Efficacy and Safety of Carbetocin in Comparison to Oxytocin in the Active Management of Third Stage of Labour Following Vaginal Delivery: An Open Label Randomized Control Trial

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Abstract:
Objective(S): This study was conducted to evaluate the efficacy and safety of carbetocin in comparison to oxytocin in the active management of third stage of labour following vaginal delivery.

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, 2015. Patients who got admitted in ICMH with labour pain were assessed by general examination, abdominal examination and labour status was confirmed by per vaginal examination. On the basis of selection criteria total 94 pregnant women who had undergone vaginal delivery were randomized for two groups of drugs. According to computer generated randomization sequential number was allocated for cases. One group of patients received intravenous 100 micro gram carbetocin and another group of patients received intramuscular 10 IU oxytocin in third stage of labour. Outcome measures such as amount of blood loss in 24 hours, primary PPH, massive blood loss, need of fundal massage, need for additional uterotonic therapy, blood transfusions as well as other adverse effects were all documented.

Results: In this study, massive blood loss did not occur in any of patients in carbetocin group. But massive blood loss occurred in 8.5% women of oxytocin group. Further fundal massage, immediate blood transfusion and additional uterotonic were not needed by any patient in carbetocin group. In oxytocin group, fundal massage required in 10.6% of women, blood transfusion was needed for 6.4% patients and additional uterotonics was needed for 10.6% women. Average amount of blood loss were 64 ml less in carbetocin group and adverse effects of drugs were almost similar in both groups. Primary PPH was developed 6.4% in oxytocin group but none of patients developed PPH in carbetocin group.

Conclusion: 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 carbetocin is more effective than oxytocin for maintaining adequate uterine tone, less blood loss and preventing postpartum bleeding in women undergoing vaginal delivery. So, carbetocin can be considered as a good alternative to oxytocin in the active management of third stage of labour in vaginal delivery.

Key words: Post-partum hemorrhage, uterotonic drugs, carbetocin, oxytocin.

Introduction:
Active management of the third stage of labour (AMTSL) is a critical intervention for PPH prevention. AMTSL has become a central component for the PPH reduction strategies of governments around the world. In 2012, WHO has issued new recommendations regarding AMTSL, which can be used to strengthen and focus the implementation of this life saving
Anaemia after delivery of a child (postpartum anaemia) is a common problem throughout the world. The prevalence of postpartum anaemia is highest in developing countries where it is a major cause of maternal morbidity and mortality. It has been estimated that of the 500,000 maternal deaths occurring each year on a global scale in association with delivery, 20% are caused by peripartum hemorrhage and anaemia. However, postpartum anaemia also constitutes a significant and partly unrecognized problem even in developed countries. The use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour is recommended for all births. Postpartum haemorrhage is the single most important cause of maternal mortality worldwide. It is the leading cause of maternal deaths accounting for nearly one-quarter of all maternal death. 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%. In developing countries, mortality from PPH remains high. In low income setting, PPH accounting for 30% of maternal death, while in Bangladesh it is 31%. In 1990, the maternal mortality ratio was 574 per 100,000 live births. In 2001 the MMR was 322 per 100,000 live births. In 2010 the ratio was 194 per 100,000 live births. In 2015 the ratio was 176 per 100,000 live births. So far the picture is really looking promising for Bangladesh. 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 3.1 of SDG 3 is to reduce the global MMR to less than 70 per 100 000 live births by 2030.

PPH may be primary that occur within 24 hours of delivery and secondary where bleeding appears after 24 hours. Primary PPH is the most common one and up to 80% cases it occurs due to uterine atony, while secondary PPH related to infection.

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. In addition, the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension. Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability. Bleeding due to uterine atony can be prevented by active management of third stage labour (AMTSL). Till now it is recommended that oxytocin should be used as a oxytocic agent either in the form of intramuscular injection or intravenous infusion. But it’s adverse effects limit its random use. Moreover, oxytocin potency deteriorates when it is exposed to temperatures greater than 30°C for prolonged periods of time. For this reason, oxytocin should be distributed and stored along a cold chain. In our country cold chain is not properly maintained for oxytocin. So, there is a chance of lowering effectiveness and stability. As a result, treatment failure may occur.

Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties. Carbetocin has prolonged duration of action (approximately 1 hour), which ensures more contraction time and less adverse effect. 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.

Patients and methods:
This randomized control trial was done from January, 2015 to September, 2015 in the Department of Obstetrics and Gynaecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh. About 94 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 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 vaginal delivery above 36 weeks of gestation (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report).
Exclusion criteria were placenta praevia, multiple gestations, and placental abruption (determined by history and ultrasound report) hypertensive disorders in pregnancy, preeclampsia, and known case of cardiac, renal, liver diseases, epilepsy, moderate anemia (Hb <9gm/dl), intrauterine foetal death and unwilling to participate in the study.

During study period we enrolled 47 women who received carbetocin 100 ìg I/V as a single dose and 47 women who received 10 IU of oxytocin after the delivery of the baby and prior to the delivery of the placenta. The primary outcome was measured by the amount of blood loss within 24 hours after delivery. Based on the experience of previous study26, the research team was provided a pre-weighted standardized delivery mat (Quaiyum’s mat) and pre-weighted sanitary pads for blood collection after delivery to each of the pregnant woman to measure blood loss in 24 hours postpartum period. We had measured the amount of blood loss in gram by digital postal scale. Then we multiplied the amount in gram by 1.06 to get the amount of blood loss in ml. It would be mentioned that 1000 gram is equivalent to 1056 ml. Primary PPH was considered when blood loss is 500 ml within 24 hours of delivery in both groups. The secondary outcomes were need for additional uterotonic therapy, massive blood loss, additional massage, blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation and by need of additional uterotonics to contract the uterus.

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

Results:
A total of 110 pregnant women with a single pregnancy were initially recruited for inclusion in this study. Sixteen cases were excluded (5 had preeclampsia, 5 eclampsia, 2 placenta praevia, 2 placental abruption and 2 multiple gestation). Thus 94 women were recruited for final study and analysis. Mean age of study patients was 22.7 ± 3.2 and 22.1 ±3.2 years in carbetocin and oxytocin group respectively. Among study population 20 (42.6%) patients in carbetocin group and 23 (48.9%) patients in oxytocin group had mild anaemia. Mean systolic and diastolic BP was 110±9.6 mm of Hg and 73 ±5.3 mm of Hg in carbetocin group and 108±7.7 mm of Hg and 70±12.5 mm of Hg in oxytocin group. Mean gestational age at delivery was 39±1.1 and 39.09± 1.7 weeks in carbetocin and oxytocin group respectively.

It shows that baseline parameters are equal in both the groups (Table I).

Table-I: Shows that massive blood loss took place in 8.5% cases, fundal massage required by 10.6% patients, blood transfusion needed for 6.4% patients and additional uterotonic needed for 10.6% patients in oxytocin group but in carbetocin group there was no massive blood loss in any patient, fundal massage and blood transfusion was not needed for any patient and none of the patient required additional uterotonics.

The mean differences were statistically significant (P<0.05). Except abdominal pain in few cases (4 in carbetocin and 5 in oxytocin) no major adverse effects observed in any group.

Average blood loss in carbetocin group was 325 ml and oxytocin group was 389 ml. Average 64 ml more blood loss was observed in oxytocin group. The mean differences were statistically significant (P<0.05) (Table III).

No patient developed PPH in carbetocin group. But 3 (6.4%) patients developed PPH in oxytocin group, though it is not statistically significant (P>0.05) (Table IV).

Table-I

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Carbetocin Group (47)</th>
<th>Oxytocin Group (47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>22.7±3.2</td>
<td>22.1±3.2</td>
<td>0.439</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>110±9.6</td>
<td>108±7.7</td>
<td>0.210</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>73±5.3</td>
<td>70±12.5</td>
<td>0.509</td>
</tr>
<tr>
<td>Gestational Age (Weeks)</td>
<td>39.01±1.1</td>
<td>39.09±1.7</td>
<td>0.799</td>
</tr>
<tr>
<td>Mild Anemia</td>
<td>20%</td>
<td>23%</td>
<td>0.386</td>
</tr>
</tbody>
</table>
Discussion:
Active management of 3rd stage of labour significantly reduces 3rd stage haemorrhage. Active management includes application of uterotonics just after delivery of the head of the baby. Oxytocin has been using widely for long time. Now a days carbetocin, which is also a oxytocic drug has gained popularity due to its more potentiality in comparison to oxytocin. We compared the effect of two drugs in terms of controlling postpartum bleeding.

