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Title:

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Authors:

Elbohoty AEH, Mohammed WE, Sweed M, Eldin AMB, Nabhan A and Abd-El-Maeboud KHI

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CLINICAL ARTICLE

Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery

Ahmed E.H. Elbohoty, Walid E. Mohammed, Mohamed Sweed*, Ahmed M. Bahaa Eldin, Ashraf Nabhan, Karim H.I. Abd-El-Maeboud

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Abbasia, Cairo, Egypt

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ABSTRACT

Objective: To compare the effectiveness and safety of carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following cesarean deliveries. **Methods:** A double-blind randomized controlled trial enrolled patients with a singleton pregnancy scheduled for an elective cesarean delivery at a maternity hospital in Cairo, Egypt, between October 1, 2012 and June 30, 2013. Participants were randomized using a computer-generated sequence to receive treatment with carbetocin, misoprostol, or oxytocin. The primary outcome was the occurrence of uterine atony necessitating additional uterotonic. Per-protocol analyses were performed. Patients, investigators, and data analysts were masked to treatment assignments. **Results:** The present study enrolled 263 patients; data were analyzed from 88 patients treated with carbetocin, 89 treated with misoprostol, and 86 women treated with oxytocin. Further uterotonics were needed for the treatment of 5 (6%) patients who were treated with carbetocin, 20 (22%) patients treated with misoprostol, and 11 (13%) patients treated with oxytocin. In the prevention of uterine atony, carbetocin was comparable with oxytocin (RR 0.41, 95%CI 0.14–1.25) and superior to misoprostol (RR 0.21, 95%CI 0.07–0.58). **Conclusion:** Additional uterotonics were needed less frequently by patients treated with carbetocin. Carbetocin was comparable to oxytocin and superior to misoprostol in the prevention of uterine atony following an elective cesarean delivery.

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1. Introduction

Globally, cesarean delivery is one of the most common major operations that women undergo, and the cesarean delivery rate is increasing worldwide [1]. Postpartum hemorrhage (PPH) following cesarean delivery is a significant problem and a major cause of maternal mortality [2]. WHO defines PPH as blood loss of at least 500 mL within 24 hours of delivery [3].

Patients benefit from reductions in operative blood loss during cesarean delivery through decreased postoperative morbidity and reduced exposure to the risks associated with blood transfusions [4]. The commonest cause of hemorrhage during delivery is uterine atony; consequently, it has generally been agreed that, during delivery, active management of the third stage of labor is preferable to expectant management [5]. Active management of third stage of labor includes controlled cord traction for the expulsion of the placenta during a cesarean delivery and the administration of intramuscular or intravenous oxytocin [3].

Oxytocin is the uterotonic agent that is most widely used and has the greatest availability [6]. Oxytocin has a rapid onset of action, a good safety profile, and has been shown to decrease the incidence of PPH by 40% [7]. Nevertheless, oxytocin has a short half-life (4–10 minutes), necessitating continuous intravenous infusion. Moreover, saturation of myometrial oxytocin receptors could reduce its effectiveness, and excessive dosing can lead to coronary-artery contraction and hypotension; additionally water intoxication can occur owing to its anti-diuretic effects [6].

Alternative treatments have been investigated, including prostaglandins, such as misoprostol, and oxytocin agonists, such as carbetocin [8]. Misoprostol is a prostaglandin E₁ analogue with strong uterotonic properties and has been suggested as an alternative to injectable uterotonic agents for preventing PPH [9]. It is cheap, heat stable, and can be administered through multiple routes; however, it is known to be less effective than oxytocin in preventing PPH [10]. In low-resource settings, patients can be at risk of PPH if oxytocin is stored in suboptimal conditions unless there is a readily available alternative, such as misoprostol [10,11].

Carbetocin, a long-acting oxytocin analogue, has been reported to decrease the need for additional uterotonics during cesarean deliveries compared with oxytocin [12]. A 100- μ g dose of carbetocin has been recommended for preventing PPH [6]. Carbetocin has been recommended for PPH prevention following elective cesarean deliveries [13]. An

* Corresponding author at: 4 Hosni Osman st., El-Sefarat, Nasr City, Cairo, Egypt.
Tel.: +20 100 122 2047; fax: +20 022 434 6058.

