31}. 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 effective 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 for the prevention of PPH in caesarian section.

Conclusion:

Carbetocin appeared to be an effective new drug for the prevention of primary PPH during cesarean section. Carbetocin has long half-life, which ensures more effective contraction and less adverse effects. Our limitation was sample size was small. So multi-center research is required to verify our findings.

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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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