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Carbetocin Vs Oxytocin for Prevention of PPH Following Vaginal Delivery: A Randomized Controlled Study

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Abstract

Background: Postpartum hemorrhage (PPH) is the leading cause of maternal mortality worldwide, accounting for approximately 35% of maternal deaths. Oxytocin has long been the gold-standard uterotonic for active management of the third stage of labour; however, carbetocin — a long-acting synthetic oxytocin analogue — offers the advantage of single-dose administration and heat-stable formulation.

Objective: To compare the effectiveness and safety of carbetocin and oxytocin for the prevention of PPH following vaginal delivery in high-risk women.

Methods: This randomized controlled trial was conducted at Karnataka Institute of Medical Sciences, Hubballi, from July 2022 to January 2024. A total of 206 women at 37–40 weeks of gestation with at least one risk factor for atonic PPH were randomly allocated to receive either carbetocin 100 µg IM (Group 1, n=103) or oxytocin 10 IU IM (Group 2, n=103) following delivery. Primary outcomes included blood loss measured by V-drape, hemoglobin difference pre- and post-delivery, and need for additional uterotonics. Secondary outcomes included blood transfusion requirement, blood pressure changes, and adverse effects. Data were analysed using the

independent t-test, paired t-test, and Chi-square test; p <0.05 was considered significant.

Results: The mean blood loss was 249.18 ± 96.28 mL in the carbetocin group and 253.41 ± 102.57 mL in the oxytocin group (p = 0.761). The need for additional uterotonics (8.7% each), blood transfusion rates (3.8% vs. 4.8%), hemoglobin decline, and blood pressure changes at 30 and 60 minutes post-administration were comparable between the groups (all p >0.05). Adverse effects including nausea, vomiting, headache, and giddiness were minimal and similar in both groups (p = 0.988).

Conclusion: Carbetocin is as effective and safe as oxytocin for the prevention of atonic PPH following vaginal delivery. Its single-dose regimen and room-temperature stability make it a practical and viable alternative for clinical use.

Keywords: Postpartum Hemorrhage, Carbetocin, Oxytocin, Uterotonic, Vaginal Delivery, Atonic PPH, Active Management of Third Stage of Labour, Randomized Controlled Trial

Introduction

Postpartum hemorrhage (PPH) remains one of the most feared obstetric emergencies, owing to its sudden onset, unpredictable course, and potential for catastrophic maternal outcomes.[1] Globally, PPH accounts for approximately 35% of all maternal deaths, making it the leading cause of maternal mortality. The incidence following vaginal delivery ranges from 2%–4%, rising to 6% after caesarean section.[2] The World Health Organization (2012) defines PPH as blood loss exceeding 500 mL after vaginal birth and more than 1000 mL after caesarean delivery, with severe PPH defined as loss exceeding 1000 mL in vaginal births.[3] The American College of Obstetricians and Gynaecologists (ACOG) further defines PPH as cumulative blood loss ≥1000 mL accompanied by signs or symptoms of hypovolemia within the first 24 hours of delivery.[4] Uterine atony is the most common underlying cause, responsible for up to 81% of PPH cases, making adequate uterine contraction and retraction central to prevention.[5]

Two-thirds of PPH cases occur in women with no identifiable risk factors, and without prompt intervention, life-threatening hemorrhage can develop within hours.[6] Active management of the third stage of labour (AMTSL) is the cornerstone of PPH prevention, with oxytocin (10 IU IM/IV) being the uterotonic of choice. However, oxytocin requires cold chain storage, limiting its utility in resource-constrained settings. Carbetocin, a long-acting synthetic oxytocin analogue, offers a prolonged duration of action and, in its heat-stable formulation, does not require refrigeration. Following the 2018 WHO-sponsored CHAMPION trial, which demonstrated comparable efficacy between heat-stable carbetocin and oxytocin in preventing blood loss ≥500 mL after vaginal delivery, the WHO updated its uterotonic recommendations to include room-temperature stable carbetocin (100 mcg IM/IV) as a first-line alternative when cost is comparable.[7,8]

Several randomized controlled trials have evaluated carbetocin against oxytocin in vaginal delivery settings with varying conclusions. Jin et al, in a meta-analysis of five RCTs, found no statistically significant difference between the two drugs in blood loss ≥500 mL,[9] while Maged et al reported significantly lower blood loss and reduced need for additional uterotonics in the carbetocin group.[10] Barua et al demonstrated superiority of carbetocin over oxytocin with respect to blood loss, PPH incidence, and hemoglobin preservation,[11] whereas Sunil et al found only a marginal, clinically insignificant

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difference in post-delivery hemoglobin between the two agents.[12] Given this heterogeneity in evidence and the limited data from Indian populations, the present study was designed to compare the effectiveness and safety of carbetocin and oxytocin in preventing PPH following vaginal delivery at a tertiary care centre in Karnataka, India.