E-mail address: dmsweed@med.asu.edu.eg (M. Sweed).

advantage of carbetocin over oxytocin is that, owing to its long half-life, it is administered as a single intravenous dose, while oxytocin requires repeated administration or continuous infusion over several hours, with variations in doses [2].

The aim of the present study was to evaluate the effectiveness and side effects of carbetocin, misoprostol, and oxytocin in the prevention of PPH in patients undergoing elective cesarean deliveries.

2. Materials and methods

The present prospective randomized double-blind trial was conducted at Ain-Shams University Maternity Hospital, Cairo, Egypt, between October 1, 2012 and June 30, 2013. Patients attending the prenatal clinic at Ain-Shams University Maternity Hospital who were scheduled to undergo an elective cesarean delivery were considered for enrollment. Patients were eligible if they had a singleton pregnancy that had reached full term (duration of pregnancy ≥ 37 weeks). The exclusion criteria included hypersensitivity to oxytocin, carbetocin, or prostaglandins; contraindication to treatment with prostaglandins (e.g. glaucoma); history of significant heart disease; severe asthma; epilepsy; history or evidence of liver, renal, or vascular disease; history of coagulopathy, thrombocytopenia, or anticoagulant therapy; HELLP syndrome or eclampsia; placental abruption; or contraindication to spinal anesthesia (carbetocin is licensed for use with regional anesthesia only). Approval for the study protocol was obtained from the ethical committee of the department of Obstetrics and Gynecology at Ain-Shams University and written informed consent was obtained from all participants.

Patients fulfilling the recruitment criteria were randomly assigned to treatment with carbetocin, misoprostol, or oxytocin using MedCalc version 13.2.2 (MedCalc Software, Ostend, Belgium). Randomization was performed in a 1:1:1 ratio using a computer-generated sequence. Numbered, sealed envelopes were prepared, with each envelope containing one of the three study drugs and placebos for the other two drugs. Tablet placebos, containing hydrogenated castor oil, hypromellose, microcrystalline cellulose, and sodium starch glycolate were prepared to be identical in size, color, shape, and packing to the tablet study drug. Intravenous placebo ampoules containing normal saline were prepared and were identical in shape and packing to the intravenous study drugs used. All envelopes were prepared by Sigma Pharmaceuticals and were already sealed when received by the research team. An envelope was allocated to each patient using the computer-generated sequence. The randomization protocol was concealed from the research team and the primary investigator contacted a central coordinating investigator to identify the envelope to be distributed to each patient. Consequently, patients, investigators, and data analysts were masked to group assignments and unmasking only occurred after data analysis was completed.

Prior to cesarean delivery, the amniotic fluid index (AFI) was estimated using abdominal ultrasonography on the day of delivery or the day before delivery. The uterus was divided into four quadrants; the right and left quadrants were defined by the linea nigra, and the upper and lower quadrants were defined by the umbilicus. The maximum vertical diameter of amniotic fluid in each quadrant was measured in centimeters. The sum of these four quadrants was used to calculate the AFI [14]. The volume of amniotic fluid in mL was estimated by multiplying the AFI by 30 [15]. Hemoglobin concentrations and hematocrit values were obtained for each patient before cesarean delivery.

Lower segment cesarean deliveries were performed under spinal anesthesia by a senior registrar who had previously performed at least 300 cesarean delivery procedures. The placenta was removed by cord traction and uterine compression. The uterus was exteriorized and compressed during closure. Closure was achieved using continuous unlocked Vicryl 0 sutures (Ethicon, Somerville, NJ, USA) in two layers. Peritoneum and muscle layers were not closed, and the sheath was closed using the same suture material.

