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Carbetocin versus Oxytocin with or without Tranexamic Acid for Prophylactic Prevention of Postpartum Hemorrhage after a Vaginal Delivery: A Randomized Clinical Trial

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Keywords
Carbetocin · Oxytocin · Tranexamic acid · Postp[illegible] hemorrhage · Prophylaxis

Abstract

Objective: Our study's primary o[illegible]ec[illegible]v[illegible]s to examine the effects of four different pro[illegible]ylac[illegible]protocols on the prevention of postpartum he[illegible]rhage following vaginal birth, including carbetoci[illegible], ox[illegible]in only, and a combination of carbetocin or o[illegible]n with tranexamic acid. ***Design:*** A multicentric [illegible]dom[illegible] controlled trial. ***Participants/Materials, Se[illegible]nd[illegible]d Methods:*** This multicentric center pros[illegible]ve [illegible]om[illegible]ed controlled trial was conducted at th[illegible]ep[illegible]ment o[illegible] Obstetrics and Gynecology of Bezmialem [illegible]or[illegible]an Health Teaching and Research Hospital fro[illegible]gust 2022 to January 2023. The collected data included age, gravidity, parity, gestational age at birth, duration of delivery stages, prepartum hemoglobin and hematocrit concentrations, changes in hemoglobin and hematocrit concentrations, intrapartum blood loss, estimated blood loss after 2 h of vaginal delivery, Apgar scores at 1 and 5 min, birth weight, and neonatal intensive care unit (NICU) admission. Intrapartum blood loss was objectively measured in milliliters using a postpartum drape with a calibrated bag. The amount of bleeding was measured by subtracting the empty weight of the pads placed under the patient in the patient's bed within 2 h after delivery. Group I: carbetocin 100 μg/mL ($n = 75$), group II: oxytocin 5 IU/mL ($n = 75$), group III: carbetocin and tranexamic acid 50 mg/mL ($n = 75$), group IV: oxytocin and tranexamic acid ($n = 75$). ***Results:*** The hemoglobin concentration decrease significantly differed between groups (1.03 ± 1.04, 1.3 ± 0.85, 1.4 ± 0.85, 1.41 ± 0.87, respectively; $p < 0.001$). Group 4 has the highest decrease in hemoglobin and hematocrit concentrations. When we investigated the subgroup differences, the decrease in hemoglobin concentration was significantly higher in group 2 than group 1 (1.30 ± 0.85 vs. 1.03 ± 1.04; $p = 0.023$), in group 2 than group 3 (1.3 ± 0.85 vs. 1.04 ± 0.9; $p = 0.013$), and in group 4 than group 3 (1.41 ± 0.87 vs. 1.04 ± 0.9; $p < 0.001$). The decrease in hematocrit level was significantly different between groups (3.07 ± 3.23, 3.55 ± 2.44, 2.13 ± 3.09, 4.25 ± 2.52; $p < 0.001$, respectively). No significant differences were observed in terms of mean blood loss between the four

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groups (277.19 ± 208.10, 294.13 ± 198.64, 274.33 ± 199.57, and 283.97 ± 178.11; $p = 0.445$, respectively). Furthermore, there was no significant difference between the groups in the rate of need for blood transfusion (1.3%, 5.4%, 4%, and 4%, respectively; $p = 0.6$). ***Limitations:*** The most important limitation of the study is a relatively small number of participants. ***Conclusion:*** In conclusion, our findings suggest that carbetocin may be more successful than oxytocin and oxytocin plus tranexamic acid regimens in terms of postpartum hemoglobin reduction, and there is no difference in terms of the need for blood transfusion when it is used for postpartum hemorrhage prophylaxis after vaginal delivery.

Introduction

The American College of Obstetricians and Gynecologists (ACOG) defines postpartum hemorrhage (PPH) as "overall blood loss greater than or equal to 1,000 mL or blood loss coupled with signs or symptoms of hypovolemia within 24 h after the birth process (including intrapartum loss)" [1]. PPH is an obstetric emergency that affects 1–10% of births globally and is the leading cause of maternal mortality [2]. For this reason, identifying patients who are at risk of experiencing obstetrical bleeding necessitating blood product transfusion in the early stages can play a pivotal role in decreasing, to some extent, the incidence of avoidable maternal fatalities caused by hemorrhaging [3]. Its distribution varies between geographies, with Africa having the highest prevalence (5.1–25.7%), followed by North America (4.3–13%) and Asia (1.8–8%) [4]. Prophylaxis and treatment of PPH, the most important cause of maternal mortality, are still the subject of extensive current research.

