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Original Research Article

Carbetocin versus oxytocin in active management of third stage of labor: a randomized controlled trial

Shanthi P. T. Reddy*, Shyamkumar Sirsam, Namita N. Raut

Department of Obstetrics and Gynecology, Government Medical College, Akola, Maharashtra, India

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***Correspondence:**
Dr. Shanthi P. T. Reddy,
E-mail: sshanthipriyatreddy@gmail.com

ABSTRACT

Background: Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality. Active management of the third stage of labor (AMTSL) using uterotonic agents significantly reduces the incidence of PPH. Oxytocin is the most commonly used uterotonic; however, its short duration of action may necessitate repeated dosing. Carbetocin, a long-acting oxytocin analogue, offers sustained uterine contraction with a single dose.
Methods: A single-blind randomized controlled trial was conducted at a tertiary care center over 18 months. A total of 200 pregnant women with singleton or multiple pregnancies ≥32 weeks of gestation undergoing vaginal delivery or cesarean section were enrolled. Participants were randomly allocated into two groups: the carbetocin group (100 µg intravenous single dose) and the oxytocin group (10 IU intramuscular or 20 IU intravenous infusion). The primary outcomes assessed were blood loss within 24 hours postpartum, uterine tone, and requirement of additional uterotonics. Secondary outcomes included changes in hemoglobin levels, need for blood transfusion, hemodynamic changes, and drug-related adverse effects.
Results: Mean blood loss in the 1st 24 hours postpartum was significantly lower in the carbetocin group compared to the oxytocin group (398±138.52 ml versus 467±189.65 ml; p=0.004). Fewer women in the carbetocin group required additional uterotonic agents. Post-delivery hemoglobin levels were significantly higher in the carbetocin group. No significant adverse effects were observed in either group.
Conclusions: Carbetocin is more effective than oxytocin in reducing postpartum blood loss during active management of the third stage of labor, with the added advantage of single-dose administration and a comparable safety profile. Carbetocin can be considered a suitable alternative to oxytocin, particularly in tertiary care and high-risk obstetric settings.

Keywords: Carbetocin, Oxytocin, Postpartum hemorrhage, Third stage of labor, Uterotonics

INTRODUCTION

Postpartum hemorrhage (PPH) remains one of the leading causes of maternal morbidity and mortality worldwide, accounting for approximately 25% of maternal deaths globally.[1] Despite improvements in obstetric care, PPH continues to pose a major public health challenge, particularly in low- and middle-income countries. The third stage of labor, defined as the period from delivery of the fetus until expulsion of the placenta, is a critical phase during which the risk of excessive maternal blood loss is highest.[2] Uterine atony is the most common cause of PPH, emphasizing the need for effective uterine contraction during this stage.[3]

Active management of the third stage of labor (AMTSL) has been widely recommended as an effective strategy to reduce the incidence of PPH.[4] AMTSL consists of prophylactic administration of a uterotonic agent immediately after delivery of the baby, controlled cord traction, and delayed cord clamping.[5] Among these components, the use of uterotonic drugs plays a pivotal

role in promoting uterine contraction, facilitating placental separation, and minimizing blood loss.[6]

Oxytocin is the most commonly used uterotonic agent for AMTSL owing to its proven efficacy, rapid onset of action, and favorable safety profile.[7] It acts by stimulating oxytocin receptors in the uterine myometrium, resulting in rhythmic uterine contractions that compress blood vessels at the placental site and reduce hemorrhage.[8] However, oxytocin has a short plasma half-life, requiring repeated dosing or continuous infusion to maintain adequate uterine tone.[9] In addition, oxytocin is heat sensitive and requires cold-chain storage, which can limit its effectiveness in resource-constrained settings.[10]

Carbetocin is a long-acting synthetic analogue of oxytocin designed to provide sustained uterine contraction following a single dose.[11] Its prolonged duration of action reduces the need for repeated administration or additional uterotonic agents.[12] Several randomized controlled trials and meta-analyses have demonstrated that carbetocin is comparable or superior to oxytocin in reducing postpartum blood loss and the need for rescue uterotonics, particularly following caesarean delivery.[13,14] Furthermore, carbetocin has a safety profile similar to oxytocin and is stable at room temperature, making it an attractive alternative in both high-resource and low-resource settings.[15]

Despite growing evidence supporting the use of carbetocin, its routine use in vaginal and caesarean deliveries remains limited in many developing countries due to cost concerns and limited region-specific data. Comparative evaluation of carbetocin and oxytocin in different clinical settings is therefore essential to guide evidence-based practice. The present study was undertaken to compare the effectiveness of carbetocin and oxytocin in the active management of the third stage of labor at a tertiary care center, with emphasis on postpartum blood loss, need for additional uterotonics, hemoglobin changes, and maternal safety outcomes.