Patients in the carbetocin group were treated with a single 1-mL ampoule of carbetocin (100 $\mu\text{g}/\text{mL}$) (Pabal; Draxis/Multipharma, Egypt) added to 10 cm^3 saline that was administered intravenously following the delivery of the neonate [3]. Patients assigned to the misoprostol group received two sublingual misoprostol tablets (each tablet 200 μg) (Misotac; Sigma Pharmaceuticals, Egypt) following the cesarean delivery [4]. Patients who received oxytocin therapy received a single 1-mL ampoule of oxytocin (10 IU/mL) (Syntocinon; Novartis Pharma, Berne, Switzerland) added to 10 cm^3 saline that was administered slowly intravenously following neonatal delivery; additionally, these patients received 20 IU oxytocin added to 500 mL saline administered as an intravenous infusion over 4 hours [3]. Patients in each group also received placebos of the other treatment modalities that were administered according to the same method of the other study drugs.

Additional uterotonics (intravenous oxytocin 10 IU or other ecbolics) were administered if uterine atony was detected through physical examination by the senior registrar and the presence of continuous postpartum bleeding.

Surgical towels were weighed with their wrapping before and after delivery using a highly accurate digital balance. The difference in mass between the dry and soaked towels was calculated. Operative blood loss was calculated using three parameters: (A) the volume of the suction bottle contents (mL), (B) the difference in towel mass (g), and (C) the amniotic fluid volume (mL). Intraoperative blood loss (mL) was calculated as:

$$\text{Intraoperative blood loss} = (A + B) - C [15].$$

Postpartum blood loss during the first 24 hours after delivery was measured by weighing used wound dressings after 24 hours and subtracting the dry weight of the pads. A 100-g increase in mass was considered equivalent to 100 mL of blood or amniotic fluid. The hemoglobin level was tested in the laboratory of the study institution by obtaining a complete blood analysis 24 hours after delivery. Any complications occurring during the postoperative period were recorded.

The primary outcome was the occurrence of uterine atony requiring the use of additional uterotonics. Secondary outcome measures included total blood loss, the difference in hemoglobin level before and 24 hours after delivery, and the development of any adverse events. Details of adverse events were obtained through verbal interviews with patients and through observations made by caregivers and the attending registrar.

A minimum sample size of 241 participants was calculated using PAS 11 (NCSS, Kaysville, Utah, USA) to provide a test significance of 0.05 and a power of 0.8. The target study group size was set at 90 patients in each study arm to account for withdrawals and other patient exclusions.

Data were analyzed on a per-protocol basis using SPSS version 21 (IBM, Armonk, NY, USA) and MedCalc version 12.5 (MedCalc Software, Ostend, Belgium). Comparisons were made between the three groups with an analysis of variance test, Kruskal–Wallis test, or χ^2 test, as appropriate. Relative risks with 95% confidence intervals were calculated to compare the risks of developing uterine atony or developing PPH between the three treatment groups. Results were reported as mean \pm SD or number (percentage) and $P < 0.05$ was considered statistically significant.

3. Results

In total, 324 patients were considered for inclusion and were 270 enrolled in the present study (90 in each treatment arm). In the carbetocin treatment arm, two patients were excluded after receiving general anesthesia; one patient was excluded from the misoprostol arm after accidentally breaking a drug ampoule and four patients were excluded from the oxytocin treatment arm (two patients received general anesthesia and two accidentally broke drug ampoules) (Fig. 1). No

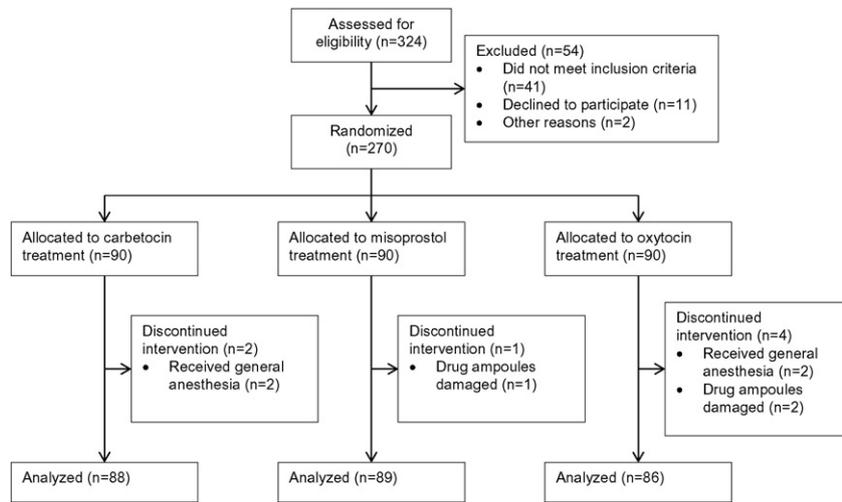


Fig. 1. Flow of participants through the study.

