Original Article

# Efficacy and Safety of Carbetocin versus Oxytocin for Prevention of Postpartum Haemorrhage in Women Undergoing Normal Vaginal Delivery in Tertiary Care Centre of Bihar

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**ABSTRACT**

***Introduction:*** With its short half-life and short duration of action, oxytocin is the current standard therapy for preventing postpartum haemorrhage. However, because it is sensitive to heat, its efficacy cannot be guaranteed in many small and medium-sized countries where cold chain transportation and storage are not possible. In contrast, carbetocin, a long-acting oxytocin analogue is heat stable. However, the evidence for saying whether carbetocin is more efficacious and tolerable than oxytocin for prevention of postpartum haemorrhage after vaginal delivery is not so strong.

***Aims/ objective:*** To compare the efficacy and safety of carbetocin and oxytocin in preventing postpartum haemorrhage in women undergoing normal vaginal delivery.

***Materials and Method:*** 100 women were randomly assigned using web generated random numbers to group C and group O with 50 women in each group. Women of group C were given a single intramuscular injection of heat-stable carbetocin at a dose of 100 µg and women of group O were given intramuscular injection of oxytocin at a dose of 10 IU. The drugs were administered immediately after the birth of the baby. The primary outcome measure was mean blood loss after vaginal delivery. Proportion of women with blood loss > 500 ml, requirement of other uterotonic or surgical procedures and incidence of adverse events were secondary outcome measures.

***Results:*** Mean blood loss after women who were given carbetocin was lower than that of women who were given oxytocin and this difference was statistically significant ($p < 0.05$). However, there was no significant difference with respect to proportion of women with PPH (blood loss > 500 ml). Number of women requiring additional uterotonic agents or blood transfusion was also lower in carbetocin group but this difference was also not statistically significant ($p > 0.05$). Carbetocin was as safe as oxytocin with no statistically significant difference between two groups ($p > 0.05$).

***Conclusion:*** In our study, carbetocin was found to be slightly better than oxytocin in preventing postpartum haemorrhage in women who have undergone a singleton vaginal delivery. Government should take step in ensuring availability of carbetocin at minimum cost.

**Keywords:** Carbetocin, Oxytocin, Post partum haemorrhage, Vaginal delivery, Uterotonic.

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## INTRODUCTION

Although great efforts have been made to reduce maternal mortality, postpartum haemorrhage remains the most common direct cause of maternal mortality. It is responsible for nearly a quarter of all deaths worldwide and is the cause of long-term disability and major maternal morbidity, including blood transfusions, emergency surgery, and ICU admissions. [1, 2] Post-partum haemorrhage is a frequent complication which is noticed following 2 to 4% of vaginal deliveries and six percent of caesarean sections. According to WHO, it is the dominant cause of maternal death worldwide, responsible for 35% of deaths. [3] 38% of maternal deaths in India can be associated to postpartum haemorrhage. [4]

Postpartum haemorrhage (PPH) is defined as bleeding of greater than 500 mL after vaginal delivery and greater than 1000 mL after caesarean section from genital tract. Primary PPH is bleeding within 24 hours after delivery, and secondary PPH is excessive bleeding after 24 hours but within 12 weeks after delivery.[5] The most frequent cause of postpartum haemorrhage is uterine atony which results due to poor contraction of the uterine muscles after childbirth. [6]

The World Health Organization (WHO) now suggests active management of the third stage of labor to prevent postpartum haemorrhage.[6] Prophylactic administration of


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uterotonic agents is recognized as the most crucial component of active management of the third stage of labor. The uterotonic agent reduces the frequency of postpartum haemorrhage by almost 50%. [7]

With its short half-life and short duration of action, oxytocin is the current standard therapy for preventing postpartum haemorrhage. However, because it is sensitive to heat, its efficacy cannot be guaranteed in many small and medium-sized countries where cold chain transportation and storage are not possible, and quality issues such as impurities and insufficient active ingredients also affect its efficacy. [8]

In contrast, carbetocin, a long-acting oxytocin analogue, has been widely used since 1997 to prevent postpartum bleeding. Thermostable carbetocin has been shown to retain activity for over 36 months at 30°C and 75% relative humidity. [9] Carbetocin can be given both intravenously and intramuscularly. The side effect rate is as low as oxytocin. It also has the advantage of requiring less additional uterotonics, making it optimal for use in primary or rural health centres.

Clinical trials of carbetocin to prevent postpartum bleeding have focused primarily on caesarean sections. A recent systematic review demonstrated that carbetocin was more effective than oxytocin in reducing the need for additional uterotonics and post-caesarean uterine massage. [10]

However, the evidence for saying whether carbetocin is more efficacious and tolerable than oxytocin for prevention of postpartum haemorrhage after vaginal delivery is not so strong. Therefore, we found it important to compare the efficacy and safety of carbetocin and oxytocin in preventing postpartum haemorrhage in women undergoing normal vaginal delivery. We compared the amount of blood loss after vaginal delivery and proportion of women with blood loss greater than 500 ml between women who were given carbetocin or oxytocin for prevention of PPH.

