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Timing of carbetocin administration in vaginal deliveries: a double-blind, randomized controlled trial

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Abstract

Objectives: This study aimed to compare the efficacy of administering carbetocin before vs. after placental delivery in preventing postpartum hemorrhage (PPH) in low-risk vaginal deliveries.

Methods: The randomized controlled trial was conducted at Kartal City Hospital, Istanbul, Turkey. A total of 160 primiparous women with uncomplicated pregnancies who underwent vaginal delivery were enrolled. Participants were randomly assigned to receive 100 μg of carbetocin either before or after placental delivery. The primary outcome was the incidence of PPH. Secondary outcomes included the need for additional uterotonics, manual removal of the placenta with consequent antibiotic administration, blood transfusions, maternal adverse events, and changes in hemoglobin levels at baseline and 24 h postpartum.

Results: The incidence of PPH was significantly lower in the carbetocin-before group than in the carbetocin-after group (p=0.015). The carbetocin-before group had a significantly lower mean hemoglobin drop compared to the carbetocin-after group (p<0.001). The need for additional uterotonics was significantly higher in the carbetocin-after group (p<0.001). Manual placenta removal and the need for antibiotics were more frequent in the carbetocin-before group (p=0.017). No significant differences in adverse maternal events were observed between the groups.

Conclusions: Administering carbetocin before placental delivery significantly reduces the incidence of PPH, blood loss, and the need for additional uterotonics. However, the increased rate of manual placenta removal necessitates individualized risk–benefit assessment; pre-placental administration may be most advantageous in women at elevated risk for PPH, in whom the hemorrhagic benefit outweighs the risks associated with manual extraction.

Keywords: carbetocin; manual removal of the placenta; postpartum hemorrhage; retained placenta; uterotonics; vaginal delivery

Introduction

Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality worldwide, responsible for approximately one-quarter of all pregnancy-related deaths [1]. The primary cause of PPH is uterine atony, a condition characterized by ineffective uterine contraction following delivery, which results in excessive bleeding [2]. Despite advances in obstetric care, PPH continues to pose a significant clinical challenge, often requiring blood transfusions, prolonged hospitalizations, and increased healthcare resources utilization [3].

Effective prevention and management of PPH are critical. Active management of the third stage of labor, which involves the use of uterotonics, uterine massage, and controlled cord traction, is widely recommended to reduce the risk of PPH. Of the uterotonic agents available, oxytocin is the most commonly used due to its proven safety and efficacy [4]. However, due to its short half-life, continuous infusion is often necessary to maintain uterine tone. Carbetocin, a long-acting synthetic analogue of oxytocin, was

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developed to overcome this limitation. A single dose of carbetocin provides sustained uterine contraction, reducing the need for additional uterotonics and the incidence of PPH in both vaginal and cesarean births.

Despite extensive research supporting the efficacy of carbetocin, the optimal timing of its administration during vaginal deliveries remains an area of ongoing investigation [5–7]. The aim of this study was therefore to evaluate the efficacy of carbetocin administration in relation to placental delivery (before vs. after placental delivery) for PPH prevention in low-risk vaginal deliveries. Through a prospective, double-blind, randomized controlled trial, we sought to elucidate the optimal timing of carbetocin administration, with the goal of improving maternal care and clinical outcomes.

Materials and methods

Study design and setting

This prospective, single-center, double-blind, randomized controlled trial was performed at the Department of Obstetrics and Gynecology, Kartal City Hospital – a tertiary referral center in Istanbul, Turkey – between January 10, and February 28, 2025. The protocol obtained Ethical Approval from the hospital's Research Ethics Committee (Approval Number: [2023/514/258/20], Date: [27.09.2023]) and was registered with ClinicalTrials.gov (NTC06776926). The study adhered to the Declaration of Helsinki. Before enrollment in the study, all participants provided written informed consent.