To prevent PPH, managing the third stage of labor is essential [5]. This includes uterotonics, early cord clamping, controlled cord traction, and uterine massage. One of the essential prophylaxis tools is the use of uterotonics. FIGO recommends that all births utilize uterotonics to prevent PPH during the third stage of labor. Oxytocin (10 IU IV/IM) is recommended to avoid PPH during vaginal and cesarean deliveries. Oxytocin, a nine amino acid neuropeptide hormone, plays a significant role in human physiology, influencing behavior and cognition. However, its primary and crucial function is triggering the initiation of labor and the birthing process [6]. In situations where oxytocin is inaccessible or whose quality cannot be assured, the use of ergometrine or methylergometrine (200 g IM/IV); oral misoprostol (400–600 g orally); or carbetocin (100 g IM) is recommended for the prevention of PPH [7]. There are several studies in the current literature to examine whether we have a better option than oxytocin prophylaxis, which currently is the standard treatment and is recommended. Studies on carbetocin and tranexamic acid (TXA) are being carried out for various cohorts, and data are accumulating. Heat-stable carbetocin, a uterotonic recommended for PPH prevention and TXA, an antifibrinolytic recommended for PPH treatment, were recently added to the core list of reproductive health medicines in the 2019 Model List of Essential Medicines by the WHO [8–10]. Data suggest that carbetocin may be as good an option as oxytocin for PPH prevention [11]. However, randomized controlled studies on the subject are limited. Our study's primary objective was to examine the effects of four prophylaxis protocols on preventing PPH following vaginal birth, including carbetocin only, oxytocin only, and the combination of carbetocin or oxytocin with TXA.

Materials and Methods

This multicentric center is prospective randomized (balanced allocation 1:1:1:1 and parallel-group study) controlled trial conducted at the Department of Obstetrics and Gynecology of Bezmialem University Hospital and Van Health Teaching and Research Hospital from August 2022 to January 2023. The Institutional Review Board approved the study with a study number of 04.07.2022-E.69157 from Bezmialem Vakif University. All patients in this study signed a written informed consent form before inclusion. A clinical registration with trial number NCT05467462 was submitted.

Patients with maternal ages 18–40 years with singleton pregnancies with a gestational week greater than 37 weeks were included in our study. Patients with pregnancies less than 37 weeks, non-volunteers, those allergic to carbetocin, oxytocin, or TXA, those with severe cardiac disease, severe liver disease, renal disease, epilepsy, those at risk for embolism or bleeding, and those who refused voluntary consent were excluded from our study.

The collected data included age, gravidity, parity, gestational age at birth, duration of delivery stages, prepartum hemoglobin and hematocrit concentrations, changes in hemoglobin and hematocrit concentrations (difference between prepartum and postpartum 24th-h levels), intrapartum blood loss, estimated blood loss after 2 h of vaginal delivery, Apgar scores at 1 and 5 min, birth weight, and neonatal intensive care unit (NICU) admission. Intrapartum blood loss was objectively measured in milliliters using a postpartum drape with a calibrated bag. The amount of bleeding was calculated by subtracting the empty weight of the pads placed under the patient in the patient's bed within 2 h after delivery.

A total of 352 patients were included in this study after the initial assessment for eligibility starting in August 2022. In the second stage of labor, when vaginal delivery is imminent, eligible

