International Journal of Science and Healthcare Research
[Indexed, Peer-Reviewed Journal]
Vol. 11; Issue: 1; Jan.-March 2026
Website: ijshr.com
Original Research Article *ISSN: 2455-7587*

Comparative Study of Efficacy and Safety of Carbetocin versus Oxytocin for Prevention of Postpartum Haemorrhage in Women with Normal Vaginal Delivery in Tertiary Care Hospital of Bihar

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DOI: https://doi.org/10.52403/ijshr.20260129

ABSTRACT

Introduction: Given its short half-life as well as duration of activity, oxytocin is now the preferred therapy for preventing postpartum haemorrhage (PPH). Nevertheless, in many developing nations where it is not possible to transport and store the product in the cold chain, its efficiency cannot be guaranteed because of its increased susceptibility to heat. Conversely, the long-acting synthetic oxytocin analogue carbetocin remains stable even at high temperatures. However, the available fact is inadequate to establish the superiority and tolerability of carbetocin or oxytocin in the prevention of PPH after vaginal delivery.

Aims/ objective: To compare the efficacy and safety of oxytocin versus carbetocin in preventing PPH in women with normal vaginal delivery.

Materials and Method: A sample of 150 women was randomly assigned to groups A and B, each consisting of 75 women, utilizing randomly generated numbers gathered through the internet. Women assigned to group A were administered 100 microgram doses of heat-stable carbetocin via a single injection, whereas women in group B had received a 10 IU dose of oxytocin intramuscularly. The primary outcome measure of interest was the average blood loss after vaginal birth. The secondary outcome measures included the percentage of women who experienced blood loss over 500 millilitres, the requirement for further uterotonic or surgical interventions, and the frequency or rate of adverse events.

Results: Mean blood loss in carbetocin group (363.58 ± 31.98) was significantly less than oxytocin group (395.83 ± 39.37) ($p<0.0001$). There was less requirement of additional uterotonic, blood transfusion, manual removal of placenta or additional surgical procedure in carbetocin group but the difference was not statistically significant ($p>0.05$). Incidence of adverse event such as abdominal pain was less in carbetocin group as compared to oxytocin group but the difference was not statistically significant ($p>0.05$).

Conclusion: Our study has shown that carbetocin is more efficacious than oxytocin in preventing PPH in women who have undergone a singleton vaginal delivery. It is imperative for the government to implement measures that ensure the affordability and easy accessibility of carbetocin.

Keywords: Carbetocin, Oxytocin, Post-partum haemorrhage, Vaginal delivery, Blood Loss.

INTRODUCTION

Notwithstanding substantial efforts to reduce it, PPH remains the leading cause of maternal death. It is responsible for significant maternal morbidity, including emergency blood transfusions, surgical procedures, and admissions to the intensive care unit, as well as around 25 percent of all deaths worldwide. [1, 2] An often-seen outcome following approximately two to 4% of vaginal deliveries along with six percent of caesarean procedures is PPH. Globally, it is responsible for thirty-five percent of maternal mortality, establishing it as the primary cause of death for mothers. [3] 38 percent of maternal deaths in India are attributed to PPH.[4]

According to the World Health Organization (WHO), "postpartum haemorrhage (PPH) is defined as a blood loss of 500 ml or more within 24 hours after birth." [3]PPH can be classified into two categories: primary, which refers to bleeding occurring during the first 24 hours after delivery, and secondary, which refers to severe bleeding occurring after 24- hours and before 12 weeks.[5] Insufficient contraction of uterine muscles following childbirth can result in uterine atony, the predominant etiology of PPH.[6] To prevent PPH, the WHO now recommends intensive care during the third stage of labour.[6] An essential component of effectively controlling the third stage of labour is the proactive administration of uterotonic medications. The incidence of PPH is approximately 50% lower when the uterotonic medication is administered.[7]

Given its short half-life as well as duration of activity, oxytocin is now the preferred therapy for preventing PPH. Yet, its effectiveness is not guaranteed in many developing nations wherein cold chain transportation and storage are not possible due to its heat susceptibility as well as problems such as impurities and insufficient active components.[8]

