

Comparative Double Blind Randomised Study of Heat Stable Carbetocin versus Oxytocin for the Prevention of Postpartum Haemorrhage Following Vaginal Birth

Prachi Tiwari¹, Sangeeta Raman Jogi², Dipika Singh³, Anish Kumar Bhagat⁴

¹Postgraduate, Obstetrics and Gynaecology, Chhattisgarh Institute of Medical Sciences Bilaspur Chhattisgarh

²Professor and HOD, Obstetrics and Gynaecology, Chhattisgarh Institute of Medical Sciences Bilaspur Chhattisgarh

³Associate Professor, Obstetrics and Gynaecology, Institute of Medical Sciences Bilaspur Chhattisgarh

⁴Postgraduate, Obstetrics and Gynaecology, Chhattisgarh Institute of Medical Sciences Bilaspur Chhattisgarh

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Corresponding Author: Dr. Sangeeta Raman Jogi

Conflict of interest: Nil

Abstract:

Background: Postpartum hemorrhage (PPH) is a leading cause of maternal mortality worldwide, often due to uterine atony. Traditional uterotonic drugs like oxytocin have limitations, particularly in low-resource settings. Carbetocin, a heat-stable, long-acting synthetic analogue of oxytocin, offers potential advantages.

Objective: This study aimed to compare the efficacy and safety of carbetocin versus oxytocin for PPH prevention following vaginal delivery.

Methods: A double-blind, randomized controlled trial was conducted with 200 antenatal women at the Chhattisgarh Institute of Medical Sciences. Participants were randomized into two groups: Group C (carbetocin) and Group O (oxytocin). Primary outcomes measured were blood loss, additional uterotonic requirement, and hemoglobin levels. Secondary outcomes included neonatal parameters.

Results: The carbetocin group demonstrated significantly lower mean blood loss (264.63 ± 38.97 mL) compared to the oxytocin group (341.40 ± 31.12 mL) ($p = 0.001$). The requirement for additional uterotonic agents was also lower in the carbetocin group (5%) versus the oxytocin group (13%) ($p = 0.04$). Post-operative hemoglobin levels were higher in the carbetocin group (9.19 ± 0.79 g/dL) than in the oxytocin group (8.86 ± 0.81 g/dL) ($p = 0.005$). Neonatal outcomes were comparable between groups.

Conclusion: Carbetocin is more effective than oxytocin in reducing blood loss and the need for additional uterotonic agents for PPH prevention. Its longer duration of action and stability in higher temperatures make it a valuable option, especially in low-resource settings. However, individualized patient care remains crucial for optimal outcomes.

Keywords: Postpartum Hemorrhage (PPH), Carbetocin, Oxytocin, Uterine Atony, Uterotonic Agents, Maternal Health, Randomized Controlled Trial (RCT).

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Introduction

Postpartum hemorrhage (PPH) is a significant and potentially life-threatening complication following both vaginal and cesarean deliveries. It remains the leading cause of maternal mortality globally, accounting for up to 25% of all maternal deaths. Even when fatality is avoided, PPH often necessitates blood transfusions and carries a high risk of morbidity [1]. The primary cause of PPH is uterine atony, responsible for 76-81% of cases, where the uterus fails to contract adequately after the delivery of the placenta. The management of the third stage of labor with uterotonic drugs is crucial for reducing blood loss, the need for

transfusions, and maternal deaths [2]. The World Health Organization (WHO) defines primary PPH as blood loss exceeding 500 ml after a normal vaginal delivery and over 1000 ml following a cesarean section within 24 hours of delivery. Risk factors for PPH include uterine atony, sepsis, placental abruption, placenta previa, multiple pregnancies, preeclampsia, obesity, anemia, prolonged labor, and advanced maternal age [3]. Conventional uterotonics like oxytocin have been widely used to prevent PPH, but they come with limitations such as a short half-life, a requirement for cold storage, and a range of side effects,

including fluid overload and hypotension. Additionally, oxytocin's efficacy is compromised in high temperatures, which is a significant concern in low-resource settings where refrigeration may not be consistently available.