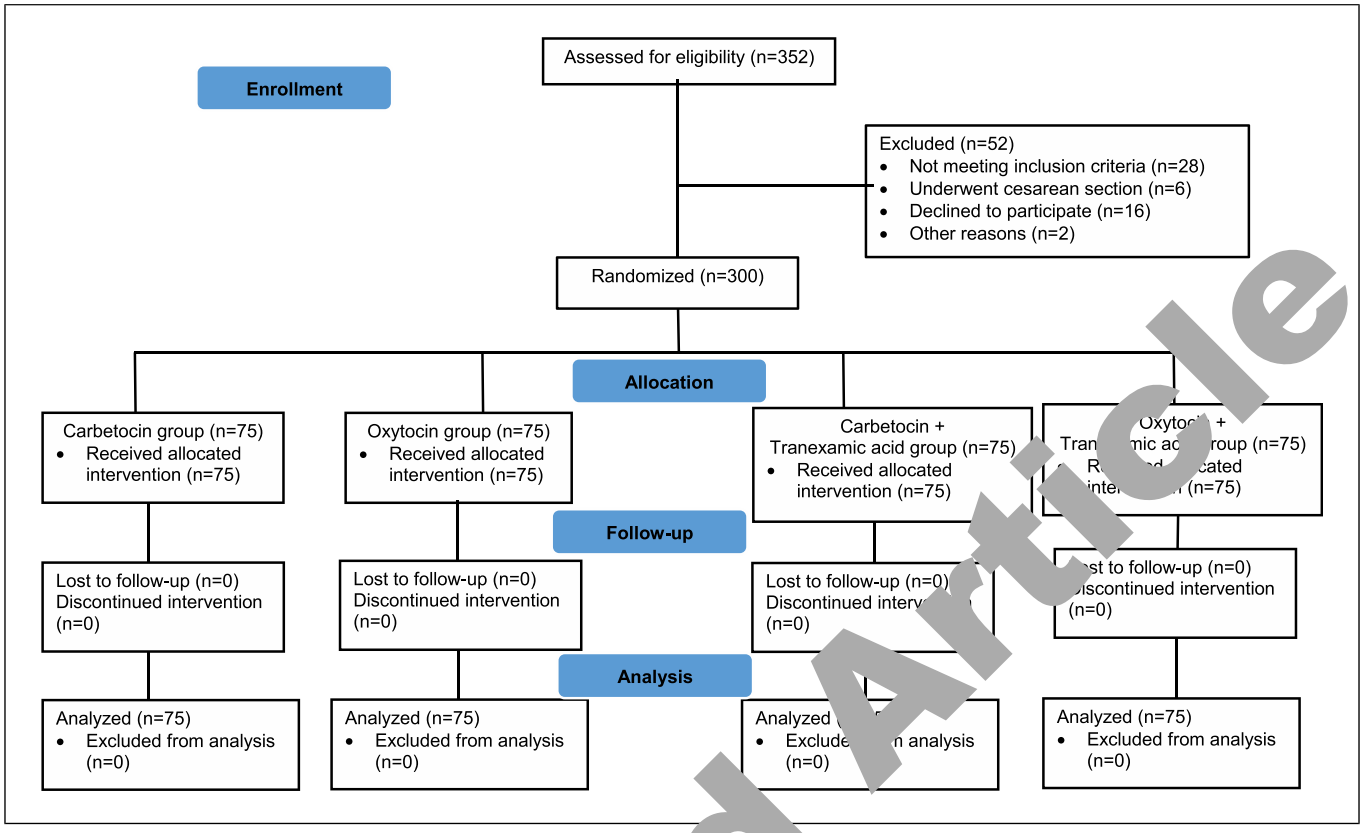

Fig. 1. Flowchart of the study.

women were randomized to receive oxytocin, carbetocin, oxytocin + TXA, and carbetocin + TXA (Fig. 1). Patients were randomly divided into four groups by allocating a computer-generated random number. Group I: carbetocin 100 μg/mL (Pabal®; Ferring Pharma, Istanbul, Turkey) ($n = 75$) was intravenously administered immediately after the birth of the baby. Group II: oxytocin 5 IU/mL (Syntocinon Forte®; Deva Pharma, Istanbul, Turkey) ($n = 75$) oxytocin infusion consisting of 20 IU dissolved in 500 mL of normal 0.9% sodium chloride solution and infused at a rate of 125 mL/h was administered immediately after clamping the umbilical cord. Group III: carbetocin + TXA, 100 mg/mL (Transamin; TEVA Pharma, Istanbul, Turkey) ($n = 75$) 100-mg carbetocin was intravenously administered immediately after the birth of the baby, and TXA infusion consisting of 1 g dissolved in 100 mL of normal 0.9% sodium chloride solution was administered immediately after clamping of the umbilical cord. Group IV: oxytocin and TXA ($n = 75$) an oxytocin infusion consisting of 20 IU in 500 mL of normal 0.9% sodium chloride solution was infused at a rate of 125 mL/h, and a TXA infusion consisting of 1 g dissolved in 100 mL of normal 0.9% sodium chloride solution was administered immediately after clamping the umbilical cord. The patients and obstetricians were blinded to drug and administrated. The primary outcome of our study was planned as the change in postpartum bleeding parameters, postpartum hemoglobin, and hematocrit change, and the secondary outcomes were postpartum blood loss (measured with calibrated bag), "need for additional uterotonic treatment," "the need for blood transfusion."

Statistical Analysis

The study would require a sample size of 68 subjects for each group (assuming equal group sizes) to achieve a power of 80% (1-b) and at a 95% confidence level (1-a) for detecting a true difference in means between the groups of 199 for the amount of bleeding (standard deviations were taken as 389.17 and 525.66). The power calculation was based on the amount of bleeding reported by Maged et al. [12]. With a 10% drop-out, a sample size of approximately 75 women would be required for each group, and at least 75 patients have already been included in each group.

Descriptive statistics for categorical variables in the study were provided in frequency and percentage. In contrast, descriptive statistics for quantitative variables were given as mean, standard deviation, median, minimum, and maximum: Pearson's χ^2 test and Fisher's exact test examined relationships between categorical variables. Detailed comparisons of groups showing differences were conducted with Bonferroni correction. The standard distribution suitability of quantitative variables was investigated using the Kolmogorov-Smirnov test.