Participants

The inclusion criteria consisted of primiparous women aged 18–45 years with a healthy singleton pregnancy delivered vaginally at or beyond 38 weeks of gestation. The exclusion criteria were divided into five main categories: (1) Medical history associated with an increased risk of PPH, including previous placental abruption, uterine curettage, uterine rupture, peripartum blood transfusion or parenteral iron administration, and placental retention; (2) Pregnancy-related increased risk factors for PPH in the current pregnancy, including multifetal pregnancies, fetal macrosomia, polyhydramnios, labor induction or augmentation with oxytocin for ≥4 h, prolonged active labor (>12 h), and BMI>35; (3) Comorbidities, including hypertensive disorders and pre-eclampsia syndromes, cardiovascular, hepatic, renal or endocrine disorders; (4) Known bleeding diathesis or coagulopathy, and current use of anticoagulant or antiplatelet agents including low-dose aspirin; (5) Patient non-participation and hypersensitivity to oxytocin and/or carbetocin.

Randomization and intervention

Eligible participants were randomly assigned to receive 100 μg of intravenous carbetocin either before or after placental delivery using a computer-generated randomization scheme. Vaginal deliveries were performed by the attending obstetrician. In the carbetocin-before group, the drug was administered immediately after delivery of the anterior shoulder and before placental delivery. In the carbetocin-after group, carbetocin was administered after placental delivery. Randomization envelopes were opened by a designated research midwife who was not involved in patient care. This same midwife prepared and administered the carbetocin intravenously through the pre-existing peripheral venous catheter, which was located on the maternal arm – away from the obstetrician's primary operative field. The delivering obstetrician was not informed of the group allocation at any point during the delivery. Both participants and attending clinicians were blinded to group allocation.

Carbetocin (Pabal®; Ferring Pharmaceuticals, Saint-Prex, Switzerland) was administered as a 100 μg (1 mL) intravenous bolus over 1 minute. Blood loss was quantified using a standardized quantitative blood loss protocol employing calibrated under-buttocks collection drapes, supplemented by gravimetric weighing of blood-soaked materials [8]. Data on the need for additional uterotonics (intramuscular methilergonovine and/or rectal misoprostol), additional surgical treatment methods for PPH including baloon tamponade, compression sutures, ligation of the internal iliac artery and/or uterine artery and hysterectomy, blood transfusions, antibiotics (not routinely administered in uncomplicated vaginal deliveries. However, in cases requiring manual removal of the placenta, a single dose of 2 g cefazolin was administered intravenously per institutional protocol) and manual removal of the placenta, were collected. The study protocol also included monitoring adverse maternal events, such as nausea, vomiting, dizziness, and shivering, within the first 24 h after delivery.

Outcomes

The primary outcome was the incidence of PPH, defined as quantitatively measured blood loss ≥500 mL. Secondary outcomes included the need for additional uterotonic drugs, blood transfusion, manual removal of the placenta, institutional protocol-driven use of antibiotics, maternal adverse events, and changes in hemoglobin levels measured before delivery and 24 h after delivery.

Statistical analysis

Statistical analyses were conducted in SPSS v.23 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± SD and between-group comparisons were analyzed via independent two-tailed Student's t-tests. Categorical data were reported as counts (%) and evaluated using Pearson's chi-square or Fisher's exact tests, contingent on expected cell frequencies. Significance thresholds were set at α=0.05. An *a priori* power analysis was performed in Python's Statsmodels (v0.14.0) using the TTestIndPower function, deriving a minimum sample size of 64 per group (total n=128) to detect a clinically meaningful effect (Cohen's d=0.64, extrapolated from reference [9]) with β=0.20 and α=0.05 under a two-sample t-test framework.

Results

A total of 229 women were assessed for eligibility, of whom 63 were excluded due to failure to meet inclusion criteria. Of the remaining 166 women, three were excluded from each group due to conversion to cesarean delivery, resulting in 80 women in each study arm. No participants were lost to follow-up. The flowchart depicting the inclusion, exclusion, and randomization of participants is presented in Figure 1.