significant differences in patient demographic data were recorded between the three groups (Table 1). Recognizable risk factors for PPH were recorded in 220 patients (83.6%); the most common risk factors were anemia, previous cesarean delivery, multiple pregnancy, polyhydramnios, and macrosomia.

The use of additional uterotonics was lowest in the carbetocin group ($P = 0.004$) (Table 2). The relative risk of needing additional uterotonics was lower among patients treated with carbetocin compared with patients treated with misoprostol ($P = 0.003$). No significant difference was observed in the relative risk of needing additional uterotonics between patients in the carbetocin and oxytocin groups ($P = 0.114$), and between the patients in the misoprostol and oxytocin groups ($P = 0.097$) (Table 3). The calculated effect size for use of additional uterotonics was 0.198. The power of the study with this effect size, in a sample of 270 patients with an alpha level of 0.05, was calculated to be 82.5%.

No significant difference was observed between the three groups in the total blood loss ($P = 0.054$), although higher blood loss was noted in patients treated with misoprostol. The relative risk of developing PPH was significantly lower in the carbetocin group when compared with both the misoprostol and oxytocin groups (Table 3). The incidence of blood loss of 500–1000 mL and >1000 mL were highest in the patients treated with misoprostol (both $P = 0.001$); the misoprostol treatment group also demonstrated the greatest decrease in hemoglobin levels following delivery ($P = 0.001$). One patient in the oxytocin group required further surgical intervention in the form of the application of B-Lynch compression sutures to control PPH due to uterine atony; the same patient required a blood transfusion. A patient in the misoprostol

group required a blood transfusion but did not require any further surgical intervention (Table 2).

The incidence of heat sensation, metallic taste, fever, and shivering were all highest in the misoprostol group; the incidence of abdominal pain was highest in the carbetocin group (Table 4).

4. Discussion

The present study demonstrated significantly lower rates of using additional uterotonics following cesarean deliveries in patients treated with carbetocin compared with patients treated with misoprostol or oxytocin; the relative risk of needing additional uterotonics was comparable between the carbetocin and oxytocin treatment arms, and was lower in the carbetocin treatment arm than in the misoprostol arm. The frequency of patients experiencing postpartum blood loss of 500–1000 mL and >1000 mL was significantly lower among carbetocin-treated patients compared with the misoprostol-treated and oxytocin-treated patients. Misoprostol use was associated with greater decreases in hemoglobin levels compared with the other drugs.

Choices in postpartum uterotonics are influenced primarily by the effectiveness of drugs; however many additional factors should be considered, including potential adverse events and, particularly in low-resource settings, cost-effectiveness. Oxytocin has been considered the first-line drug for the prophylaxis of PPH owing to its effectiveness and favorable adverse-effect profile [16]. The present study investigated different uterotonics for the prevention of PPH following elective cesarean deliveries in a low-resource setting. The alternatives to oxytocin included

Table 1
Patient characteristics.^a

Variable	Carbetocin-treated patients (n = 88)	Misoprostol-treated patients (n = 89)	Oxytocin-treated patients (n = 86)	P value
Age, y	28.0 ± 5.5	27.9 ± 5.2	27.7 ± 5.5	0.922 ^b
Weight, kg	86.0 ± 13.3	85.3 ± 13.3	84.2 ± 11.2	0.633 ^b
BMI	33.0 ± 5.2	32.8 ± 5.4	32.2 ± 4.3	0.541 ^b
Duration of pregnancy at enrollment, wk	38.4 ± 0.8	38.4 ± 0.8	38.3 ± 0.8	0.639 ^b
Gravidity	3 (1–8)	3 (1–9)	3 (1–7)	0.973 ^c
Parity	1 (0–5)	1 (0–6)	1 (0–6)	0.988 ^c
PPH risk factors present	70 (80)	77 (87)	73 (85)	0.424 ^d

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); PPH, postpartum hemorrhage.