For the comparison of means among more than two independent groups, the Kruskal-Wallis test was employed, and for post hoc multiple comparisons, the Dunn test was used. A

Table 1. Baseline obstetric and demographic characteristics of groups

Characteristics	Group 1	Group 2	Group 3	Group 4	*p* value
	carbetocin (*n* = 75)	oxytocin (*n* = 75)	carbetocin + tranexamic acid (*n* = 75)	oxytocin + tranexamic acid (*n* = 75)	
Age, years	28.57±6.06 28 (18–40)	28.33±5.67 28 (18–40)	27.48±5.92 26 (18–40)	29.17±6.29 29 (18–40)	0.382
Gravida	3.11±2.46 2 (1–14)	2.64±1.66 2 (1–7)	2.71±1.68 2 (1–10)	2.31±1.65 2 (1–9)	[illegible]
Parity	1.67±1.72 1 (0–7)	1.35±1.35 2 (0–5)	1.4±1.53 2 (0–8)	1.05±1.33 1 (0–6)	[illegible]
Gestational age, weeks	39.02±1.19 39 (37–42)	39.49±1.1 40 (37–41)	39.18±1.16 39.40 (37–41.7)	39.3±1.21 39.28 (37–42)	0.058
Nulliparity	23 (30.7)	24 (32)	28 (37.3)	34 (45.3)	0.230
Indication of birth					0.170
Pain	42 (56)	44 (58.7)	39 (52)	39	
Water breaks	13 (17.3)	17 (22.7)	25 (33.3)	[illegible] (29.[illegible]	
Postterm	3 (4)	6 (8)	5 (6.7)	[illegible]6.7)	
Olygohidramnios	17 (22.7)	8 (10.7)	6 (8)	[illegible])	
Labor induction					
Dinoprostone, vaginal	14 (48.3)	10 (33.3)	11 (32.4)	[illegible]2 (35.3)	0.549
Oxytocin, intravenous	15 (51.7)	20 (66.7)	23 (67.6)	22 (64.7)	
None	46 (61.3)	45 (60)	41 (54.7)	41 (54.7)	0.769
Stages of birth, min					
Second	52.87±25.16 40 (30–110)	45.85±21.5 35 (30–126)	50.13±[illegible] [illegible]–110)	48.65±18.93 45 (25–105)	0.243
Third	8.81±3.38 10 (3–20)	6.01±4.06 5 (1–2[illegible]	9[illegible]3±[illegible]41 [illegible]35)	4.59±2.68 4 (1–13)	<0.001*

Data are expressed as mean ± standard deviat[illegible]edian (minimum-maximum), or number (%). *$p < 0.05$ statistically significant.

significance level of 0.05 was ado[illegible]d. [illegible]BM SPSS Statistics (version 26, Armonk, NY: IBM [illegible]orp) [illegible]oft[illegible]are package was used for calculations.

Results

Of the 35[illegible] pa[illegible]ents, 28 did not meet the inclusion criteri[illegible]6 w[illegible] de[illegible]ered by cesarean section; 16 were ex[illegible]de[illegible]ecaus[illegible] they did not volunteer to participate in [illegible]2 were excluded for other reasons (Fig. 1). The[illegible]stetric and neonatal outcomes of the remaining 300 p[illegible]nts were randomly assigned to four groups (carbetocin only, oxytocin only, carbetocin and TXA, and oxytocin and TXA) for PPH prophylaxis after vaginal delivery was investigated. There was no difference between the groups in terms of age ($p = 0.382$), gravida ($p = 0.146$), parity (0.114), gestational age ($p = 0.058$), nulliparity ($p = 0.230$), indication for delivery ($p = 0.170$), length of the second stage of birth ($p = 0.243$), or method of labor induction ($p = 0.549$), except in the third stage of labor ($p < 0.001$) (Table 1). There was also no significant difference between the groups in terms of prepartum hemoglobin concentration (12.5 ± 1, 12.2 ± 1.16, 12.37 ± 1.09, 12.12 ± 0.87; $p = 0.113$, respectively) and prepartum hematocrit levels (37.58 ± 2.64, 36.74 ± 3.64, 37.26 ± 3.14, 36.47 ± 2.48; $p = 0.108$, respectively) (Table 2).