Carbetocin, a long-acting synthetic analogue of oxytocin, has emerged as a promising alternative [4]. It provides a prolonged uterotonic effect with fewer adverse reactions. Unlike oxytocin, carbetocin remains stable at higher temperatures, making it more suitable for use in low-resource settings. Its ability to sustain uterine contractions for up to an hour after administration reduces the need for repeated doses and continuous infusion, thereby enhancing its practical application in preventing PPH [5].

Several studies suggest that prophylactic administration of carbetocin may be more effective than oxytocin in preventing PPH. This research aims to evaluate the efficacy of heat-stable carbetocin compared to oxytocin in the prevention of postpartum hemorrhage following vaginal delivery [6]. By exploring this potential alternative, we hope to address the limitations associated with oxytocin and improve maternal health outcomes, especially in regions with limited healthcare resources.

Methods

Study Setting: This study was conducted as a hospital-based, double-blind, randomized controlled trial in the Department of Obstetrics and Gynecology at the Chhattisgarh Institute of Medical Sciences (CIMS, Bilaspur), Pt. Deendayal Upadhyay Memorial Health Science & Ayush University of Raipur.

Type of Study: A comparative, double-blind, randomized controlled trial.

Study Duration: The study was carried out from January 2023 to February 2024.

Sampling and Sample Size: A total of 200 consecutive patients who met the inclusion criteria were enrolled in the study after obtaining written informed consent.

Minimum Sample Size Determination: The sample size was determined using the formula for equivalent design in randomized controlled trials (RCTs) for qualitative data: $N=2 [(Z1-\alpha/2 + Z1-\beta)/\delta]^2 \times P (1 - P)$

Where:

- N = minimum sample size per group
- P = Prevalence rate (assumed 50% = 0.50)
- α = Level of significance, taken as 0.05
- $1-\beta$ = Power of the test (80%)
- Δ = Clinical acceptance margin of error (10% = 0.10)

- $Z1-\alpha/2 = 1.96$
- $Z1-\beta = 0.845$

Hence, the minimum sample size required per group was calculated as 100, with a total sample size of 200.

Study Population: Antenatal women expected to deliver vaginally and admitted to the Department of Obstetrics and Gynecology were included.

Inclusion Criteria

- Women expected to deliver vaginally with no contraindications for vaginal delivery.
- Women who gave informed consent.
- Age between 18 and 35 years.
- Women with risk factors for PPH, including grand multiparity, uterine over distension, fetal macrosomia, polyhydramnios, chorioamnionitis, antepartum hemorrhage, induction or augmentation of labor with oxytocin, prolonged labor, eclampsia, pre-eclampsia, rapid excessive labor.

Exclusion Criteria

- Women with known allergies to carbetocin, oxytocin, or their excipients.
- Women younger than 18 years.
- Women with serious cardiovascular, hepatic, renal disorders, or epilepsy.
- Women who refused participation or were distressed to provide informed consent.

Method of Data Collection: Patients admitted to the ward during the study period were screened based on the inclusion and exclusion criteria. Data was collected through a pre-tested and structured proforma for each patient. Detailed histories, clinical examinations, and laboratory investigations were conducted.

Methodology

1. **Randomization:** Participants were randomly divided into two groups using opaque, sealed envelopes indicating group assignment.
 - Group C (study group): Received 100 micrograms of carbetocin intramuscularly during the third stage of labor.
 - Group O (control group): Received 10 IU/ml of oxytocin intramuscular during the third stage of labor.
2. **Drug Administration:** Respective drugs were administered immediately after the delivery of the baby. The management of the third stage of labor followed WHO guidelines.
3. **Blood Collection and Measurement:** After clamping and cutting the umbilical cord, a plastic drape was placed under the woman's buttocks. Blood loss was measured for one hour (or two hours if bleeding continued). The

drape with collected blood was weighed, and the blood volume was calculated by subtracting the drape's weight and converting the weight in grams to milliliters.

4. Trial Participation: Participation ended at discharge, transfer to a higher care unit, or death.
5. Laboratory Investigations: Included Complete Blood Count (Hb), ESR.
6. Monitoring and Vital Statistics: Urine output, and vital statistics (blood pressure, heart rate, respiratory rate, temperature, and SpO₂) were also measured.