Materials And Methods

This randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology at Karnataka Institute of Medical Sciences (KIMS), Hubballi, Karnataka, over a period of 18 months from July 2022 to January 2024. A total of 206 women between 37–40 weeks of gestation with at least one risk factor for atonic PPH attending the labour room were enrolled. Sample size was calculated based on the incidence of PPH in vaginal delivery (P = 0.80, q = 0.20) using the standard formula for comparison of two means with appropriate α and β values, yielding a minimum sample of 103 participants per group.

Participants were randomly allocated into two equal groups of 103 each. Group 1 received a single dose of carbetocin 100 µg intramuscularly, and Group 2 received a single dose of oxytocin 10 IU intramuscularly, both administered immediately following delivery of the baby in singleton pregnancies or after delivery of the second twin in multiple pregnancies. Inclusion criteria comprised multigravida status, primigravida aged more than 36 years, history of prolonged labour exceeding 12 hours, multiple pregnancy, previous PPH, BMI >35, or estimated fetal weight exceeding 4 kg. Women with pre-eclampsia, placenta previa, cardiac, renal, or liver disease, bleeding disorders, epilepsy, or known hypersensitivity to either drug were excluded.

Blood loss was quantified using a calibrated V-drape collector. Blood loss between 500–1000 mL was classified as minor PPH and >1000 mL as major PPH. Hemoglobin levels were assessed before delivery and 24 hours after delivery. Systolic and diastolic blood pressure were measured at 30 and 60 minutes post-delivery. The need for additional uterotonic agents, blood transfusion, and occurrence of side effects including nausea, vomiting, headache, and giddiness were recorded and compared between groups. Data were analyzed using SPSS software. Continuous variables were compared using the independent samples t-test for between-group comparisons and the paired t-test for within-group pre- and post-delivery hemoglobin differences. Categorical variables were compared using the Chi-square (χ^2) test. A p-value of <0.05 was considered statistically significant.

Results

The following tables summarize the key findings from the study comparing carbetocin and oxytocin for prevention of PPH in 206 women (103 per group) who underwent vaginal delivery between 37–40 weeks of gestation.

Table 1: Baseline and Demographic Characteristics of Study Participants

Characteristic	Group 1 (Carbetocin) n=103	Group 2 (Oxytocin) n=103	p value
Mean Age ± SD (years)	27.19 ± 3.52	27.76 ± 3.204	0.534
Socioeconomic Status: Lower Middle (%)	42.7%	45.6%	0.083
Parity G2–G3 (%)	63.1%	56.3%	0.076
Mode of Delivery: Spontaneous (%)	68.9%	66.1%	0.655
Most Common Risk Factor: Multigravida (%)	94.2%	91.3%	0.99

The two groups were comparable across all baseline parameters including age, socioeconomic status, parity, mode of delivery, and risk factors for PPH. None of the observed differences were statistically significant (Table

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1), confirming adequate randomization and baseline homogeneity between the groups.

Table 2: Blood Loss, Hemoglobin, and Blood Transfusion Outcomes

Outcome Parameter	Group 1 (Carbetocin)	Group 2 (Oxytocin)	p value
Mean Blood Loss ± SD (mL)	249.18 ± 96.28	253.41 ± 102.57	0.761
Blood Loss 200–300 mL (%)	45.7%	47.6%	—
Blood Loss >500 mL (%)	3.9%	4.8%	0.99
Pre-delivery Hb (g/dL) Mean ± SD	10.36 ± 1.081	10.28 ± 1.15	—
Post-delivery Hb (g/dL) Mean ± SD	9.87 ± 1.30	9.78 ± 1.21	—
Hb Difference <0.5 g/dL (%)	73.8%	62.1%	0.155
Required Blood Transfusion (%)	3.8% (1 PRBC)	4.8% (1–2 PRBC)	0.778

The mean blood loss was comparable between the carbetocin group (249.18 ± 96.28 mL) and the oxytocin group (253.41 ± 102.57 mL), with no statistically significant difference (p = 0.761) (Table 2). The majority of participants in both groups experienced blood loss in the 200–300 mL range. A statistically significant decline in hemoglobin was observed within each group from pre- to post-delivery (p <0.001 by paired t-test in both groups); however, the inter-group difference in hemoglobin drop was not statistically significant (p = 0.155). The vast majority of participants required no blood transfusion (96.2% in Group 1 and 95.2% in Group 2) (Table 2).