However, commencing in 1997, the management of PPH has been successfully achieved by the use of carbetocin, a durable oxytocin analogue. Scientific evidence has shown that thermostatic carbetocin retains its effectiveness for a duration exceeding three years when exposed to temperatures of 30 degrees Celsius with relative humidity of 75 percent.[9] Carbetocin can be delivered either intravenously or intramuscularly. Similar to oxytocin, the incidence of adverse effects is negligible. Furthermore, it is well-suited for implementation at primary or distant health facilities due to its reduced need for additional uterotonics.

Most clinical studies on the prevention of PPH with carbetocin have focused on caesarean operations. Based on a recent thorough evaluation, carbetocin was shown to be more effective than oxytocin in reducing the need for additional uterotonics as well as uterine massage after delivery.[10] However, the available data is inadequate to establish the comparative effectiveness and tolerability of carbetocin versus oxytocin in the prevention of PPH after vaginal delivery. Therefore, we deemed it essential to assess the efficacy and safety of oxytocin versus carbetocin in reducing incidence and severity of PPH in women who opted for a standard vaginal delivery. We analysed the blood loss resulting from vaginal birth and the percentage of women who lost over 500 millilitres of blood among those who were administered oxytocin or carbetocin as a prophylactic measure against PPH.

MATERIALS & METHODS

A one-year open label randomized controlled trial was carried out at SKMCH from July 2023 to June 2024, employing a parallel 1:1 assignment of participants. The study was conducted in accordance with the Helsinki Declaration and guidelines for good clinical practice. Each participant in the study was provided with a Participant Information Sheet and their signed written informed consent was collected.

Sample Size: With reported blood loss of 361.34 ± 46.71 ml in carbetocin group and

387.68 ml in oxytocin group in the study of Jha A et al. (2023),[3] minimum sample size required for 90% power with 0.05 alpha value was found to be 132. So, 150 patients were randomised to group C and group O to adjust with expected attrition rate of 10%.

Inclusion criteria: Women eligible for the study were aged 18 to 35, scheduled to have a vaginal birth, and experiencing a singleton pregnancy having an estimated gestational age between 37 and 40 weeks with a cervical dilatation of less than 6 centimetres.

Exclusion criteria: Women with previous LSCS, women undergoing forceps or vacuum vaginal delivery, women with placenta praevia or abruption placentae, women with multiple gestations, women with perineal tear or episiotomy during delivery, women with any systemic illness.

Women were randomly assigned to undergo vaginal birth when it was imminent. A sample of 150 women was randomly assigned to groups A and B, each consisting of 75 women, using randomly generated numbers obtained from the internet. Women assigned to group A were administered 100 microgram doses of heat-stable carbetocin via a single injection, whereas women in group B had received a 10 IU dose of oxytocin intramuscularly. After the baby was delivered, the therapy was promptly initiated, and the third stage of labor was controlled following the recommendations set by the WHO.[11] Upon clamping and cutting the umbilical cord, a plastic drape was placed over the woman's buttocks with the purpose of collecting blood.

Blood samples were collected either for a duration of one hour or for a duration of two hours when the bleeding persisted beyond that period. Following the first deduction of the overall weight of the drape, the amount (in millilitres) of the drape holding the collected blood was determined by measuring its weight on a digital scale and documenting the weight in grammes.

Participation in the trial concluded when the women received permission to depart from the hospital. Documentation of data on adverse occurrences was conducted from the moment informed consent was obtained to the moment of release.

Primary Outcome Measure: Average vaginal blood loss measured in millilitres.