^a Values are given as mean ± SD, median (interquartile range), or number (percentage), unless indicated otherwise.

^b Analysis of variance test.

^c Kruskal–Wallis test.

^d χ^2 test.

Table 2
Postpartum outcomes.^a

Outcome measure	Carbetocin-treated patients (n = 88)	Misoprostol-treated patients (n = 89)	Oxytocin-treated patients (n = 86)	P value
Blood loss, mL	437 (168–1194)	583 (178–1184)	439 (188–1079)	0.054 ^b
Bleeding of 500–1000 mL	18 (20)	42 (47)	29 (34)	0.001 ^c
Bleeding > 1000 mL	3 (3)	7 (8)	5 (6)	0.001 ^c
Hemoglobin decrease, g/dL	6.0 (3.0–16.0)	10.0 (–3.0 to 19.0)	7.0 (–3.0 to 16.0)	0.001 ^b
Additional uterotonics	5 (6)	20 (22)	11 (13)	0.004 ^c
Blood transfusion	0	1 (1)	1 (1)	NA ^d
Additional surgical interventions	0	0	1 (1)	NA ^d

Abbreviation: NA, not applicable.

^a Values are given as median (range) or number (percentage), unless indicated otherwise.^b Kruskal–Wallis test.^c χ^2 test.^d No P value was calculated owing to the very low incidence.

in the present study were one highly cost-effective drug (misoprostol) and a long acting single-dose oxytocin agonist (carbetocin).

In the authors' experience, oxytocin and misoprostol are the most commonly used uterotonics in Egypt especially, in rural areas, while carbetocin is a relatively new alternative in this setting. To the best of our knowledge, this is the first trial to compare these three agents. A recent Egyptian study [17] that enrolled 380 patients compared combination sublingual misoprostol and oxytocin infusion with intravenous carbetocin in the prevention of PPH during cesarean delivery in high-risk patients. The authors concluded that combined misoprostol–oxytocin was as effective as intravenous carbetocin in reducing the need for additional uterotonics [17].

In the present study, oxytocin was more effective than misoprostol in reducing blood loss during cesarean delivery and in reducing the need for postoperative uterotonics; additionally, adverse effects were found to be more common with misoprostol than with oxytocin. A recent systematic review [18] that compared sublingual misoprostol with placebo or oxytocin for reducing PPH reviewed data from 72 trials including a total of 52 678 patients. Generally, sublingual misoprostol was more effective than placebo in reducing blood loss following delivery; however, misoprostol was no better than conventional injectable uterotonics, especially in low-risk study populations [18].

Additionally, this systematic review [18] included only 11 studies that specifically investigated cesarean deliveries and these trials tested misoprostol alone or combined with oxytocin against oxytocin alone.

Some studies have demonstrate misoprostol 400–600- μ g to be as effective as oxytocin [4,15,19], and a combination of misoprostol 200 μ g with oxytocin has been demonstrated to reduce blood loss and the need for additional uterotonics [20,21]. A Chinese study [22] reported that a 600- μ g dose of misoprostol was superior to oxytocin in the prevention of postpartum bleeding. Another systematic review [9], which examined the use of prophylactic misoprostol during cesarean deliveries, included data from 17 studies (3174 patients). Generally, when compared to oxytocin, misoprostol alone did not demonstrate any significant improvements in the prevention of intra- and postoperative hemorrhage [9]; however, combination misoprostol–oxytocin

was more effective than oxytocin alone in reducing intra- and postoperative hemorrhage during cesarean deliveries [9]. Other trials and reviews have examined the effectiveness of misoprostol during vaginal deliveries. Varying results have been reported; however, misoprostol has not been found to be superior to oxytocin in reducing postpartum blood loss and the use of additional uterotonics in general [23,24].