Baseline characteristics

No statistically-significant differences were observed between baseline maternal, obstetric, and neonatal parameters – including maternal age, body mass index, gestational age, smoking status, duration of first and second stages of labor, neonatal birth weight, episiotomy rate, and APGAR scores at the 1st and 5th minutes (all p>0.05) (Table 1). No cases of shoulder dystocia, third- or fourth-degree perineal lacerations requiring surgical repair beyond standard technique, or clinical chorioamnionitis were observed in either group.

Primary and secondary outcomes

The incidence of PPH (blood loss ≥500 mL) was significantly lower in the carbetocin-before group (3/80, 3.8 %) compared with the carbetocin-after group (12/80, 15.0 %) (p=0.015). The mean hemoglobin drop (ΔHb) was significantly lower in the carbetocin-before group (0.76 ± 0.47 g/dL) compared to the carbetocin-after group (1.30 ± 0.61 g/dL) (p<0.001). Manual removal of the placenta and consequent protocol-driven antibiotic administration were required in eight women (10 %) in the carbetocin-before group, significantly higher than in one woman (1.3 %) in the carbetocin-after group (p=0.017). The carbetocin-before group exhibited a statistically significant prolongation of the third stage of labor compared to the carbetocin-after group (10.5 ± 10.5 min vs. 7.0 ± 5.7 min; p=0.009), attributable to the higher incidence of delayed placental separation requiring manual removal in this arm. No significant difference was observed between groups in the blood transfusion rates (p=0.123) (Table 1). Hemoglobin reductions exceeding >5 %, >10 %, and >15 % were significantly higher in the carbetocin-after group compared to the carbetocin-before group (88 vs. 56 %, 50 vs. 18 %, and 25 vs. 3 %, respectively; all p<0.001). The requirement for additional uterotonics was higher in the carbetocin-after group (p<0.001) (Table 2). The maternal adverse events listed in Table 3 showed no significant difference in the frequency of symptoms and signs between the two groups (p=0.837).

Discussion

This study compared the efficacy of carbetocin administration before vs. after placental delivery in reducing PPH and related outcomes in low-risk vaginal deliveries. The results indicated that administration of carbetocin before placental delivery significantly reduced the incidence of PPH, hemoglobin drop and the need for additional uterotonics. However, the higher incidence of manual placental removal and consequent protocol-driven antibiotic use in this group warrants further clinical consideration. In our study, administering carbetocin immediately after the delivery of fetal shoulder was associated with a significant reduction in PPH incidence, mean hemoglobin drop (ΔHb) and the need for additional uterotonic agents, thereby supporting its potential role in the prevention of PPH.

While prior studies evaluating carbetocin administration during the third stage of labor reported a reduced need for uterine massage and fewer additional uterotonics without a significant increase in placental retention [3, 5–10],