Secondary Outcome Measures:

- Prevalence of postpartum blood loss above 500 millilitres among women; prevalence of females requiring additional uterotonic medications.
- Percentage of women requiring blood transfusions
- Relative proportion of women requiring manual placental removal and those requiring a hysterectomy and other further surgical interventions
- Proportion of neonates requiring mechanical ventilation or resuscitation
- Percentage of women who experienced adverse events directly attributed to interventional drugs
- Percentage of women who experienced adverse events directly caused by interventional medications

Statistical Analysis

A tabular display of the gathered data was generated utilizing Microsoft Excel 2019. Subsequently, the data was transferred to GraphPad Prism version 8.4.3 for further statistical analysis. Continuous data such as age, gestational age, and post-partum blood loss were expressed as mean±SD. A Fisher's exact test was conducted to evaluate the statistical significance of differences in primary as well as secondary outcome measures expressed as proportions. The criterion for statistical significance was established at a P-value below 0.05.

OBSERVATIONS & RESULTS

The figure 1 presents a CONSORT flow diagram illustrating the process of participant enrolment, allocation, follow-up, and analysis in the study. Initially, 197 individuals were assessed for eligibility. Of these, 47 participants were excluded, including 38 who did not meet the inclusion criteria and 7 who declined to participate. The remaining 150 eligible participants were randomized into two equal groups.

During the allocation phase, 75 participants were assigned to the Carbetocin group and all received the allocated intervention, while 75 participants were assigned to the Oxytocin group and similarly all received the allocated intervention. No participants in either group failed to receive the assigned treatment. During the follow-up period, there were no discontinuations of the intervention and no participants were lost to follow-up for the primary outcome in either group. In the final analysis phase, all randomized participants were included, with 75 individuals analyzed in the Carbetocin group and 75 in the Oxytocin group. No participants were excluded from the analysis, indicating complete follow-up and full adherence to the study protocol.

