Carbetocin versus Oxytocin in Active Management of 3rd stage of Labour following Vaginal Delivery

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Ashraf F[1], Akther P[2], Yasmin N[3], Islam JA[4], Akther M[5], Rahman R[6], Ahmad SA[7], Faruquee MH[8], Islam GMR[9] and Rakib MHA[10]

[1]Department of Obstetrics and Gynecology Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh. [2]Department of Obstetrics and Gynecology, Mugda Medical College and Hospital,Dhaka. [3]Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka. [4]Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka. [5]Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka.[6]Department of Medicine, Shaheed Suhrawardy Medical College and Hospital. [7]Occupational and Environmental Health Bangladesh University of Health Sciences (BUHS). [8]Department of Occupational and Environmental Health, Bangladesh University of Health Sciences(BUHS). [9]Medical Services Department, Beacon Pharmaceuticals Ltd. [10]Medical Services Department, Beacon Pharmaceuticals Ltd.

ABSTRACT: Background: Every day more than 220 women around the world die from severe bleeding after childbirth. Globally post-partum hemorrhage is the number one direct cause of maternal mortality. Most postpartum hemorrhages are caused by uterine atony and occur in the immediate postpartum period. Most of these tragic deaths can be prevented by active management of third stage of labour. Active management of the third stage of labor should be practiced routinely to decrease the risk of postpartum hemorrhage. 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. This study was done to see the efficacy and safety of carbetocin over oxytocin for prevention of PPH after vaginal delivery. **Methodology:** A randomized controlled clinical trial was conducted in the Department of Obstetrics and Gynecology, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh over a period of 9 months from January 2015 to September 2015. Ninety four patients undergoing vaginal delivery at term were randomized into two groups receiving either 10IU oxytocin or 100 µg carbetocin. Outcome measures such as primary PPH, massive blood loss, need for additional uterotonic drug, additional blood transfusion as well as adverse effects were documented. **Results:** In this study, massive blood loss did not occur none of patients in carbetocin group. But massive blood loss occured 6.4% women of oxytocin group. Further fundal massage , immediate blood transfusion and additional uterotonics didn't need any patient in carbetocin group. In oxytocin group, fundal massage required in 8.5% of women, blood transfusion needed in 10.6% patients and additional uterotonics needed in 10.6% women. Average amount of blood loss was 88 ml less in carbetocin group and adverse effects of drugs were almost similar in both group. Primary PPH developed in oxytocin group 8.5% but none of patients had developed PPH in carbetocin group. **Conclusion:** Carbetocin is an effective new drug than oxytocin for prevention of postpartum hemorrhage in vaginal delivery.

KEYWORDS: Carbetocin, Oxytocin, Postpartum hemorrhage

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CORRESPONDING AUTHOR: Dr. Pervin Akther, Department of Obstetrics and Gynecology, Mugda Medical College and Hospital,Dhaka, Email: aktherpervin121@gmail.com

Introduction

In every minute one mother dies due to postpartum hemorrhage in this modern world. [1]Postpartum hemorrhage occurs in approximately 4 percent of vaginal deliveries and estimates are that it causes significant morbidity and 25 percent of all maternal childbirth-related deaths.[2] In developing countries, mortality from PPH remains high.[3] In low income setting, PPH accounting for 30% of maternal death, while in Bangladesh it is 31%.[3,4] The majority of these deaths occur within 4 hours of delivery, which indicates that they are a consequence of the third stage of labour. [5,6] That's why active management during third stage of labour recommended. The third stage of labor is the time from the delivery of the baby until delivery of the maternal placenta.[7] Primary PPH is defined by the World Health Organization as the loss of blood estimated to be > 500 ml from the genital tract within 24 hours of vaginal delivery[8]. Volume of blood loss depends on how long it takes the placenta to separate from the uterine wall and how effectively the uterine muscle contracts in the immediate postpartum period. Attempts to prevent postpartum hemorrhage have focused on the prophylactic use of uterotonic agents and the active clinical management of the third stage of labour. Active management of labour incorporates three main interventions: administration of a uterotonic medication after delivery of the baby; early cord clamping and cutting and controlled traction on the umbilical cord while awaiting placental separation and delivery.[9,10] If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation and ultimately death.[11] Conventional uterotonics like oxytocin has used for preventing PPH but it has some limitations like shorter half- life, less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema.[12] In addition,

the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension.[13] Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability.[14] 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.[15] 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.[16,17] Carbetocin has prolonged duration of action (approximately 1 hour) which ensures more contraction time and less adverse effect.[18,19] 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.[14] A single dose of carbetocin has been hypothesis to act upto 16 hours in comparison to intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in vaginal delivery.[13] Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain and pruritus.[14] Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum hemorrhage.[20]

Materials and Methods

This randomized controlled clinical trial was done from January'2015 to September'2015 in the Department of Gynecology and Obstetrics, Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh. Ninety four pregnant women with a single pregnancy undergoing vaginal delivery above 36 weeks or greater (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report) were included in this study. Pregnant women with 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 were excluded. According to computer generated randomization sequential number was allocated for the cases.