The hemoglobin concentration decrease significantly differed between groups (1.03 ± 1.04, 1.3 ± 0.85, 1.4 ± 0.85, and 1.41 ± 0.87, respectively; $p < 0.001$). The decrease in hematocrit level was significantly different between groups (3.07 ± 3.23, 3.55 ± 2.44, 2.13 ± 3.09, 4.25 ± 2.52, $p < 0.001$, respectively). No significant

Table 2. Comparison of prepartum characteristics, hemorrhage, and postpartum characteristics between groups

Characteristics	Group 1	Group 2	Group 3	Group 4	*p* value
	carbetocin (*n* = 75)	oxytocin (*n* = 75)	carbetocin + tranexamic acid (*n* = 75)	oxytocin + tranexamic acid (*n* = 75)	
The prepartum hemoglobin concentration, g/dL	12.5±1 12.60 (9.60–15.50)	12.2±1.16 12.20 (10–15)	12.37±1.09 12.6 (9.40–14.5)	12.12±0.87 12.10 (10.50–13.90)	0.113
The prepartum hematocrit concentration, g/dL	37.58±2.64 38 (30.10–42.30)	36.74±3.64 36.6 (30–45)	37.26±3.14 38 (29–42)	36.47±2.48 36.40 (31–42.2)	[illegible]
The decrease in the hemoglobin concentration, g/dL**	1.03±1.04 0.90 (−1.70 to 4.80)	1.3±0.85 1.4 (−1.10 to 3.70)	1.04±0.9 0.90 (−0.30 to 3.90)	1.41±0.8[illegible] 1.5 (−[illegible] to 3.20)	0.001*
The decrease in the hematocrit concentration, g/dL***	3.07±3.23 2.80 (−5.8 to 16.6)	3.55±2.44 3.3 (−2.5 to 9.90)	2.13±3.09 1.9 (−8.5 to 9.8)	4.25±2[illegible] 4[illegible]30 to 9.5)	<0.001*
Postpartum blood loss, mL	277.19±208.10 224 (33–1,382)	294.13±198.64 272 (58–1,354)	274.33±199.57 208 (10–871)	283.9[illegible]78.11 [illegible] (30–1,250)	0.445
Postpartum blood loss, mL ≥500 mL, *n* (%) ≥1,000 mL, *n* (%)	 8 (10.7) 1 (1.3)	 9 (12) 1 (1.3)	 7 (9.3) –	 6 (8) 1 (1.3)	 0.864 1.000
Presence of episiotomy	33 (44)	35 (46.7)	32 [illegible].7)	35 (46.7)	0.948
Presence of tears	15 (20)	22 (29.3)	14 ([illegible])	26 (34.7)	0.075
Presence of atony	–	2 (2.7)	2 (2.7)	–	0.338
Need for additional uterotonics	15 (20)	28 (37.3)	6 (8)	22 (29.3)	<0.001*
Need for blood transfusion	1 (1.3)	4 (5.4)	3 (4)	3 (4)	0.600

Data are expressed as mean ± standard deviation, medi[illegible] (m[illegible]um-maximum), or number (%). *$p < 0.05$ significant difference, comparison of groups. **Comparison of changes in the [illegible]oglobin concentration; group 1 versus group 2 $p = 0.023$, group 1 versus group 3 $p = 0.835$, group 1 versus group 4 $p = 0.00$[illegible] group 2 versus group 3 $p = 0.013$, group 2 versus group 4 $p = 0.401$, group 3 versus group 4 $p < 0.001$. ***Comparison[illegible]anges in the hematocrit concentration; group 1 versus group 2 $p = 0.726$, group 1 versus group 3 $p = 0.180$, group 1 versus grou[illegible] = 0.056, group 2 versus group 3 $p = 0.012$, group 2 versus group 4 $p = 0.439$, group 3 versus group 4 $p < 0.001$.

differences were observed in [illegible]ean blood loss between the four groups (277.[illegible]9 ± 208.1, 294.13 ± 198.64, 274.33 ± 199.5[illegible] and [illegible]3.97 ± 178.11; $p = 0.445$, respectivel[illegible]ig. 1). Furthermore, statistically significant differe[illegible] were not found between the groups in the p[illegible]rtio[illegible] patients with postpartum blood loss of more t[illegible]n [illegible]0 mL or 1,000 mL (Table 2). The needs for ad[illegible]ona[illegible]rotonics were statistically different among the [illegible]ou[illegible]roups ([illegible]0%, 37.3%, 8%, and 29.3%, $p < 0.001$, [illegible]ct[illegible]). When we investigated the subgroup differenc[illegible]e needs for additional uterotonic were statistically higher[illegible] group 2 than group 3 (37.3% vs. 8%, $p < 0.05$) and higher in group 4 than group 3 (29.3% vs. 8%, $p < 0.05$). Other subgroup differences are not statistically significant (Table 2). There was no significant difference between the groups in the rate of episiotomy (44%, 46.7%, 42.7%, and 46.7, respectively; $p = 0.948$), presence of tears (20%, 29.3%, 18.7%, and 34.7%, respectively; $p = 0.075$), atony ($p = 0.338$), and need for blood transfusion (1.3%, 5.4%, 4%, and 4%, respectively; $p = 0.6$) (Table 2). No statistically significant difference was found between the groups in terms of nausea, vomiting, tachycardia, flushing, dizziness, headache, shivering, itching, dyspnea, or palpitation in the side effect profile (Table 3).