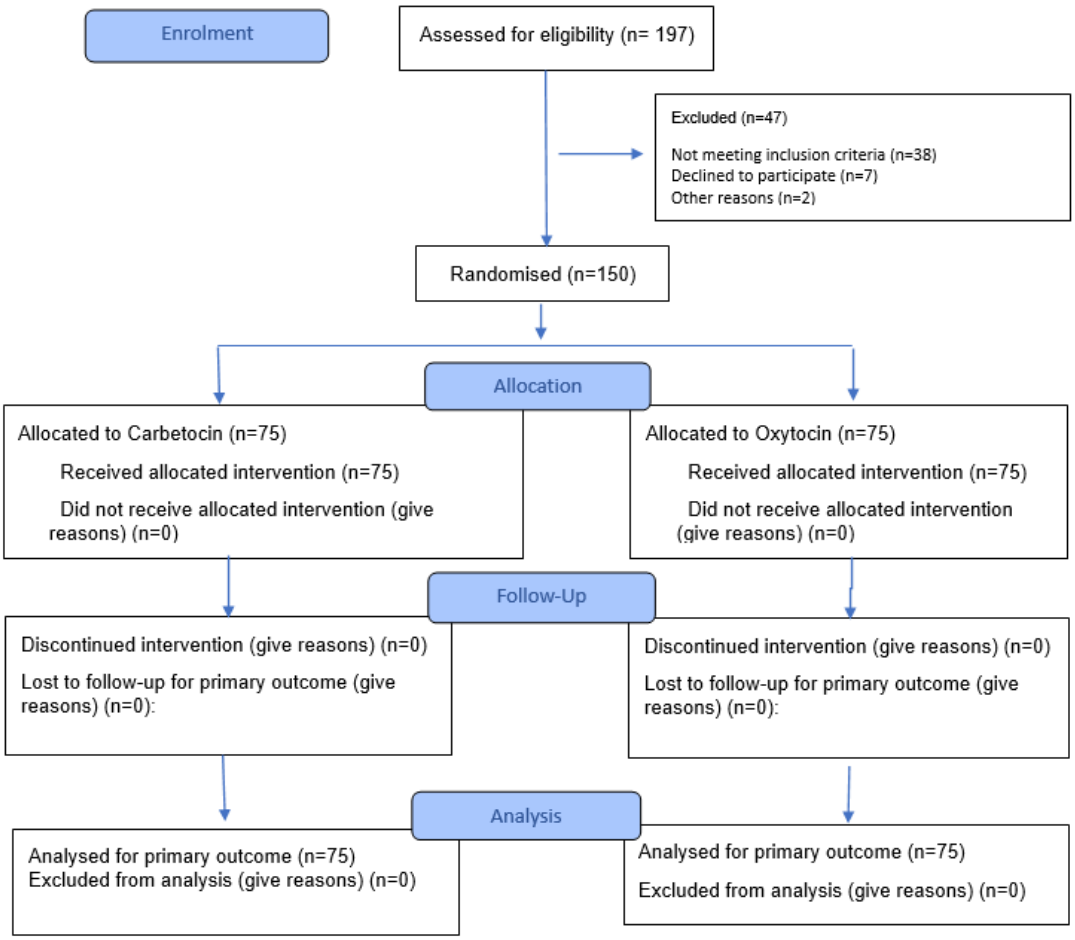

Figure 1: CONSORT flow diagram.

Table 1: Comparison of baseline demographic and clinical characteristics between group A (Carbetocin) and group B (Oxytocin)

Variables	Group A (n = 75)	Group B (n = 75)	P-Value
Age in years (Mean ± SD)	28.08± 4.46	29.37± 4.19	0.07*
Number of primi-gravida	35 (46.67)	31 (41.33)	0.84**
Gestation age years (Mean ± SD)	38.46± 1.09	38.84± 1.12	0.14*
Number of women in which labour was induced	13 (17.33)	15 (20)	0.83**
Number of women in which labour was augmented	30 (40)	28 (37.33)	0.87**
Number of women with previous postpartum haemorrhage	5 (6.67)	3 (4)	0.72**
*Unpaired t-test **Fisher's exact test			

Most of the subjects in carbetocin or oxytocin group belonged to 25-35 years of age group. Most of the subjects didn't have previous history of PPH. Induction of labour was done in less than 20% of subjects whereas augmentation of labour was done in approximately 40% of subjects. There was no difference between carbetocin and oxytocin group with respect to age, gestational age, and other baseline characteristics (p>0.05).

Table 2: Comparison of efficacy of group A (Carbetocin) and group B (Oxytocin) in post-partum haemorrhage

Outcome Measures	Group A (n = 75)	Group B (n = 75)	P-Value (Fisher's exact test)
Mean blood loss in ml ± SD	363.58± 31.98	395.83± 39.37	**<0.0001** (Unpaired t test)
Number of women with post-partum blood loss > 500 ml	10 (13.33)	18 (24)	0.14
Number of women requiring additional uterotonic agents	13 (17.33)	17 (22.67)	0.54
Number of women requiring blood transfusion	1 (1.33)	6 (8)	0.12
Number of women requiring manual removal of placenta	0 (0)	3 (4)	0.24
Number of women requiring additional surgical procedure	1 (1.33)	4 (5.33)	0.37
S- Significant NS- Non-Significant			

Mean blood loss in carbetocin group (363.58 ± 31.98) was significantly less than oxytocin group (395.83±39.37) (p<0.0001). Incidence of PPH was less in carbetocin group (13.33%) as compared to oxytocin group (24%) but the difference was not statistically significant (p=0.014). There was less requirement of additional uterotonic, blood transfusion, manual removal of placenta or additional surgical procedure in carbetocin group but the difference was not statistically significant (p>0.05).