During the study period 47 women received carbetocin 100 µg I/V as a single dose and 47 women received 10 IU of oxytocin after vaginal delivery. The primary outcome was measured by the amount of blood loss within 24 hours after delivery. The research team provided a standardized delivery mat (Quaiyum's mat) and five (05) pre-weighed standard sanitary pads for blood collection after delivery to each of the pregnant woman to measure blood loss in 24 hours postpartum period. Women were advised to preserve the soaked mat and all soaked pads in a sealable container which was provided by the study staff members. The secondary outcomes were measured by massive blood loss, need for additional uterotonics 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. The study protocol was approved by the ethical committee of Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh. Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were expressed as mean ± SD. 95% confidence interval was calculated and p value of <0.05 was considered as significance.

Results

Total 107 pregnant women with a single pregnancy were initially recruited in this study. 13 cases were excluded (4 had pre-eclampsia, 3 eclampsia, 3 multiple gestation, 3 severely anaemic). Thus 94 women were included in the analysis. Mean age of study population were 23.9 ± 3.2 in carbetocin group and 23.3 ± 3.2 in oxytocin group (Table I). Among the study patients 36.1% (17) had mild anemia in carbetocin group and 42.6% (20) had mild anemia in oxytocin group. Mean systolic BP of patients were 112±5.6 mm of Hg and diastolic BP were 75 ±4.3 mm of Hg in carbetocin group and mean systolic BP were 110±1.7 mm of Hg and diastolic BP were 72±11.5 mm of Hg in oxytocin group. Mean gestational age at delivery were 38.01±1.1 weeks in carbetocin group and 38.09±1.7 weeks in oxytocin group (Table-1).

Table-1. Baseline characteristics of study patients (n=94)

	Carbetocin Group (47)	Oxytocin Group (47)	P value
Age	**23.9 ± 3.2**	**23.3± 3.2**	**0.439**
Mild Anemia	**36.1% (n=17)**	**42.6% (n=20)**	**0.386**
Systolic BP	**112±5.6 mm of Hg**	**110±1.7**	**0.210**
Diastolic BP	**75 ±4.3 mm of Hg**	**72±11.5 mm of Hg**	**0.509**
Gestational Age	**38.01±1.1 weeks**	**38.09□1.7 weeks**	**0.799**

Data were presented as mean ±SD. The mean differences were not statistically significant (P>0.05). Massive blood loss occurred 6.4 %, fundal massage required 8.5 %, blood transfusion needed 10.6 % and additional uterotonics needed for 10.6% patients in oxytocin group but in carbetocin group massive blood loss, fundal massage, and immediate blood transfusion and additional uterotonics did not needed to any patient and no patient was required additional uterotonics (Table-2). There were no major adverse effecst observed in both the groups (Table-3). Average blood loss was 320 ml in carbetocin group and 408 ml in oxytocin group. Average 88 ml more blood loss was observed in oxytocin group (Table-4). No patients had developed PPH in carbetocin group. But 8.5% (4) patients had developed PPH in oxytocin group (Table-5).

Table-2. Outcome of third stage of Labour (n = 94). Massive blood loss occurred in 6.4% patient, fundal massage required in 8.5% patients, blood transfusion needed in 10.6% patients and additional uterotonics needed in 10.6% patients of oxytocin group but in carbetocin group massive blood loss, fundal massage, blood transfusion and additional uterotonics did not require in any patient. The mean differences were statistically significant (P<0.05).

Outcome of 3rd stage of Labour	**Carbetocin**	**Group (47)**	**Group(47)**		**P value**
	Yes (%)	No (%)	Yes (%)	No (%)	
Massive blood loss	00%	100%	6.4% (3)	93.6%(44)	**0.07**
Fundal massage required	00%	100%	8.5%(4)	91.5%(43)	**0.002**
Blood transfusion	00%	100%	10.6%(5)	89.4%(42)	**0.002**
Need for additional uterotonics	**00%**	**100%**	**10.6%(5)**	**89.4%(42)**	**0.002**

Table-3. Adverse effects (n = 94). There were no major adverse effects observed in both groups. The differences were not statistically significant (P>0.05).

Side effects	**Carbetocin (n=47) n (%)**	**Oxytocin (n=47) n (%)**	**P value**
Nausea	**0(0.0)**	**0(0.0)**	**0.50**
Vomiting	**0(0.0)**	**0(0.0)**	**0.50**
Fever	**0(0.0)**	**0(0.0)**	**0.50**
Arrhythmia	**0(0.0)**	**0(0.0)**	**0.50**
Pulmonary edema	**0(0.0)**	**0(0.0)**	**0.50**
Abdominal Pain	**0(0.0)**	**1(2.1)**	**0.30**
Headache	**0(0.0)**	**1(2.1)**	**0.30**
Tremor	**0(0.0)**	**0(0.0)**	**0.50**
Hypotension	**0(0.0)**	**0(0.0)**	**0.50**
Pruritus	**0(0.0)**	**0(0.0)**	**0.50**

The differences were not statistically significant (P>0.05).

Table-4. Blood loss in 24 hours (n = 94).