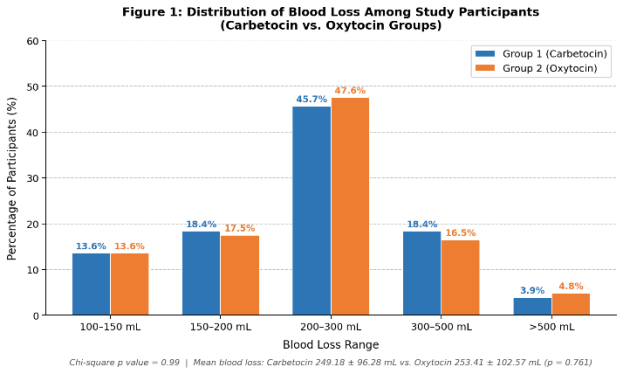

Figure 1: Distribution of Blood Loss Among Study Participants (Carbetocin vs. Oxytocin Groups). Chi-square p value = 0.99; mean blood loss: Carbetocin 249.18 ± 96.28 mL vs. Oxytocin 253.41 ± 102.57 mL (p = 0.761).

Table 3: Need for Additional Uterotonics and Blood Pressure Parameters

Parameter	Group 1 (Carbetocin)	Group 2 (Oxytocin)	p value
No additional uterotonics required (%)	91.3%	91.3%	—
Tab. Misoprostol 800 mcg alone (%)	3.8%	3.8%	—
Misoprostol + Oxytocin infusion + Carboprost (%)	4.9%	4.9%	—
SBP at 30 min (mmHg) Mean ± SD	115.43 ± 8.01	115.45 ± 7.15	0.985
DBP at 30 min (mmHg) Mean ± SD	73.86 ± 5.5	74.31 ± 5.5	0.563
SBP at 60 min (mmHg) Mean ± SD	113.57 ± 5.7	113.86 ± 6.201	0.728
DBP at 60 min (mmHg) Mean ± SD	72.21 ± 5.5	72.89 ± 6.05	0.401

The requirement for additional uterotonic agents was identical in both groups — 91.3% required none, 3.8% required misoprostol alone, and 4.9% required the full combination regimen of misoprostol, oxytocin infusion, and carboprost injection (Table 3). In the carbetocin group, additional uterotonics were only required when blood loss exceeded 300 mL, representing a statistically significant association between blood loss and additional uterotonic use within that group (p <0.001). No such significant association was observed in the oxytocin group (p = 0.992). Blood pressure measurements at 30 and 60 minutes post-administration showed no significant differences between the groups (Table 3).

Table 4: Side Effects and Delivery Outcomes

Parameter	Group 1 (Carbetocin)	Group 2 (Oxytocin)	p value
No side effects (%)	94.3%	92.3%	0.988
Nausea/Vomiting (%)	3.9%	3.9%	—
Headache (%)	0.9%	1.9%	—
Giddiness (%)	0.9%	1.9%	—
Live birth (%)	99.1%	100%	—
Birth weight <2.5 kg (%)	38.8%	17.5%	—
Birth weight 2.5–3.5 kg (%)	57.3%	78.6%	—

The overall incidence of side effects was low and comparable between the two groups, with no statistically significant difference (p = 0.988) (Table 4). Nausea and vomiting were reported equally (3.9% in each group). Headache and giddiness were marginally more frequent in the oxytocin group (1.9% each) compared to the carbetocin group (0.9% each), though these differences were not significant. One intrauterine death (0.9%) occurred in the carbetocin group, and all remaining deliveries resulted in live births (Table 4).

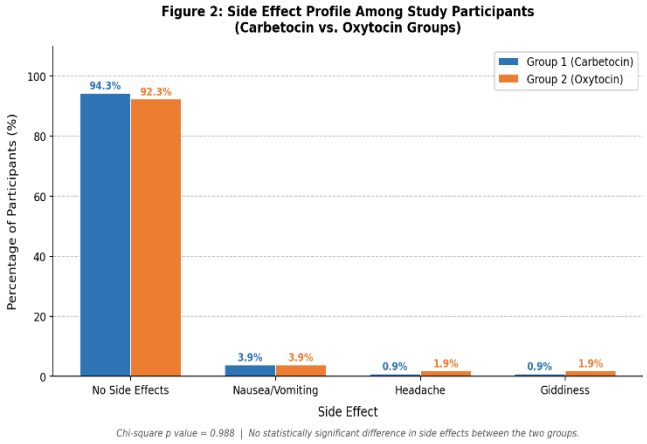

Figure 2: Side Effect Profile Among Study Participants (Carbetocin vs. Oxytocin Groups). Chi-square p value = 0.988; no statistically significant difference in side effects between the two groups.