## MATERIALS AND METHODS

It was an open label randomised controlled trial with parallel 1:1 allocation of study participants done in tertiary care centre of eastern India in one year. The study was done as per guidelines of good clinical practice and declaration of Helsinki. Participant Information Sheet was provided to all the study participants and written informed consent was taken from them.

**Inclusion criteria:** Women of age between 18-35 years who expected to give birth vaginally and who had a singleton pregnancy of gestational age 37-40 weeks and cervical dilatation of 6 cm or less were eligible.

**Exclusion criteria:** Women who have undergone lower segment caesarean section previously, women who required instrumental vaginal delivery including forceps or vacuum assisted; women who had perineal or cervical tears during labor and delivery; women who had antepartum haemorrhage due to placenta previa or abruptio placentae, women who were diagnosed with preeclampsia or eclampsia or gestational diabetes mellitus or multiple pregnancies or polyhydramnios; women with gynaecological disorders such as myomas; Women with coagulation disorders; women having known allergies to carbetocin, oxytocin or excipients; or having a serious cardiovascular disease, serious liver or renal disease, or epilepsy.

Women were randomized when vaginal birth was imminent. 100 women were randomly assigned using web generated random numbers to group C and group O with 50 women in each group. Women of group C were given a single intramuscular injection of heat-stable carbetocin at a dose of 100 µg and women of group O were given intramuscular injection of oxytocin at a dose of 10 IU. The drugs were administered immediately after the birth of the baby and the management of the third stage of labor was carried out as per recommendation in the WHO guidelines.[11] Just after the umbilical cord clamping and cutting was done, a plastic drape for collecting blood was placed beneath the woman's buttocks. Blood collection was done for 1 hour or for 2 hours when the bleeding persisted beyond 1 hour. The drape with the collected blood was then weighed using a digital scale and the weight of drape was recorded in grams and then it was converted to volume (milliliters) after subtracting the weight of the drape at initial stage.

Participation in the trial ended when women were discharged from the hospital. Information on serious and other adverse events was recorded from the time of informed consent to the time of discharge.

**Primary Outcome Measure:** Mean blood loss in ml.

**Secondary Outcome Measures:**

- Proportion of women with post-partum blood loss greater than 500 ml
- Proportion of women requiring additional uterotonic agents
- Proportion of women requiring blood transfusion
- Proportion of women requiring manual removal of placenta
- Proportion of women requiring additional surgical procedure such as hysterectomy
- Proportion of new-born requiring resuscitation or mechanical ventilation
- Proportion of women who had adverse event causally related to interventional drugs

**Statistical Analysis:** Data collected were entered into tabular form using Microsoft Excel 365. Data was then transferred to SPSS version 25.0 for further statistical analysis. Unpaired t test was done to evaluate statistical significance of difference in mean blood loss, women age and gestational age expressed in mean ± standard


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deviation (SD). Fisher's exact test was done to evaluate statistical significance of differences in primary and secondary outcome measures expressed as proportion. P-value of less than 0.05 was taken as the marker of statistical significance.

## OBSERVATIONS AND RESULTS

**Table 1:** Comparison of baseline demographic and clinical characteristics between two groups

| Variables | Group C (n = 50) | Group O (n = 50) | P-Value |
|---|---|---|---|
| Age in years (Mean ± SD) | 27.13 ± 2.37 | 26.81 ± 1.92 | 0.46* NS |
| Number of primigravida | 22 | 20 | 0.8396** NS |
| Gestation age years (Mean ± SD) | 38.94 ± 0.95 | 39.08 ± 1.04 | 0.4838* NS |
| Number of women in which labor was induced | 8 | 9 | >0.9999** NS |
| Number of women in which labor was augmented | 21 | 19 | 0.8384**NS |
| Number of women with previous postpartum haemorrhage | 1 | 2 | >0.9999** NS |
| *Unpaired t-test **Fisher's exact test S- Significant NS- Non-Significant | | | |

Both the groups were similar regarding baseline demographic and clinical characteristics. There was no statistically significant difference between two groups with respect to parity, gestational age, induction or augmentation of labor or history of PPH (p > 0.05).