Statistical Analysis: Data was entered and cleaned using MS-Excel and analyzed using IBM SPSS version 25. Quantitative variables were expressed as mean \pm standard deviation or median \pm interquartile range, and qualitative data as percentages and proportions. Associations between

variables were inferred using appropriate statistical tests, with a p-value of <0.05 considered statistically significant.

Ethical Considerations: The study protocol was approved by the institutional ethical committee. Informed written consent was obtained from participants or their legally acceptable representatives. Patient information was kept confidential and used solely for scientific purposes without disclosing personal identities. Participation was voluntary, and there was no additional risk to patients from the study.

Funding Details: No external funding was required. Investigations were part of routine care, and carbetocin was supplied by government provisions and an NGO.

Results

Table 1: Comparison of Blood Loss Measured Using Drapes

Variable	Carbetocin (Mean \pm SD)	Oxytocin (Mean \pm SD)	t-value, p-value
Blood Loss (mL)	264.63 \pm 38.97	341.40 \pm 31.12	-15.39, 0.001

Table 2: Comparison of Blood Loss Measured Using Pads

Variable	Carbetocin (Mean \pm SD)	Oxytocin (Mean \pm SD)	t-value, p-value
Blood Loss (mL)	61.00 \pm 17.69	78.64 \pm 7.13	-9.25, 0.001

Table 3: Comparison of Total Blood Loss

Variable	Carbetocin (Mean \pm SD)	Oxytocin (Mean \pm SD)	t-value, p-value
Total Blood Loss (mL)	325.63 \pm 40.26	420.04 \pm 33.25	-25.09, 0.001

Table 4: Comparison of Additional Uterotonic Requirement

Additional Uterotonic Requirement	Carbetocin (n = 100)	Oxytocin (n = 100)	χ^2 , p-value
Yes	5 (5%)	13 (13%)	3.90, 0.04
No	95 (95%)	87 (87%)	
Total	100 (100%)	100 (100%)	

Table 5: Comparison of Hemoglobin Levels between Two Groups

Variable	Carbetocin (Mean \pm SD)	Oxytocin (Mean \pm SD)	t-value, p-value
Pre-operative Hb (g/dL)	9.52 \pm 0.93	9.33 \pm 0.82	1.58, 0.12
Post-operative Hb (g/dL)	9.19 \pm 0.79	8.86 \pm 0.81	2.87, 0.005

Table 6: Comparison of Fetal Parameters between Two Groups

Fetal Parameters	Carbetocin (n = 100)	Oxytocin (n = 100)	χ^2 , p-value
Low Birth Weight	5 (5%)	11 (11%)	2.45, 0.12
Need for Resuscitation	11 (11%)	11 (11%)	0, 1.00
Admission to NICU	9 (9%)	15 (15%)	1.70, 0.19
Total	100 (100%)	100 (100%)	

Discussion

Comparison of Carbetocin and Oxytocin for PPH Prevention

Carbetocin and oxytocin are both effective medications for preventing postpartum hemorrhage (PPH) in women at risk following vaginal delivery.

1. Mechanism of Action:

- **Oxytocin:** A natural hormone that stimulates uterine contractions to help the uterus contract and prevent excessive bleeding after childbirth.
- **Carbetocin:** A synthetic analogue of oxytocin with a longer duration of action, also working by stimulating uterine contractions.

2. Administration:

- **Oxytocin:** Typically administered as an intravenous infusion or intramuscular injection.
 - **Carbetocin:** Usually given as a single intravenous or intramuscular dose.
3. **Duration of Action:**
- **Oxytocin:** Has a relatively short half-life, requiring frequent dosing or continuous infusion to maintain its effect.
 - **Carbetocin:** Provides sustained uterine contraction for several hours after a single dose due to its longer duration of action.
4. **Efficacy:**
- Both medications are effective in preventing PPH when administered after vaginal delivery in women at risk.
 - Some studies suggest that carbetocin may have a slight advantage due to its longer duration of action, potentially reducing the need for additional uterotonic agents.
5. **Side Effects:**
- **Oxytocin:** Common side effects include nausea, vomiting, headache, and transient hypotension. In rare cases, it can cause uterine hyper stimulation, leading to fetal distress.
 - **Carbetocin:** Side effects are generally similar but may occur less frequently due to its longer duration of action. It may still cause transient hypotension and other adverse effects.
6. **Cost:**
- **Oxytocin:** Generally, less expensive.
 - **Carbetocin:** Can be more costly due to its synthetic nature and longer duration of action.