METHODS

This single-blind randomized controlled trial was conducted at a tertiary care center - Government Medical college, Akola, over a period of 18 months, from October 2022 to April 2024, after obtaining approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrollment, and the study was conducted in accordance with the principles of the Declaration of Helsinki.[16]

Study population

Pregnant women with singleton or multiple pregnancies of gestational age ≥32 weeks who underwent vaginal delivery or cesarean section were included in the study. Women who delivered outside the institution, had ambulance deliveries, or did not provide consent were excluded.

Sample size and randomization

A total of 200 eligible participants were enrolled and randomly allocated into two equal groups of 100 each using computer-generated randomization. Allocation concealment was maintained, and participants were blinded to the uterotonic agent administered.

Group A (carbetocin group) received a single dose of carbetocin 100 µg intravenously.

Group B (oxytocin group) received oxytocin either as 10 IU intramuscular injection or 20 IU intravenous infusion diluted in 500 ml Ringer lactate at a rate of 150 ml/hour.

The uterotonic drug was administered immediately after delivery of the anterior shoulder of the baby in both vaginal and caesarean deliveries.

Study procedure

All participants underwent detailed clinical evaluation, including obstetric history, general and obstetric examination, ultrasonography, and baseline laboratory investigations such as complete blood count, liver function tests, and coagulation profile. Following delivery, patients were monitored for 24 hours postpartum.

Blood loss during the 1st 24 hours postpartum was estimated using an Archit calibrated blood collection cup. Uterine tone was assessed clinically by abdominal palpation and categorized as well-contracted or soft. Hemoglobin levels were measured pre-delivery and 24 hours after delivery.

Maternal vital parameters, including systolic and diastolic blood pressure, were recorded immediately after delivery and at 30 and 60 minutes postpartum. The need for additional uterotonic agents was determined if blood loss exceeded 500 ml with or without associated uterine atony or hypotension. Adverse effects such as nausea, vomiting, flushing, shivering, tachycardia, headache, dizziness, dyspnea, pruritus, and palpitations were actively monitored and documented.

Outcome measures

The primary outcomes assessed were the volume of blood loss within the first 24 hours after delivery, adequacy of uterine tone, and the need for additional uterotonic medications. The secondary outcomes evaluated included changes in hemoglobin levels, requirement for blood transfusion, alterations in hemodynamic parameters, and the occurrence of drug-related adverse effects.

Statistical analysis

Data were entered into Microsoft Excel and analyzed using statistical software. Continuous variables were expressed as mean±standard deviation, and categorical variables

were presented as frequencies and percentages. Student's t-test was used to compare continuous variables, and chi-square test was applied for categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

A total of 200 women were included in the study, with 100 participants each in the carbetocin and oxytocin groups. The baseline demographic and obstetric characteristics were comparable between the two groups.

Baseline demographic and obstetric profile

The mean age of women in the carbetocin group was 24.2±3.98 years and in the oxytocin group was 24.89±4.25 years, with no statistically significant difference (p=0.23). Parity distribution was comparable between groups. Most women delivered at term in both groups.

Caesarean section was the predominant mode of delivery, reflecting the tertiary care setting.

Table 1: Baseline demographic and obstetric characteristics.

Parameter	Carbetocin (n=100)	Oxytocin (n=100)	P value
Age (years, mean±SD)	24.2±3.98	24.89±4.25	0.23
Primigravida, N (%)	34 (34)	39 (39)	NS
Term deliveries, N (%)	73 (73)	79 (79)	NS
Caesarean section, N (%)	88 (88)	73 (73)	NS

Maternal and fetal conditions

Preeclampsia was significantly more common in the carbetocin group, while a history of previous caesarean section and fetal distress were more frequent in the oxytocin group.