**Table 2:** Comparison of efficacy of Carbetocin and oxytocin in post-partum haemorrhage

| Outcome Measures | Group C (n = 50) | Group O (n = 50) | P-Value (Fisher's exact test) |
|---|---|---|---|
| Mean blood loss in ml ± SD | 361.34 ± 46.71 | 387.68 ± 55.13 | 0.0114 S (Unpaired t test) |
| Number of women with post-partum blood loss > 500 ml | 8 | 11 | 0.6111 NS |
| Number of women requiring additional uterotonic agents | 9 | 12 | 0.6242 NS |
| Number of women requiring blood transfusion | 1 | 2 | >0.9999 NS |
| Number of women requiring manual removal of placenta | 0 | 1 | >0.9999 NS |
| Number of women requiring additional surgical procedure | 1 | 2 | >0.9999 NS |

S- Significant NS- Non-Significant

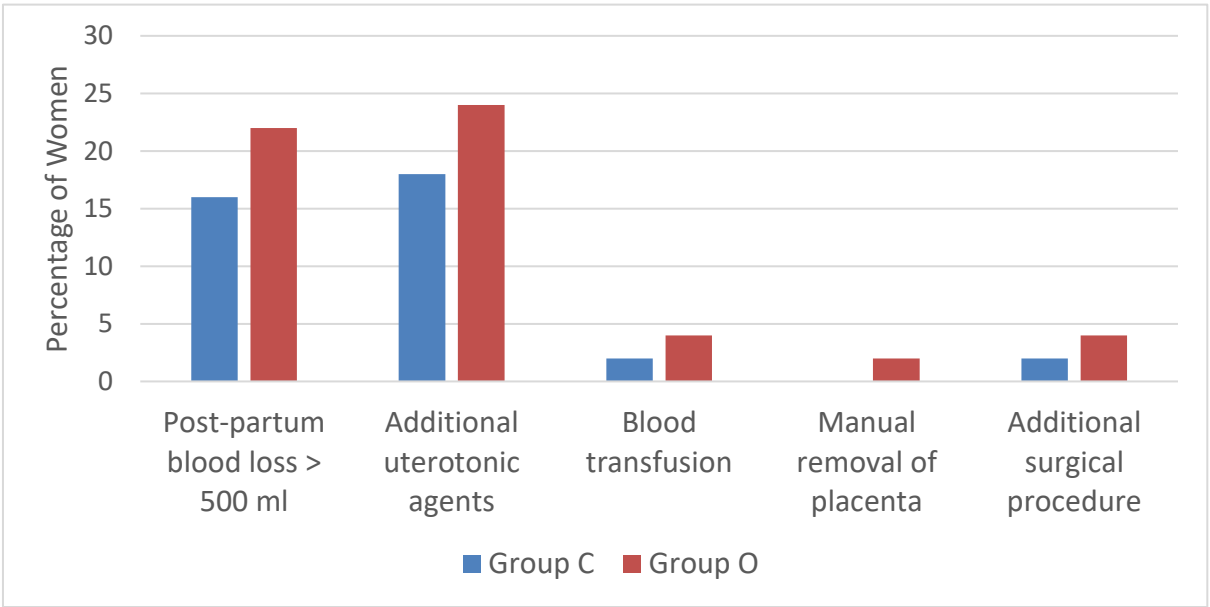


**Figure 2:** Comparison of efficacy of Carbetocin and oxytocin in post-partum haemorrhage


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**Table 3:** Comparison of neonatal outcomes between two groups

| Outcome | Group C (n = 50) | Group O (n = 50) | P-Value (Fisher's exact test) |
|---|---|---|---|
| Number of new-borns requiring resuscitation | 3 | 4 | >0.9999 NS |
| Number of new-borns requiring mechanical ventilation resuscitation | 2 | 1 | |

There was no significant difference between two groups with respect to neonatal outcomes (p>0.05).

**Table 4:** Comparison of frequency of different adverse events between two groups

| Adverse Events | Group C (n = 50) | Group O (n = 50) | P-Value (Fisher's exact test) |
|---|---|---|---|
| Abdominal pain | 3 | 2 | >0.9999 NS |
| Nausea & Vomiting | 1 | 2 | |
| Chest pain | 1 | 0 | |
| Flushing | 0 | 1 | |

Carbetocin was as safe as oxytocin with no statistically significant difference between two groups (p>0.05).

Mean blood loss after women who were given carbetocin was lower than that of women who were given oxytocin and this difference was statistically significant ($p < 0.05$). However, there was no significant difference with respect to proportion of women with PPH (blood loss > 500 ml) although there was slightly better result in carbetocin group. Number of women requiring additional uterotonic agents or blood transfusion was also lower in carbetocin group but this difference was also not statistically significant (p >0.05). Only one woman in carbetocin group required manual removal of placenta or surgical procedure as compared to 3 women in oxytocin group.

## DISCUSSION

In this study, we have attempted to compare the efficacy and safety of 100 mcg carbetocin and 10 IU oxytocin for the prevention of postpartum haemorrhage in patients who have undergone singleton vaginal deliveries at term. We have noticed that incidence rates of postpartum haemorrhage were slightly low in carbetocin group as compared to oxytocin group. This confirms the non-inferiority of carbetocin in comparison to oxytocin for its indication in prophylaxis of post-partum haemorrhage.