Discussion

The present randomized controlled trial compared the efficacy and safety of carbetocin (100 µg IM) and oxytocin (10 IU IM) in preventing atonic PPH following vaginal delivery in 206 high-risk women. The primary finding was that both drugs resulted in comparable blood loss (mean 249.18 ± 96.28 mL vs. 253.41 ± 102.57 mL; p = 0.761), similar PPH rates (3.9% vs. 4.8%), and equivalent hemoglobin decline post-delivery, with no statistically significant inter-group differences in any of the primary outcome parameters. These results are consistent with the conclusions of Jin et al, whose meta-analysis of five RCTs encompassing over 30,000 women demonstrated no significant difference between carbetocin and oxytocin in blood loss ≥500 mL following vaginal delivery (RR 0.52; 95% CI 0.24–1.15; p = 0.11), and similarly found no significant differences in the need for additional uterotonics, blood transfusion, or side effect profiles.[13] The CHAMPION trial of 2018 also reported non-inferior performance of heat-stable carbetocin compared to oxytocin in preventing blood loss ≥500 mL, forming the basis for the subsequent WHO recommendation of room-temperature stable carbetocin as a first-line uterotonic alternative.[7,8]

In contrast to our findings, several individual trials have reported superiority of carbetocin over oxytocin in certain outcome parameters. Maged et al found significantly lower blood loss (337.73 ± 118.77 vs. 378 ± 143.2 mL), lower PPH incidence (4% vs. 16%), and reduced need for additional uterotonics (23% vs. 37%) in favour of carbetocin after vaginal delivery, along with a significantly greater systolic and diastolic blood pressure reduction in the carbetocin group — hemodynamic differences not observed in our study.[14] Similarly, Barua et al reported significantly lower blood loss (335.70 ±

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117.71 vs. 375.12 ± 145.30 mL), lower PPH rates (3% vs. 12%), reduced uterotonic requirement (18% vs. 30%), and better hemoglobin preservation in the carbetocin group.[15] Taheripanah et al, studying caesarean deliveries, reported significantly lower hemoglobin drop (1.01 vs. 2.05 g/dL) and reduced bleeding volume with carbetocin.[16] The divergence of our findings from these studies may be attributed to differences in the study population — particularly the higher baseline prevalence of multigravida women in our cohort (>90% in both groups), more uniform risk factor distribution, and the possibly superior uterine contractility response to standard oxytocin in our setting. Sunil et al's findings partially align with ours, demonstrating no significant difference in pre-delivery hemoglobin or postpartum blood loss between the two drugs, though they observed a marginally lower post-delivery hemoglobin with carbetocin.[17]

Regarding the need for additional uterotonic agents, an important observation in our study was that while the overall rate of additional uterotonic requirement was identical between the two groups (8.7% each), the pattern differed: in the carbetocin group, rescue uterotonics were exclusively required when blood loss exceeded 300 mL — a finding that was statistically significant ($p < 0.001$) — whereas in the oxytocin group, additional agents were needed even at lower blood loss ranges, though without statistical significance ($p = 0.992$). This suggests that carbetocin may offer a more predictable, threshold-based uterotonic response, potentially limiting polypharmacy to cases of genuine clinical escalation. The safety profile of both drugs was equivalent, with no significant differences in blood pressure at 30 or 60 minutes post-administration, and comparably low incidences of nausea, vomiting, headache, and giddiness — findings consistent with Maged et al,[14] Barua et al,[15] and the meta-analysis by Jin et al.[13] An additional practical advantage of carbetocin is its room-temperature stability, eliminating the requirement for cold chain maintenance and potentially improving accessibility and compliance in resource-limited settings, as affirmed by WHO guidelines.[8]

Conclusion

This randomized controlled trial demonstrated that carbetocin 100 µg IM and oxytocin 10 IU IM are comparable in efficacy and safety for the prevention of atonic postpartum hemorrhage following vaginal delivery. There was no statistically significant difference between the two groups in the amount of blood loss, incidence of major PPH, need for additional uterotonic agents, blood transfusion requirement, hemoglobin decline, blood pressure changes, or adverse effects. Carbetocin, with its single-dose administration, prolonged duration of action, and room-temperature stability — obviating the need for cold chain logistics — represents a clinically viable and practically advantageous alternative to oxytocin. It should be considered for inclusion in standard clinical protocols for the management of atonic PPH after vaginal delivery, particularly in settings where cold chain maintenance is a challenge.

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