In terms of neonatal outcomes, although there was a statistically significant difference between the groups in terms of mean birth weight (3,217.78 ± 352.79, 3,282.49 ± 360.27, 3,175.06 ± 363.26, 3,383.6,±392.08, respectively; $p = 0.004$), there was no significant difference between the groups in terms of the proportion of fetuses born with a birth weight above 90th percentile (20%, 18.7%, 18.8%, 30.7%, respectively; $p =$

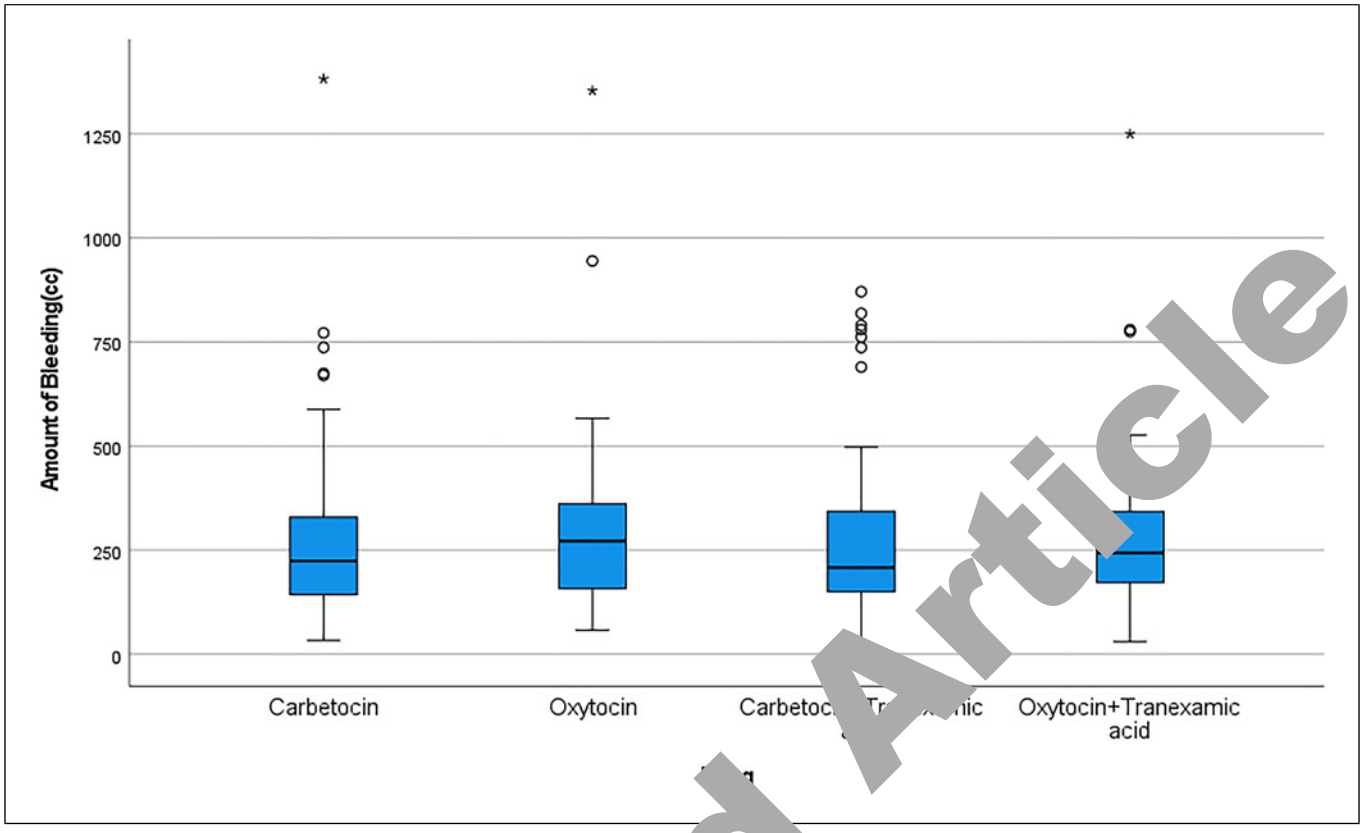

Fig. 2. Amount of bleeding.