Other maternal and fetal conditions showed no statistically significant difference.

Table 2: Distribution of maternal and fetal conditions.

Condition	Carbetocin N (%)	Oxytocin N (%)	P value
Preeclampsia	55 (55)	14 (14)	<0.001
Previous cesarean section	14 (14)	41 (41)	<0.001
Fetal distress	3 (3)	12 (12)	0.015
Anemia	4 (4)	0 (0)	0.01

Primary outcome: postpartum blood loss

Mean blood loss within the 1st 24 hours postpartum was significantly lower in the carbetocin group compared to the oxytocin group (398±138.52 ml versus 467±189.65 ml; p=0.004). This indicates better efficacy of carbetocin in reducing postpartum blood loss.

Table 3: Postpartum blood loss (24 hours).

Parameter	Carbetocin	Oxytocin	P value
Blood loss (ml, mean±SD)	398±138.52	467±189.65	0.004

Secondary outcomes

Hemoglobin levels

Pre-delivery hemoglobin levels were comparable between the two groups (11.14±1.95 g/dl in the carbetocin group versus 11.48±1.45 g/dl in the oxytocin group, p=0.163).

However, post-delivery hemoglobin levels were significantly higher in the carbetocin group (9.85±1.87 g/dl) compared to the oxytocin group (8.45±1.34 g/dl, p=0.0001), reflecting a smaller post-partum hemoglobin drop with carbetocin.

Blood transfusion requirement

Blood transfusion was required in 6% of women in the carbetocin group compared to 15% in the oxytocin group. This difference was statistically significant (p=0.037), suggesting that carbetocin reduced the severity of postpartum blood loss to a level that minimized transfusion requirements.

Additional uterotonic requirement

None of the women in the carbetocin group required additional uterotonic agents. In contrast, 9% of women in the oxytocin group required additional uterotonics (Methergin or Carboprost).

This difference was statistically significant (Chi-square=9.42, p=0.009), demonstrating better uterine tone maintenance with carbetocin.

Hemodynamic parameters

Post-delivery systolic and diastolic blood pressures were significantly higher in the carbetocin group (SBP: 128.4±15.22 mmHg, DBP: 83.6±9.16 mmHg) compared to the oxytocin group (SBP: 117.3±7.77 mmHg, DBP: 77.2±5.52 mmHg), with p values of 0.0001 for both. This likely reflects reduced blood loss and better circulatory stability rather than an adverse drug effect.

Table 4: Secondary outcome measures.

Outcome	Carbet-ocin	Oxytoc-in	Signifi-cance
Hb before delivery (g/dl, mean±SD)	11.14± 1.95	11.48± 1.45	0.163
Hb after delivery (g/dl, mean±SD)	9.85±1. 87	8.45±1. 34	0.0001
Blood transfusion required	6 (6%)	15 (15%)	0.037
Additional uterotonics	0 (0%)	9 (9%)	0.009

Adverse effects

No maternal adverse effects were observed in either the carbetocin group or the oxytocin group. The incidence of nausea, vomiting, flushing, tachycardia, shivering, headache, palpitations, dyspnea, and pruritus was 0% in both groups, with no statistically significant difference between them (p=1.000 for all parameters). This indicates that both carbetocin and oxytocin were equally safe and well tolerated, with no drug-related adverse maternal effects observed in the study population.

Table 5: Hemodynamic parameters.

Outcome	Carbet-ocin	Oxytoc-in	Signifi-cance
SBP after delivery (mean±SD)	128.4± 15.22	117.3± 7.77	0.0001
DBP after delivery (mean±SD)	83.6± 9.16	77.2± 5.52	0.0001

Overall findings

Carbetocin significantly reduced postpartum blood loss and the need for additional uterotonic agents compared to oxytocin, with comparable hemoglobin levels, transfusion rates, and safety profiles.

Table 6: Comparison of adverse effects between carbetocin and oxytocin groups.