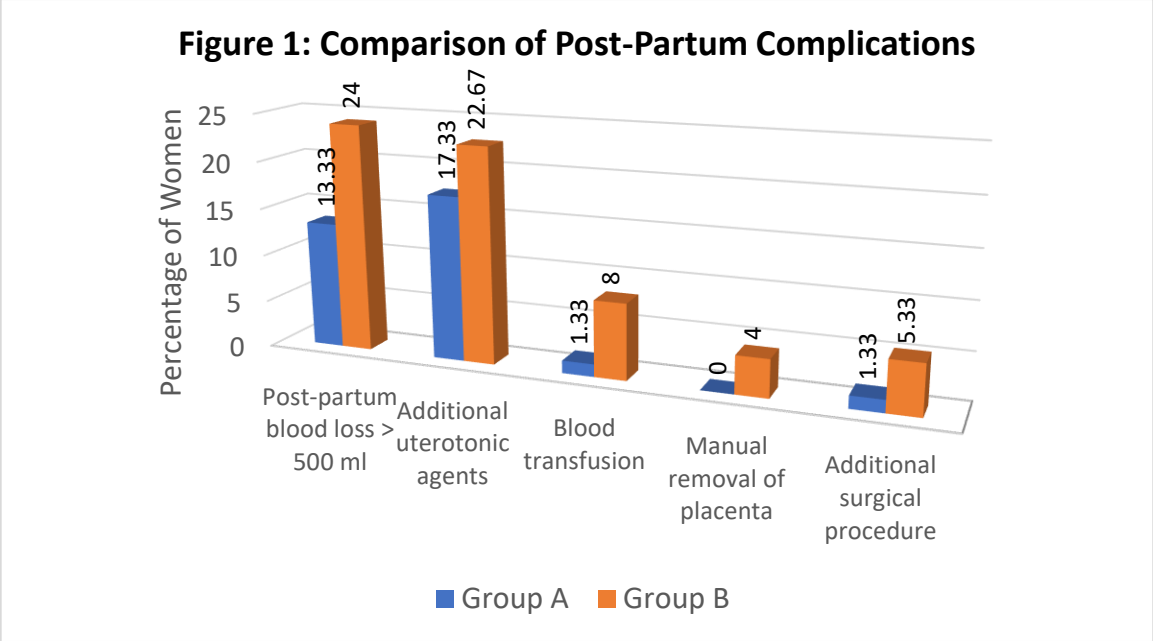

Table 3: Comparison of neonatal outcomes between group A (Carbetocin) and group B (Oxytocin)

Outcome	Group A (n = 75)	Group B (n = 75)	P-Value (Fisher's exact test)
Number of new-borns requiring resuscitation	4 (5.33)	7 (9.33)	0.53
Number of new-borns requiring mechanical ventilation resuscitation	1 (1.33)	5 (6.67)	0.21

There was less requirement of resuscitation in newborns of carbetocin group as compared to oxytocin group but the difference was not statistically significant (p>0.05).

Table 4: Comparison of frequency of different adverse events between group A (Carbetocin) and group B (Oxytocin)

Adverse Events	Group A (n = 75)	Group B (n = 75)	P-Value (Fisher's exact test)
Abdominal pain	3 (4)	9 (12)	0.13
Nausea & Vomiting	4 (5.33)	11 (14.67)	0.099
Chest pain	3 (4)	4 (5.33)	>0.99
Flushing	5 (6.67)	9 (12)	0.40

Incidence of adverse event such as abdominal pain was less in carbetocin group as compared to oxytocin group but the difference was not statistically significant (p>0.05).

DISCUSSION

The objective of this trial was to assess the safety and efficacy of 100 mcg of carbetocin versus 10 IU of oxytocin in reducing PPH in women undergoing singleton vaginal birth at full term. Our findings indicate that the carbetocin group had reduced rates of incidence of PPH in comparison to the oxytocin group. This finding illustrates that carbetocin is superior to oxytocin in terms of its efficacy in reducing PPH.

The group receiving oxytocin had a higher incidence of PPH within 1-3 hours after birth and indicated a larger need for further uterotonics to prevent PPH. These findings align with the study conducted by Rath W et al., which demonstrated that the extended duration of carbetocin's impact played a role in comparable incidence rates.[12] The women who were administered carbetocin experienced reduced postpartum blood loss, and this outcome was found to be statistically significant. Analysis revealed that the safety characteristics of oxytocin as well as carbetocin were similar, and neither group had any serious adverse effects within the initial 24-hour period after taking the medication.