Table 3. Adverse events

	Group 1	Group 2	Group 3	Group 4	*p* value
	carbetocin (*n* = 75)	oxy[illegible] (*n* = 75)	carbetocin + tranexamic acid (*n* = 75)	oxytocin + tranexamic acid (*n* = 75)	
Nausea	1 (1.3)	[illegible]	1 (1.3)	2 (2.7)	0.890
Vomiting	1 (1.3)	[illegible]	1 (1.3)	2 (2.7)	0.870
Tachycardia	7 (9.3)	8 ([illegible]0.7)	7 (9.3)	11 (14.7)	0.690
Flushing	1 (1.3)	[illegible]	1 (1.3)	1 (1.3)	1.000
Dizziness	1 ([illegible])	1 (1.3)	2 (2.7)	1 (1.3)	0.890
Headache	1 ([illegible])	2 (2.7)	1 (1.3)	1 (1.3)	0.890
Shivering	2 ([illegible])	1 (1.3)	1 (1.3)	1 (1.3)	0.890
Itching	1 ([illegible])	–	1 (1.3)	1 (1.3)	1.000
Dyspnea	[illegible]	1 (1.3)	1 (1.3)	1 (1.3)	1.000
Palpitations	1 ([illegible])	–	1 (1.3)	–	1.000

[illegible]ta [illegible] expressed as number (%).

0.23[illegible]d the proportion of fetus born with a birth weight above 95 percentile (10.7%, 10.7%, 6.7%, 17.3%, respectively; $p = 0.244$). There was a statistically significant difference between the 1st minute (7.95 ± 0.32, 8.21 ± 0.92, 7.93 ± 0.251, 8.64 ± 0.65, respectively; $p < 0.001$) and the 5th minute (8.97 ± 0.23, 9.41 ± 0.54, 9.08 ± 0.273, 9.8 ± 0.45, respectively; $p < 0.001$). There was no significant difference between the groups in terms of NICU admission rates (Table 4).

Table 4. The neonatal outcomes of the study

Characteristics	Group 1	Group 2	Group 3	Group 4	*p* value
	carbetocin (*n* = 75)	oxytocin (*n* = 75)	carbetocin + tranexamic acid (*n* = 75)	oxytocin + tranexamic acid (*n* = 75)	
Birth weight, g	3,217.78±352.79 3,250 (2,600–3,950)	3,282.49±360.27 3,300 (2,500–3,950)	3,175.06±363.26 3,120 (2,470–3,990)	3,383.6±392.08 3,410 (2,220–3,960)	0.004*
Birth weight, g					
Over 90 percentile (LGA)	15 (20)	14 (18.7)	14 (18.7)	23 (30.7)	[illegible]
Over 95 percentile	8 (10.7)	8 (10.7)	5 (6.7)	13 (17.3)	0.2[illegible]
Apgar score at 1 min	7.95±0.32 8 (6–8)	8.21±0.92 8 (4–10)	7.93±0.251 8 (8–8)	8.64±0.65 9 (6–10)	0.001*
Apgar score at 5 min	8.97±0.23 9 (7–9)	9.41±0.54 9 (8–10)	9.08±0.273 9 (9–9)	[illegible]±0.4 10 [illegible]0)	<0.001*
NICU admission	6 (8)	6 (8)	5 (6.7)	[illegible] (8)	0.986

Data are expressed as mean ± standard deviation, median (minimum-maximum), or nu[illegible]er (%). [illegible] < 0.05 significant difference, comparison of groups.

Discussion

Principal Findings

The main objective of our study was to determine whether any specific protocol, including carbetocin only, oxytocin only, and a combination of carbetocin or oxytocin with TXA, was associated with a decrease in postpartum blood loss at the time of vaginal delivery. The results of our study revealed that the carbetocin-only group might be related to lower decreases in hemoglobin and hematocrit concentration from the preoperative to postoperative assessments at the time of vaginal delivery compared to others because they were significantly lower in the carbetocin-only group. Based on this result, the carbetocin-only regimen is not inferior to carbetocin plus TXA, oxytocin alone, or oxytocin plus TXA. However, a significant clinical difference between the four groups about postpartum blood loss, which is clinically relevant in postpartum hemorrhage, was not demonstrated. Based on the findings of similar blood loss and similar blood transfusion rates, the carbetocin-only regimen seems successful at least carbetocin plus TXA, oxytocin alone, or oxytocin plus TXA to prevent PPH. However, the combination of carbetocin with TXA regimen may decrease the need for additional uterotonic. When we look at the neonatal outcomes, although there was a difference in terms of 1st and 5th min Apgar scores, there was no difference between the groups in terms of the need for a NICU, which can be interpreted as a difference that is not reflected in clinical practice. In addition, no significant difference was found between the groups in terms of side effect profile. In our study, although the third stage of labor was statistically reported to be 2 min longer in the carbetocin group, it still does not meet the criteria for a prolonged third stage and is not a significant difference in terms of clinical practice. When we look at the related literature, we see that Amornpetchaku et al. [13] reached similar results.