Generalizability of Results

Our study aimed to compare the efficacy and safety of carbetocin versus oxytocin for the prevention of PPH following vaginal birth. The findings are discussed below in comparison to existing literature.

Socio-Demographic Factors

The socio-demographic characteristics were comparable between the carbetocin and oxytocin groups. The majority of patients in both groups were in the age range of 21 to 25 years, followed by 26 to 30 years. Most patients were Hindus, and the educational distribution was similar across both groups, with no statistically significant differences. Our findings align with a similar trial by Attilakos G et al., where the median age was 32 years for both groups.

Obstetric History

In both groups, the majority of women were multigravida. The distribution of high-risk pregnancies and the history of induction were

comparable, with no significant differences observed. This is consistent with findings from Attilakos G et al., who reported comparable obstetric histories and high-risk pregnancies across both groups [7].

BMI and Abdominal Examination

The mean body mass index (BMI), fundal height, symphysiofundal height, and abdominal girth were comparable between the two groups, with no statistically significant differences. Attilakos G et al. reported similar BMI values for both carbetocin and oxytocin groups, supporting our findings [7].

Blood Loss

- **Mean Blood Loss:** Our study showed significantly lower mean blood loss in the carbetocin group (264.63 mL) compared to the oxytocin group (341.40 mL). This difference was statistically significant ($p = 0.001$). Similar results were observed for blood loss measured using pads and total blood loss, with carbetocin showing significantly lower values.
- **Comparison with Existing Studies:** Studies by Maged AM et al., El Beheri M et al., and Ortiz SR et al. also reported lower blood loss and reduced incidence of PPH with carbetocin compared to oxytocin. Our findings are in line with these studies, indicating that carbetocin is more effective in reducing blood loss and preventing PPH.

Hemoglobin Levels

There was a statistically significant difference in post-delivery hemoglobin levels between the two groups ($p = 0.005$), with the carbetocin group showing higher levels. This suggests less blood loss and better preservation of hemoglobin in the carbetocin group. Studies by Maged AM et al. and El Beheri M et al. reported similar findings, supporting our results [8].

Neonatal Outcomes: Low birth weight, need for resuscitation, and NICU admissions were comparable between the two groups, with no statistically significant differences. Attilakos G et al. reported similar neonatal outcomes in their study.

Summary

Our study demonstrates that carbetocin is more effective than oxytocin in reducing blood loss and the need for additional uterotonic agents in preventing PPH following vaginal delivery [9].

The longer duration of action and sustained uterine contractions provided by carbetocin likely contribute to these better outcomes. Although carbetocin is more expensive, its efficacy and potential to reduce the need for additional interventions make it a valuable option for PPH

prevention. These findings are consistent with existing literature and support the use of carbetocin as a superior alternative to oxytocin for PPH prevention in clinical practice.

Conclusion

In our comparative study of carbetocin versus oxytocin for the prevention of postpartum hemorrhage (PPH) following vaginal birth, carbetocin demonstrated a notable efficacy advantage in reducing blood loss and the need for additional uterotonic agents. Its longer duration of action and ability to provide sustained uterine contractions make it an effective option for PPH prevention. However, a comprehensive understanding of the available evidence and consideration of various factors is essential when concluding that carbetocin is categorically superior to oxytocin.

While carbetocin offers clear benefits such as a longer duration of action and potentially reduced side effects, medication selection should be individualized based on efficacy, safety, cost, availability, and patient-specific considerations [10]. In clinical scenarios where sustained uterine contraction is particularly desirable or where patients may have a higher risk of adverse reactions to oxytocin, carbetocin may be the preferred choice.

Healthcare providers should collaborate with patients to weigh the benefits and risks of each medication, making informed decisions tailored to the specific clinical situation. Despite the promising results of carbetocin in our study, it is not universally "better" than oxytocin in all cases. Both medications have valuable roles in obstetric care, and the optimal choice will depend on a comprehensive assessment of individual patient needs and clinical factors.

Our study supports the use of carbetocin as a valuable option for PPH prevention, but it also underscores the importance of personalized

medical decision-making to ensure the best outcomes for patients.

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