Hence, the important factor to consider when determining the use of carbetocin in a specific situation, particularly in basic and rural health facilities, should be accessibility. In impoverished countries such as India, atonic PPH is the primary factor contributing to maternal mortality. 4 Based on the study conducted by Jackson Jr. KW et al., uterotonics remains the most efficacious approach for the management and prevention of PPH. Consequently, oxytocin has become widely used in this context.[13] Maintaining the critical cold chain necessary for oxytocin activity is challenging in India, particularly in rural areas. Given such circumstances, "heat-stable carbetocin" might prove very life-preserving.

Moreover, the study conducted by Maged AM et al. revealed that a single dose of carbetocin administered either intramuscularly or intravenously has equivalent benefit.[14] Furthermore, the study conducted by Malm M et al. has demonstrated that Carbetocin has a commendable safety profile when administered intravenously or intramuscularly, with an extremely low

incidence of side effects. Indeed, this enables its utilization in fundamental healthcare environments.[15] On the Indian market, carbetocin is priced higher than oxytocin. Nevertheless, carbetocin is a valuable medicine in the Indian context because of its efficacy achieved with a single dose and its lack of need for a cold chain.

A meta-analysis of five RCT encompassing 30,314 women found no statistically significant difference in incidence of PPH between women who opted for vaginal birth and those who received carbetocin or oxytocin. The sensitivity studies yielded similar results. Furthermore, the meta-analysis revealed no statistically significant differences between the groups of women receiving oxytocin versus carbetocin in relation to blood loss above 1000 ml, the need for "additional uterotonic medication," the risk of blood transfusion, the need for uterine massage, or the occurrence of complications.[16]

Access to potent uterotonic medications is crucial for preventing PPH caused by atony. Nevertheless, as per the study conducted by Theunissen FJ et al., low- and middle-income nations sometimes have challenges regarding"the quality of uterotonic drugs."[17] Latest data shows that in these nations, inadequate amounts of the active component led to failures in quality testing for "45.6% to 74.2% of oxytocin samples." [8, 18] Therefore, it is crucial to enhance the effectiveness and quality of uterotonic therapy in order to stop PPH.

Following labour, carbetocin has a superior effect compared to oxytocin in preventing bleeding. In contrast to oxytocin, carbetocin does not require cold-chain transit or storage due to its heat resistance. Thus, it is convenient to store carbetocin at ambient temperature in countries with low or moderate incomes where cold-chain transportation and storage are not accessible. Carbetocin has a "half-life of 40 minutes, which is 4 to 10 times longer than that of oxytocin." The tests conducted by Amornpetchakul P et al. demonstrate that the "intramuscular administration of carbetocin" can effectively mitigate the negative consequences of intravenous injection. The period of action after IM injection was 120 minutes.[19]

As to a study done by Combs CA et al., "the risk of PPH is increased by the following conditions: placenta retention in the uterus, polyhydramnios, multiple pregnancies, or previous experiences with prolonged labour."[20] The efficacy of the dosage of carbetocin in preventing PPH in women remains uncertain. Future study should prioritize specific populations that include "women with polyhydramnios, twin pregnancies, or previous experiences of prolonged labour." Further research efforts should investigate the optimal dosage, dosage schedule, and method of delivering carbetocin for the previously described categories.

CONCLUSION

Evidence suggests that carbetocin is more efficacious than oxytocin in preventing PPH in women who have undergone a singleton vaginal delivery. The safety profile of carbetocin was further demonstrated to surpass that of oxytocin. The excellent stability at room temperature renders it well-suited for application in emerging countries such as India. Carbetocin is the most cost-effective choice for regular preventive management. Presently, the cost of carbetocin exceeds that of oxytocin, therefore potentially limiting its use in remote healthcare facilities. It is imperative for the government to implement measures that ensure the affordability and easy accessibility of carbetocin.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Bhagyashree, Pratima. Comparative study of efficacy and safety of carbetocin versus oxytocin for prevention of postpartum haemorrhage in women with normal vaginal delivery in tertiary care hospital of Bihar. *Int. J. Sci. Healthc. Res.* 2026; 11(1): 280-288. DOI: *10.52403/ijshr.20260129*