Carbetocin is a recent innovation in the prevention of PPH [5]. Carbetocin is currently approved for the prevention of uterine atony after cesarean delivery under spinal or epidural anesthesia in 23 countries [5]. Carbetocin is characterized by a longer duration of action than oxytocin and has been demonstrated, in many studies [5,25], to have few adverse effects. Few studies are available that have compared carbetocin and oxytocin. A systematic review of 11 studies [5] included four studies that compared carbetocin (100 μ g administered intravenously) with oxytocin in patients undergoing a cesarean delivery. In comparison with oxytocin, carbetocin demonstrated a statistically significant reduction in the use of additional uterotonics. However, no statistically significant difference was reported between carbetocin and oxytocin in terms of the risk of patients experiencing PPH (500–1000-mL blood loss) or severe PPH (>1000-mL blood loss) [5]. One study has found carbetocin to be as effective as a combination of misoprostol plus oxytocin in the reduction of PPH and the use of additional uterotonics [17]. To the best of our knowledge, no other studies have compared carbetocin with misoprostol and few clinical trials have been registered with this as an explicit aim.

In the present study, a lower relative risk of experiencing PPH was demonstrated for carbetocin treatment in comparison with oxytocin but there was no significant difference between the two in the relative risk of developing uterine atony. Carbetocin was demonstrated to be superior to misoprostol in preventing both PPH and uterine atony. Consequently, it is suggested that carbetocin can be considered a superior choice to misoprostol and oxytocin. Moreover, carbetocin demonstrated a lower incidence of several common adverse effects, including abdominal pain due to uterine contractions. Additionally, carbetocin has a long duration of action, producing rhythmic uterine contractions for 60 minutes following intravenous administration [6].

Table 3
Relative risk of developing uterine atony and PPH.

Variable	Regression coefficient	Standard error	P value	Relative risk (95% confidence interval)
Risk of developing uterine atony				
Carbetocin vs oxytocin	–0.890	0.562	0.114	0.41 (0.14–1.25)
Misoprostol vs oxytocin	0.681	0.411	0.097	1.98 (0.88–4.42)
Carbetocin vs misoprostol	–1.571	0.526	0.003	0.21 (0.07–0.58)
Risk of developing PPH (\geq 500 mL)				
Carbetocin vs oxytocin	–0.735	0.333	0.027	0.48 (0.25–0.92)
Misoprostol vs oxytocin	0.628	0.307	0.041	1.87 (1.03–3.42)
Carbetocin vs misoprostol	–1.363	0.329	<0.001	0.26 (0.13–0.49)

Abbreviation: PPH, postpartum hemorrhage.

Table 4
Adverse events.^a

Adverse event	Carbetocin-treated patients (n = 88)	Misoprostol-treated patients (n = 89)	Oxytocin-treated patients (n = 86)	P value ^b
Headache	20 (23)	24 (27)	24 (28)	0.706
Heat sensation	14 (16)	34 (38)	17 (20)	0.001
Abdominal pain	72 (82)	47 (53)	44 (51)	<0.001
Palpitations	17 (19)	24 (27)	44 (51)	<0.001
Metallic taste	5 (6)	14 (16)	2 (2)	0.003
Fever	12 (14)	31 (35)	12 (14)	<0.001
Shivering	8 (9)	28 (31)	16 (19)	0.001
Nausea	12 (14)	12 (13)	12 (14)	0.996
Vomiting	6 (7)	9 (10)	7 (8)	0.728
Pruritus	4 (5)	4 (4)	2 (2)	0.779

^a Values are given as number (percentage) unless indicated otherwise.

^b χ^2 test.

One limitation of the present study was comparing carbetocin and oxytocin to misoprostol without including a combination of misoprostol plus oxytocin as a comparator. Combining both drugs could have produced comparable effects to carbetocin alone and could be a good low-cost alternative to carbetocin, which is expensive, in low-resource settings like Egypt.

In conclusion, carbetocin appears to be an attractive alternative to compared to oxytocin and misoprostol for the prevention of atonic PPH following cesarean delivery.

Conflict of interest

The authors have no conflicts of interest.

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