Adverse effect	Carbetocin (n=100), N (%)	Oxytocin (n=100), N (%)	P value	Inference
Nausea/vomiting	0 (0)	0 (0)	1.000	Not significant
Flushing	0 (0)	0 (0)	1.000	Not significant
Tachycardia	0 (0)	0 (0)	1.000	Not significant
Shivering	0 (0)	0 (0)	1.000	Not significant
Headache	0 (0)	0 (0)	1.000	Not significant
Palpitation	0 (0)	0 (0)	1.000	Not significant
Dyspnea	0 (0)	0 (0)	1.000	Not significant
Pruritus	0 (0)	0 (0)	1.000	Not significant

DISCUSSION

Postpartum hemorrhage (PPH) remains a major cause of maternal morbidity and mortality, and effective uterotonic therapy during the third stage of labor is central to its prevention. The present randomized controlled study compared carbetocin and oxytocin for active management of the third stage of labor and demonstrated that carbetocin significantly reduced postpartum blood loss and the need for additional uterotonic agents, with comparable hemoglobin changes, transfusion requirements, and safety profiles.

In the present study, mean blood loss within the 1st 24 hours postpartum was significantly lower in women receiving carbetocin compared to those receiving oxytocin. This finding can be attributed to the pharmacological properties of carbetocin, a long-acting oxytocin analogue with a prolonged half-life that produces sustained uterine contractions after a single dose. Similar results have been reported by Attilakos et al, who observed reduced blood loss and decreased requirement for additional uterotonics in women receiving carbetocin compared to oxytocin following caesarean section.[17] El Behery et al also demonstrated significantly lower postpartum blood loss with carbetocin, supporting its superior uterotonic efficacy.[18]

Despite the uneven distribution of certain maternal risk factors—such as a higher prevalence of preeclampsia in the carbetocin group and a greater proportion of previous caesarean sections in the oxytocin group—the reduction in blood loss remained significant in favor of carbetocin. Preeclampsia is a recognized risk factor for uterine atony and postpartum hemorrhage; therefore, reduced blood loss in this higher-risk group further strengthens the evidence for carbetocin's effectiveness in preventing PPH.

The requirement for additional uterotonic agents was lower in the carbetocin group, indicating improved uterine tone and sustained uterine contraction. Reduced dependence on rescue uterotonics has also been reported in multiple randomized trials and systematic reviews.[19] This is clinically relevant, as it minimizes drug exposure, reduces nursing workload, and may contribute to better overall postpartum care, particularly in busy tertiary care settings.

Post-delivery hemoglobin levels were significantly higher in the carbetocin group compared to the oxytocin group. This difference could be attributed to the higher blood loss observed in the oxytocin group. Postpartum hemoglobin levels were better maintained in the carbetocin group, which is consistent with findings by Maged et al. Larciprete et al also reported better hemoglobin

preservation with carbetocin, particularly in high-risk caesarean deliveries.[20] However, Su et al found no significant difference in hemoglobin levels between the two groups.[19]

Hemodynamic assessment revealed significantly lower systolic and diastolic blood pressures in the oxytocin group compared to the carbetocin group. Oxytocin is known to cause transient hypotension due to vasodilation, particularly when administered intravenously.[21] Carbetocin, owing to its sustained and gradual uterotonic action, appears to offer better hemodynamic stability, which may be advantageous in women with cardiovascular compromise or hypertensive disorders of pregnancy.

No significant adverse drug-related effects were observed in either group, indicating that both carbetocin and oxytocin are safe for use in active management of the third stage of labor. This finding is consistent with earlier studies reporting similar safety pro les for both drugs.[18,22] The availability of heat-stable carbetocin further enhances its suitability in settings where cold-chain maintenance for oxytocin is unreliable.[22]

Strengths and limitations

The strengths of this study include its randomized design, adequate sample size, and comprehensive assessment of both efficacy and safety outcomes. However, the study was conducted at a single tertiary care center, which may limit generalizability. Cost effectiveness analysis was not included and should be addressed in future studies, particularly in low-resource settings.

CONCLUSION

Carbetocin is more effective than oxytocin in reducing postpartum blood loss during active management of the third stage of labor, with the added advantage of single-dose administration and a comparable safety profile. Carbetocin can be considered a suitable alternative to oxytocin, particularly in tertiary care and high-risk obstetric settings.

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