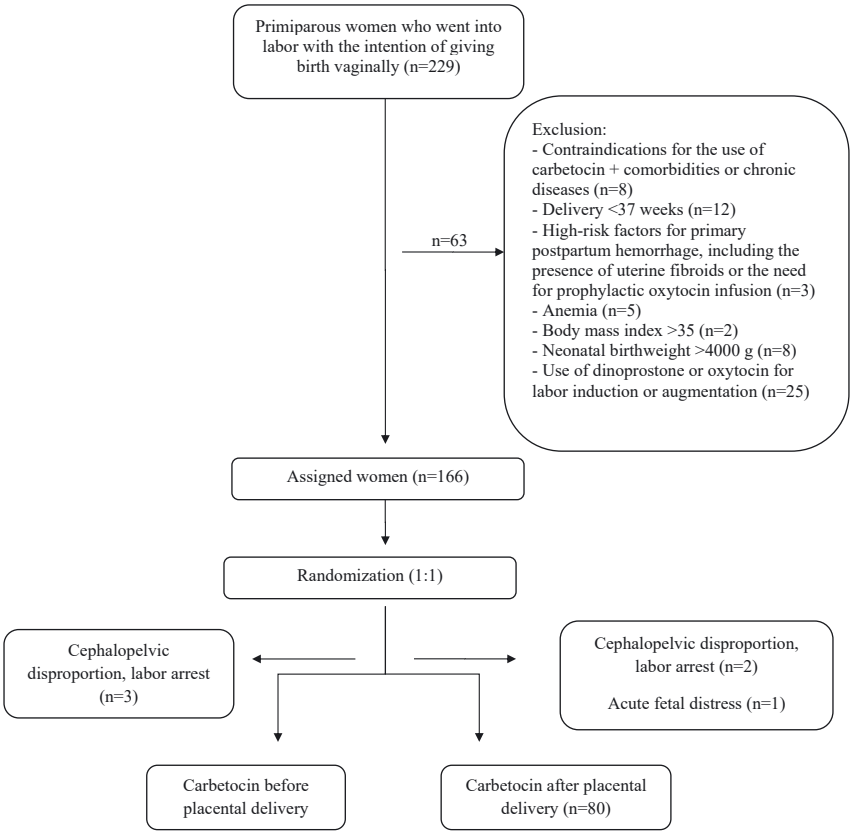


Figure 1: The flow diagram depicting the inclusion, exclusion, and randomization of participants.

our findings diverge on this latter point. In contrast to the existing literature, pre-placental carbetocin administration in our study was associated with a significantly higher rate of manual placental removal. This discrepancy may reflect differences in the timing of administration – specifically, the pre-placental timing in our protocol, which may induce premature uterotonic constriction of the lower uterine segment before physiologic placental separation is complete – as well as methodological differences including the route, dose, and pharmacokinetic profile of carbetocin formulations used in earlier investigations.

The effects of carbetocin on placental delivery have not yet been well researched in clinical practice. Earlier studies have suggested an increased incidence of placental retention when large doses of carbetocin (200 µg IM) are administered immediately after delivery of shoulder, prompting a shift in subsequent protocols to delay carbetocin administration until after placental delivery [11].

Clinical and research implications

Our study comparing the administration of 100 µg IV carbetocin pre-vs. post-placental delivery revealed a clinically significant increase in manual placental extraction rates and consequent protocol-driven antibiotic requirement in the carbetocin-before group. Of note, antibiotic administration in both groups was exclusively linked to manual placental removal, with a single dose of 2 g intravenous cefazolin administered following manual extraction per institutional protocol. Thus, the increased antibiotic use in the carbetocin-before group was a direct consequence of the higher rate of manual placental removal rather than an independent pharmacologic effect of carbetocin timing. This stark contrast underlines an important pharmacodynamic aspect. While early administration of carbetocin improves immediate postpartum hemostasis, its uterotonic effect may prematurely constrict the lower uterine segment, impairing physiologic mechanisms for placental detachment and potentially leading to placental retention and associated complications. The incidence of retained placenta may, in turn, increase the risk of infection and the need for interventions, such as manual removal of placenta or curettage. These findings necessitate rigorous risk-benefit analysis when determining optimal administration timing in PPH prophylaxis protocols.

Accordingly, the net clinical benefit of pre-placental carbetocin administration depends on the patient's baseline hemorrhagic risk profile. In women at elevated risk for PPH – such as those with prior PPH, uterine overdistension,

Table 1: Maternal demographic and obstetric characteristics and primary and secondary outcomes.

Variable	Carbetocin-before group (n=80)	Carbetocin-after group (n=80)	p-Value
Age, years	27.6 ± 4.9	27.1 ± 4.9	0.522
Body mass index, kg/m^2	28.6 ± 2.9	28.1 ± 2.9	0.241
Gestational age, weeks	39.0 ± 1.1	39.3 ± 1.1	0.069
Birth weight, g	3,269.6 ± 370.7	3,354.4 ± 347.7	0.138
Apgar 1st minute (score)	7.4 ± 0.5	7.5 ± 0.5	0.271
Apgar 5th minute (score)	8.58 ± 0.52	8.68 ± 0.5	0.202
Episiotomy, n	12 (15.0)	14 (17.5)	0.664
3rd–4th degree perineal laceration, n	1 (1.3)	2 (2.5)	1.000
Duration of 1st stage of labor, min	279.9 ± 244.0	269.8 ± 230.7	0.789
Duration of 2nd stage of labor, min	20.4 ± 13.9	20.5 ± 12.1	0.966
Duration of 3rd stage of labor, min	10.5 ± 10.5	7.0 ± 5.7	0.009
Smoking, n	6 (7.5)	5 (6.3)	0.755
PPH incidence (blood loss ≥500 mL), n	3 (3.8)	12 (15.0)	0.015
Manual removal of placenta, n	8 (10)	1 (1.3)	0.017
Need for additional uterotonics, n	1 (1.3)	14 (17.5)	<0.001
Need for antibiotics (protocol-driven linked to manual removal), n	8 (10)	1 (1.3)	0.017
Need of blood transfusion, n	0 (0)	3 (3.8)	0.123
Total adverse effects, n	14 (17.5)	15 (18.75)	0.837