Our results 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 decreased the need for additional uterotonics, uterine massage and massive blood loss in the active management of third stage of labour after vaginal delivery. None of the patients in carbetocin group needed blood transfusion but in oxytocin group blood transfusion was needed in 6.4% patients. A similar study showed that none of the woman in carbetocin group required blood transfusion, while 15.5% in oxytocin group required it. Agnes et al. investigated carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal delivery among high risk women and found that fundal massage was needed for 10% patients in carbetocin group and 83% patients in oxytocin group. In our study, none of patients in carbetocin group needed fundal massage but in oxytocin group fundal massage was needed in 10.6% patients.

A single dose of oxytocin is not adequate and it always follows by additional uterotonics to keep the uterus contractile. But a single dose of carbetocin is enough for controlling bleeding by keeping the uterus contractile for long time. Ortiz et al. showed that only 1.5% patients needed additional uterotonics in carbetocin group and 5.8% patients in oxytocin group. Another study 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. Prophylactic use of carbetocin and oxytocin after an elective caesarean section showed significantly diminished need for additional uterotonics in carbetocin group. Similar result shown by Debbie et al. where 5.7% patients needed additional uterotonics in carbetocin group whereas, 34.3% patients needed in oxytocin group. In our study, none of patients of carbetocin group required additional uterotonic but in oxytocin group additional uterotonic was needed for 10.6% patients.

### Table-II

<table>
<thead>
<tr>
<th>Outcome of 3rd stage of Labour</th>
<th>Carbetocin Group (47)</th>
<th>Oxytocin Group (47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massive blood loss</td>
<td>0 (0%)</td>
<td>4 (8.5%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fundal massage required</td>
<td>0 (0%)</td>
<td>5 (10.6%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Blood transfusion requirement</td>
<td>0 (0%)</td>
<td>3 (6.4%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Need for additional uterotonics</td>
<td>0 (0%)</td>
<td>5 (10.6%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

### Table-III

<table>
<thead>
<tr>
<th>Amount of blood loss</th>
<th>Carbetocin group (47)</th>
<th>Oxytocin group (47)</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average blood loss in 24 hours (in ml)</td>
<td>325 ml (306 g)</td>
<td>389 ml (366 gm)</td>
<td>64 ml</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Table-IV

<table>
<thead>
<tr>
<th>Outcome (Primary PPH)</th>
<th>Carbetocin group (47)</th>
<th>Oxytocin group (47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>3 (6.4%)</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>47 (100%)</td>
<td>44 (93.6%)</td>
<td></td>
</tr>
</tbody>
</table>
Ortiz et al.\textsuperscript{29} also showed the mean amount of blood loss in carbetocin group was 366 ml and in oxytocin group was 400 ml when compared the efficacy of carbetocin with oxytocin. Average 34 ml more blood loss was observed in oxytocin group. Similar results shown by other two studies that average blood loss was more in oxytocin group than carbetocin group\textsuperscript{32,33}. In this study average blood loss in carbetocin group was 325 ml and oxytocin group was 389 ml. Average 64 ml more blood loss was observed in oxytocin group. This fact can be explained by the known longer half-life of carbetocin. Carbetocin is effective in preventing postpartum hemorrhage in both high- and low-risk groups.\textsuperscript{33}

Maged et al.\textsuperscript{32} 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 6.4\% but in carbetocin group none of patients developed PPH. Primary postpartum haemorrhage is the most common form of major obstetric hemorrhage.\textsuperscript{34} It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide.\textsuperscript{35,36} 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\% cases of postpartum hemorrhage are due to uterine atonicity\textsuperscript{30,37}. Bleeding due to uterine atonicity, can be prevented by active management of third stage labour (AMTSL)\textsuperscript{10,26}.

In conclusion the promising findings of this study 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 carbetocin is more effective than oxytocin for maintaining adequate uterine tone, decreased 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.

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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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