Amount of blood loss	**Carbetocin group (47)**	**Oxytocin group (47)**	**Difference**	**P Value**
Average blood loss in 24 hours(in ml)	**320 ml (302 gm)**	**408 ml (385gm)**	**88 ml**	**0.001**

The mean differences were statistically significant (P<0.05).

Table-5. Outcome of the patient: Primary PPH (n = 94)

Outcome (Primary PPH)	**Carbetocin group (47)**	**Oxytocin group (47)**	**P Value**
Yes	**0(0.0)**	**4(8.5%)**	**0.002**
No	**47(100)**	**43(91.5%)**	

The mean differences were not statistically significant (P>0.05).

Discussion

Results of our study had shown that carbetocin is superior in comparison to oxytocin in the reduction of blood loss during the active management of third stage of labour. Carbetocin also reduced the need for additional uterotonics, uterine massage and massive blood loss in the active management of third stage of labour after vaginal delivery. Reyes OA and Gonzalez GM et al.[21] performed a prospective double-blind randomized controlled trial with severe preeclampsia for prevention of PPH where the mean age of study patient in carbetocin group were 26.5 years and 26.7 years in oxytocin group .In our study mean age of study patients were 23.9 ± 3.2 years in carbetocin group and 23.3 ± 3.2 years in oxytocin group. Debbie-lynuy and Nelindac Atherinep et al 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.[22] In this study, mean preoperative systolic BP

of patients were 112±5.6 mm of Hg and diastolic BP were 75 ±4.3 mm of Hg in carbetocin group and mean systolic BP were 110±1.7 mm of Hg and diastolic BP were 72±11.5 mm of Hg in oxytocin group. All patients of both the groups were with normal blood pressure. Ahmed Mohamed Maged et al have randomized 200 women undergoing vaginal delivery in high risk women the average gestational age were 39.4±1.3 weeks in carbetocin group and 39.2±1.4 weeks in oxytocin group, which is almost similar to this study; 39.01±1.1 weeks in carbetocin group and 39.09± 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.[23] In this study, there were no major adverse effects observed in both groups. Manal M. E Behery et al showed that none of women in carbetocin group required blood transfusion, while 15.5% in oxytocin group required blood transfusion.[24] In this study, none of patients in carbetocin group were needed blood transfusion but in oxytocin group blood transfusion were required 10.6% patients. Agnes P. Monteo-Fenix et al investigated carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal delivery among high risk women and found that fundal massage required 10% patients in carbetocin group and 83% patients in oxytocin group.[25] In this study, none of patients in carbetocin were needed fundal massage but in oxytocin group fundal massage were required 8.5% patients. Sergio Rosales-Ortiz, Rogelio Perez Aguado et all also showed that only 1.5% patients need additional uterotonics in carbetocin group and 5.8% patients in oxytocin group.[26] Manal M. E Behery et al showed that none of the patient in carbetocin group required additional uterotonics while as high as 71.5% of women in oxytocin group need additional oxytocin to ensure adequate uterine contraction for long period.[24] C. A. G. Holleboom, J. van Eyck et al 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.[27] Debbie-lynuy et al showed that only 5.7% patients were need for additional uterotonics in carbetocin group and 34.3% patients in oxytocin group.[22] In this study, none of patients of carbetocin group were required additional uterotonic but in oxytocin group additional uterotonics were required for 10.6% patients. Sergio Rosales-Ortiz et al also showed the mean amount blood loss in carbetocin group was 366 ml and oxytocin group were 400 ml when compared the efficacy of carbetocin with oxytocin.[26] Average 34 ml more blood loss was observed in oxytocin group. Ahmed Mohamed Maged[23] showed the mean amount blood loss in carbetocin group were 337 ml and oxytocin group were 378 ml.[23] Average 41 ml more blood loss was observed in oxytocin group. Mohammed S. E. Elsafty showed that amount blood loss was an average of 207 ml of blood in the oxytocin group and an average of 87 ml of blood loss in carbetocin group.[28] Average 120 ml more blood loss was observed in oxytocin group. In this study average blood loss in carbetocin group was 320 ml and oxytocin group was 408 ml. Average 88 ml more blood loss was observed in oxytocin group. Ahmed Mohamed Maged et al also showed the occurrence of PPH were 4% in carbetocin group and 16% in oxytocin group.[23] In this study, occurrence of PPH in oxytocin group was 8.5% patients but in carbetocin group none of patients had developed PPH. Primary postpartum haemorrhage (PPH) is the most common form of major obstetric hemorrhage.[29] It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide.[30,31] 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 due to uterine atony.[32] Bleeding due to uterine atony can be prevented by active management of third stage labour (AMTSL).[33] The promising findings suggested that carbetocin appears to be an effective new drug in the active management of third stage of labour in vaginal delivery. A single dose of 100 microgram IV carbetocinis more effective than oxytocin for maintaining adequate uterine tone, decreases blood loss and preventing postpartum hemorrhage in women undergoing vaginal delivery. carbetocin can be considered as a good alternative to oxytocin in managing third stage of labour in vaginal delivery.

Conclusion

Carbetocin is an effective new drug than Oxytocin for prevention of postpartum hemorrhage in vaginal delivery**.**

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