Values are expressed as mean ± standard deviation or n (%), where appropriate.

Table 2: Peripartum hemoglobin changes

Variable	Carbetocin-before group (n=80)	Carbetocin-after group (n=80)	p-Value
Hemoglobin levels at the onset of labor, g/dL	11.4 ± 1.3	11.8 ± 1.3	0.066
Hemoglobin levels on the 1st postpartum day, g/dL	10.7 ± 1.2	10.5 ± 1.5	0.430
Mean decrease in hemoglobin levels, g/dL	−0.7 ± 0.4	−1.3 ± 0.6	<0.001
Mean hemoglobin decrease, classified according to the percentage of decrease	−6.6 ± 4.0	−11.1 ± 5.6	<0.001
>5 %	45 (56)	70 (88)	<0.001
>10 %	15 (18)	41 (50)	<0.001
>15 %	2 (3)	20 (25)	<0.001
>20 %	1 (1)	4 (5)	0.184

Data are presented as mean ± standard deviation or n (%), where appropriate.

or prolonged labor – the substantial reduction in hemorrhage (absolute risk reduction of 11.2 % for PPH) achieved by early carbetocin administration would be expected to outweigh the risks associated with manual placental extraction. Conversely, in truly low-risk women, the absolute hemorrhagic benefit may not justify the increased manual removal rate and its attendant complications (endometritis, procedural pain, uterine injury). These considerations support a risk-stratified approach to the timing of carbetocin administration in clinical practice.

Carbetocin demonstrates a favorable maternal safety profile, with our analysis revealing no significant differences in adverse events (AEs) between pre- and post-placental administration, in line with prior studies [3, 12, 13]. Transient tachycardia, though more prevalent in the carbetocin-after group (5 vs. 2.5 %; p=NS), and tremor, marginally elevated in the carbetocin-before group (5 vs. 3.75 %; p=NS), did not reach statistical significance. Other transient AEs, including dizziness (2.5 % in both groups), nausea/vomiting (3.75 % in both groups), and flushing (1.25 % in both groups) were similar between groups. While carbetocin-induced tachycardia is typically transient, its clinical relevance lies in confounding hemodynamic monitoring during PPH, where heart rate serves as a critical early marker of decompensation prior to hypotensive changes. Clinicians must differentiate physiologic carbetocin effects from pathologic hemodynamic shifts in high-risk scenarios.

Strengths and limitations

This study is subject to several limitations that warrant consideration. First, the single-center design and the exclusion of women with established PPH risk factors limit the generalizability of our findings, particularly to higher-risk obstetric populations. Second, the absence of a cost analysis precludes evaluation of the cost-benefit ratios between the administration protocols – a critical consideration for resource-constrained settings. Third, although extensive measures were taken to maintain blinding – including allocation concealment, drug preparation and administration by a dedicated research midwife not involved in clinical care, and IV access distant from the operative field – we acknowledge

Table 3: Profile of adverse effects.