In a randomized controlled study by Liu et al. [14] in 2018 comparing two groups administered iv carbetocin versus oxytocin after vaginal delivery in high-risk women, no significant difference was found in terms of postpartum bleeding over 500 mL (29.6% vs. 26.8%, $p = 0.48$) and mean postpartum bleeding amount (422.9 ± 241.4 vs. 406.0 ± 257.5, $p = 0.40$), like our study. In the cohort study of Korb et al. [11] published in 2023, which included 4,832 women who had vaginal deliveries, there was no difference between the oxytocin and carbetocin groups in terms of severe PHH, but the rate of bleeding more than 500 mL was reported to be lower in the carbetocin group (4% vs. 5%; $p = 0.004$). Identical to our study, there was no significant difference between the blood transfusion recipient rates (1.45% vs. 1.36%) ($p = 0.799$). Maged et al. [15] compared the effects of oxytocin and carbetocin on PPH prophylaxis in 200 women and reported that postpartum hemoglobin drop was significantly less in the carbetocin group, like our study (0.55 ± 0.35 g/dL vs. 0.96 ± 0.62 g/dL; $p = 0.001$). In the CHAMPION study of

29,645 women who had vaginal deliveries published by Widmer et al. [16] new information was offered to compare oxytocin and carbetocin. The data demonstrated that carbetocin was not inferior to oxytocin for blood loss of at least 500 mL (risk ratio [RR]: 1.01; 95% CI: 0.95–1.06; $p < 0.001$) or the use of additional uterotonic agents for the prevention of PPH. In this study, there was no significant difference in adverse effects between the oxytocin and carbetocin groups. Additionally, in a Cochrane review, three prophylactic regimes were more effective at preventing PPH than oxytocin (ergometrine plus oxytocin RR: 0.69 [95% CI: 0.57–0.83], carbetocin RR: 0.72 [95% CI: 0.52–1.00], misoprostol + oxytocin RR: 0.73 [95% CI 0.60–0.90]). 10.5% of women receiving oxytocin had a PPH 500 mL, compared to 7.2% of women receiving ergometrine plus oxytocin, 7.6% of women receiving carbetocin, and 7.7% of women receiving misoprostol plus oxytocin [15]. Similarly, our study results showed that carbetocin was more successful than oxytocin for postpartum hemorrhage prophylaxis.

If we look at the studies on TXA, it has been reported to reduce maternal mortality in the treatment of PPH [17]. However, in the 2018 TRAAP study on the benefit of prophylaxis, it could not be shown to reduce the rate of PPH compared to placebo [18]. In our study, no significant difference was found between the carbetocin-only group and the carbetocin + TXA group in terms of postpartum hemoglobin decrease.

Clinical Implications

According to our knowledge, our study wi[illegible]he first study to compare the additive effect of [illegible]beto[illegible] and TXA combination with carbetocin [illegible]one [illegible]nd other groups. We reported that adding TXA [illegible]ro[illegible]ylaxis did not perform better than the ca[illegible]in [illegible]one group in terms of postpartum bleeding [illegible]ar[illegible]s.

Research Implications

Carbetocin is [illegible]g-l[illegible]g oxytocin analog than oxytocin. In additi[illegible]mpared to oxytocin, carbetocin is thermostable. O[illegible]ocin[illegible]bility to heat has been shown to be a signi[illegible]ar[illegible]concern, particularly in settings with limit[illegible]eso[illegible]s [illegible]. Carbetocin is considerably more co[illegible]y t[illegible]n oxyt[illegible]in, and cost-effectiveness analyses are [illegible]ir[illegible]

Str[illegible]ns and Limitations

Our study is the first randomized controlled trial on the subject in terms of combined treatments. Although the relatively low sample size provides statistical power, its reproducibility should be demonstrated with new studies with higher sample sizes. Future studies should investigate the effects of carbetocin on PPH with larger samples and cohorts in different risk groups with different outcomes. We hope it will contribute to the accumulating literature for PPH prophylaxis after vaginal delivery and shed light on future studies.

Conclusions

In conclusion, our findings su[illegible]est th[illegible]t carbetocin may not be inferior to oxyt[illegible]in a[illegible]oxy[illegible]in plus TXA regimens regarding PPH pr[illegible]ylax[illegible]ter vaginal delivery with similar bloo[illegible]ss [illegible]similar blood transfusion rates.

Statem[illegible]f Ethics

The Institu[illegible]a[illegible]w Board approved the study with a study number of 04.0[illegible]22-E.69157 from Bezmialem Vakif University. A[illegible]patients in t[illegible]study signed a written informed consent form b[illegible]inclusion. A clinical registration with trial number N[illegible]67462 was submitted.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors (C.C., F.B.T., E.H., A.G., O.P., and P.O.) read, revised, and approved the final manuscript and contributed to the design of the study. C.C., F.B.T., and E.H. made an essential effort in the acquisition of the patient data. O.P., A.G., and P.O. analyzed and all authors interpreted the data. C.C. prepared this manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this manuscript. Further inquiries can be directed to the corresponding author.

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