Requirement of other uterotonics for the prevention of PPH was slightly greater in oxytocin group and incidence of PPH within 1-3 hours of delivery was also slightly greater but the differences between two groups were not statistically significant. These results are similar to the study of Rath W et al. who have shown similar incidence rates due to long duration of action of carbetocin.[12] Blood loss after delivery was less in the women who were given carbetocin and this difference was found to be statistically significant. The safety profile of carbetocin and oxytocin was also found to be similar and there were no serious adverse events in either group within 24 hours of drug administration.

Therefore, the choice to use carbetocin in a given situation should be based on convenience specifically in primary and rural health centres. Atonic post-partum haemorrhage is the leading cause of maternal death in underdeveloped countries like India. [4] In the study of Jackson Jr KW et al., uterotonics have been shown to be the most efficient method for both preventing and treating postpartum haemorrhage, which has led to oxytocin's extensive use. [13] However, it is challenging in India, particularly in rural areas, to effectively maintain the cold chain needed for oxytocin activity. Carbetocin that is stable at room temperature can be particularly life-saving in such circumstances.

Additionally in the study of Maged AM et al., it has been discovered that a single intravenous or intramuscular dose of carbetocin is also effective. [14] In the study of Malm M et al., carbetocin has also been demonstrated to have acceptable safety profile when administered intravenously and intramuscularly, with the incidence of adverse drug reactions being extremely low. This enables its use in basic healthcare facilities. [15] In India, carbetocin is more expensive than oxytocin. However, the effectiveness of a single dose and the lack of a cold chain requirement make carbetocin a valuable drug in the Indian context.

In the meta-analysis of 5 randomized trials comprising 30,314 women, it was found that that there was no any statistically significant difference between women undergoing vaginal delivery and receiving carbetocin or oxytocin with respect to blood loss greater than 500 ml. Similar findings were obtained in the sensitivity analyses. The meta-analysis also reported that no statistically significant differences was found between women receiving carbetocin or oxytocin with respect to blood loss greater than 1000 ml, need for additional uterotonic drugs, need for blood transfusion, requirement of uterine massage, and adverse events. [16]


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The key to preventing atony postpartum haemorrhage is having access to potent uterotonic medications. However in the survey done by Theunissen FJ et al., uterotonic agent quality problems are common in low- and middle-income nations. [17] According to the most recent data, between 45.6% and 74.2% of oxytocin samples in these nations failed quality testing because of insufficient levels of the active component. [8, 18] Therefore, it becomes crucial to increase the effectiveness and quality of uterotonic drugs in order to prevent postpartum haemorrhage.

Compared to oxytocin, carbetocin offers advantages in preventing postpartum haemorrhage. Carbetocin, which is heat-stable, does not require cold-chain transmission or storage like oxytocin does. Therefore, in low- and middle-income nations where cold-chain transport and storage are not accessible, it is convenient to store carbetocin in these facilities at room temperature. Carbetocin has a half-life of 40 minutes, which is 4–10 times longer than oxytocin. From his research, Amornpetchakul P et al. has suggested that in order to avoid the negative effects of intravenous injection, intramuscular route of carbetocin can be used and duration of action is 2 hours after intramuscular injection. [19]

Currently, there are no clear guidelines regarding the use of carbetocin in prevention of postpartum haemorrhage. However, the findings of this study revealed that there was no statistically significant difference between women undergoing vaginal delivery and receiving carbetocin or oxytocin for preventing postpartum haemorrhage. We have also found a non-significant trend in favour of carbetocin. Therefore, according to the findings of our study, it is recommended that professional organizations should consider revising their clinical guidelines for clinicians and promote heat- stable carbetocin as first line therapy for preventing postpartum haemorrhage in women planned for vaginal delivery especially in resource limited countries, if cost-effectiveness of carbetocin is ensured.

Risk factors of postpartum haemorrhage consists of previous history of PPH, retained placenta in uterus, polyhydramnios, twin pregnancies or history of prolonged labor according to a survey done by combs CA et al. [20] It is not certain whether women received effective dose of carbetocin for the prevention of PPH. Further studies should focus on specific subpopulations like women having polyhydramnios, twin pregnancy, or history of prolonged labor. Future studies should also investigate to find the optimal dose, dosage schedule, and route of administration of carbetocin for these subpopulations.

## CONCLUSION

In our study, carbetocin was found to be slightly better than oxytocin in preventing postpartum haemorrhage in women who have undergone a singleton vaginal delivery. It can be conveniently used in developing countries such as India because it is stable at room temperature. The choice of carbetocin for regular prophylaxis depends on cost-effectiveness. Presently, carbetocin is costlier than oxytocin which can limit its use in rural health care centres. Government should take step in ensuring availability of carbetocin at minimum cost.

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