Variable	Carbetocin-before group (n=80)	Carbetocin-after group (n=80)	Total (n=160)	p-Value
No adverse effect	66 (82)	65 (81)	131 (82)	0.837
Any adverse effect	14 (18)	15 (19)	29 (18)	
Headache	0 (0)	1 (1.25)	1 (0.63)	
Dizziness	2 (2.5)	2 (2.5)	4 (2.5)	
Nausea + vomiting	3 (3.75)	3 (3.75)	6 (3.75)	
Nausea + vomiting + Tremors	2 (2.5)	1 (1.25)	3 (1.88)	
Flushing	1 (1.25)	1 (1.25)	2 (1.25)	
Tachycardia[a]	2 (2.5)	4 (5)	6 (3.75)	
Tremors	4 (5)	3 (3.75)	7 (4.38)	

Data are presented as n (%). [a]A heart rate of over 100 beats per minute within 60 min of delivery.

that complete blinding of the delivering obstetrician to the timing of carbetocin administration cannot be absolutely guaranteed. However, the key outcome measures – hemoglobin concentration (an objective laboratory value) and the decision for manual placental removal (based on a standardized 30-minute criterion) – are minimally susceptible to observer bias, thereby mitigating the impact of any potential unblinding. Fourth, although randomization was effective in balancing baseline characteristics (including birth weight, episiotomy rates, and labor duration), the relatively small sample size may limit the power to detect differences in rare intrapartum events such as severe perineal trauma or shoulder dystocia, and future studies with larger, more diverse populations should further evaluate these factors.

Despite these limitations, this study has several strengths. Although prior studies have examined various aspects of carbetocin use, including dosage, infusion speed, and administration routes, the impact of timing relative to placental delivery have not previously been examined [11–13]. To our knowledge, this investigation represents the first direct comparison between pre-vs. post-placental carbetocin timing for PPH prophylaxis. In addition, the rigorous methodological design, characterized by well-defined protocols and clear inclusion and exclusion criteria, bolsters internal validity. Additionally, the comprehensive evaluation of both efficacy and safety endpoints provides balanced insights into the trade-offs associated with each administration protocol. The findings reveal a clinically significant efficacy-safety balance: pre-delivery carbetocin reduced PPH incidence, hemoglobin decline (ΔHb) and additional uterotonic requirements while increasing manual placental removal rates, providing actionable insights for protocol optimization. Lastly, the findings establish a robust foundation for future multicenter randomized controlled trials in more diverse, risk-stratified populations and for subsequent cost-effectiveness analyses in resource-limited settings.

Conclusions

In conclusion, our results demonstrate that administration of carbetocin prior to placental delivery significantly reduces the incidence of PPH, hemoglobin decline (ΔHb), and the need for additional uterotonics, albeit with a markedly increased rate of manual placental removal and consequent protocol-driven antibiotic use. These results underscore a critical efficacy-safety trade-off in third-stage labor management. A risk-stratified approach, favoring pre-placental carbetocin in women at elevated hemorrhagic risk, may optimize the balance between hemostatic benefit and the risk of retained placenta. Future multicenter trials in risk-stratified populations are needed to refine these recommendations.

Research ethics: The database management in accordance with privacy legislation and the presented study in accordance with the ethical principle of the Declaration of Helsinki. Written and verbal informed consent was obtained from all study participants. Ethical approval for this study was obtained by the Research Ethics Committee of Kartal City Hospital (Approval Number: [2023/514/258/20], Date: [27.09.2023]) and was registered with ClinicalTrials.gov (NTC06776926). (online registration details: start date 2025-01-10, end date: 2025-02-28), available at: https://www.clinicaltrials.gov/study/NCT06776926?term=CARBETOCIN&viewType=Table&rank=8.

Informed consent: Written and verbal informed consent was obtained from all study participants.

Author contributions: P. Yıldız: Running the trial, collecting data, data analysis & article write-up. E. Keles: Study design, implementing the trial, data collection & article review. G. Yıldız: Running the trial, collecting data & article review. M.M. Kırlangıç and M.M. Dereli: Concept design, study conduction& creating exoskeleton. K. Turan: Study design, sourcing funding, article review and trial supervision. E.Mat: Study design, sourcing funding, article review and trial supervision.

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Conflict of interest: The authors state no conflicts of interest.

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Data availability: The data that support the findings of this study are openly available in "figshare" at 10.6084/m9.figshare.30311116.

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