

# The efficacy of three regimes of uterotonic agents for prevention of postpartum blood loss at undergoing cesarean section: a prospective randomized clinical trial

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## ABSTRACT

**Objectives:** To compare the efficacy of three regimes of uterotonic agents on PPH in women undergoing cesarean section in our RCT.

**Material and methods:** This study was a randomized controlled study (NCT05083910) performed at the Bezmialem Vakif University between July 2021 and January 2022. All women were randomly allocated into three groups: Group I (n = 52) — oxytocin only; Group II (n = 52) — the combination of oxytocin plus intrauterine misoprostol; Group III (n = 52) — carbetocin only. The primary outcome measures were: PPH to evaluate with the change between the concentrations of preoperative and postoperative hemoglobin, hematocrit and intraoperative blood loss.

**Results:** The blood loss characteristics, including the change in hemoglobin and the change in hematocrit concentration, intraoperative blood loss, intraoperative additional hemostatic uterine sutures and the need for additional uterotonics, were lowest in group III, although all groups were comparable in terms of blood loss parameters. Group III had the highest blood loss ratio, exceeding 1000 mL. For the combination of oxytocin and intrauterine misoprostol, the ARR was 3.8% (95% CI 20.02–12.33), with a RR of 1.18 (95% CI 0.58–2.39) and a NNT of 26 (95% CI 8.1–4.9); for carbetocin, the ARR was 5.8% (95% CI 22.15–10.61), with a RR of 1.27 (95% CI 0.63–2.53) and a NNT of 17 (95% CI 9.41–4.51).

**Conclusions:** Our results demonstrate that carbetocin shows no superiority in the prevention of PPH in women undergoing cesarean section. Oxytocin still seems to be a highly effective alternative to prevent PPH.

**Keywords:** postpartum hemorrhage; oxytocin; uterotonic agents

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## INTRODUCTION

Postpartum hemorrhage (PPH) is a serious but rare condition when a woman has heavy bleeding after giving birth. This is a prominent factor contributing to maternal morbidity and mortality on a global scale [1].

Various modern technological (e.g., intrauterine balloon tamponade, interventional radiological procedures) and pharmacological (e.g., anti-fibrinolytic agents, recombinant factor VIIa) advancements have been made in the management of postpartum hemorrhage (PPH). Nevertheless, the

primary focus remains on preventing PPH through active management of the third stage of labor. This involves routinely administering uterotonic agents to enhance uterine contractions, reducing maternal morbidity and mortality [2–4].

Indeed, recent guidelines suggested the routine preventive administration of uterotonic agents during the third stage of labour for all births, regardless of the route of delivery, to reduce the incidence of PPH: the Royal College of Obstetricians and Gynaecologists guidelines recommend

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5 IU of slow intravenous oxytocin injection; the World Health Organization recommend 10 IU of oxytocin injection (IU, IV/IM); French guidelines recommend 5 or 10 IU of oxytocin (IV or IM) [5–7].

In the past few decades, many studies have focused on improving the preventive regimes of uterotonic agents for PPH. Oxytocin (produced in the hypothalamus), misoprostol (a prostaglandin E1 analogue) and carbetocin (a synthetic long-acting oxytocin analogue) are the most popular uterotonic agents to have been evaluated in studies, in terms of their effectiveness in preventing PPH.

As the first-line prophylactic drug, oxytocin is still recommended to prevent PPH; however, there is currently no consensus in the literature for the optimal dose and infusion rate of oxytocin. A single 100 µg dose of intravenous carbetocin can provide a prolonged uterine contraction of up to an hour, while carbetocin has a longer half-life than oxytocin (41 min), which gives it an advantage [8, 9].

The efficacy of vaginal or rectal misoprostol has also been demonstrated in the prevention of PPH [10].

Moreover, it can be administrated by the sublingual route after rectal or vaginal administration. Some studies have assessed the effectiveness of intrauterine misoprostol in preventing postpartum hemorrhage (PPH) in women undergoing cesarean section (CS) [11, 12].

Our randomized controlled trial aimed to assess whether there were any distinctions among the three regimens of uterotonic agents concerning the primary outcome of postpartum hemorrhage occurring in women who have undergone a cesarean section.

## MATERIAL AND METHODS

### Participants

This study was a randomized controlled study (NCT05083910) performed at the Department of Obstetrics and Gynaecology of Medical Faculty of Bezmialem Vakif University between July 2021 and January 2022. The study received approval from the Ethical Committee of the Medical Faculty at Bezmialem Vakif University. (Ethic No: 20.05.2021-E.16677). All patients provided written informed consent for participation in the study. The inclusion criteria consisted of (1) women between 18–40 years old, (2) a caesarean section under spinal anaesthesia, (3) term single pregnancy, and (4) an American Society of Anesthesiology physical status of I or II. A total of 156 women were included in our study. The study was designed and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Fig. 1).

The exclusion criteria consisted of emergency surgeries due to placental pathologies, including previa or abruptia, multiple pregnancies, women with a previous history of several medical problems, such as moderate to severe hy-

pertension, preeclampsia diabetes mellitus, and any blood or thrombophilia disorders, a history of previous major abdominal surgeries and anticoagulation therapy. Data were collected relating to age, body mass index (BMI), gravida, parity, indication of CS, gestational age at birth, Apgar scores at 1 and 5 min, birth weight, neonatal intensive care unit (NICU) admission, blood loss parameters, including intraoperative blood loss as described in our previous study [13]. Intraoperative measurement of blood loss during cesarean section was done by combining the volume of the suction bottle containing blood-soaked sponges. During the procedure, two suction bottles were employed. The second suction was explicitly employed to collect the amniotic fluid at the incision of the amniotic sac. To calculate the blood loss accurately, the amniotic fluid volume in the second suction bottle was excluded from each case.

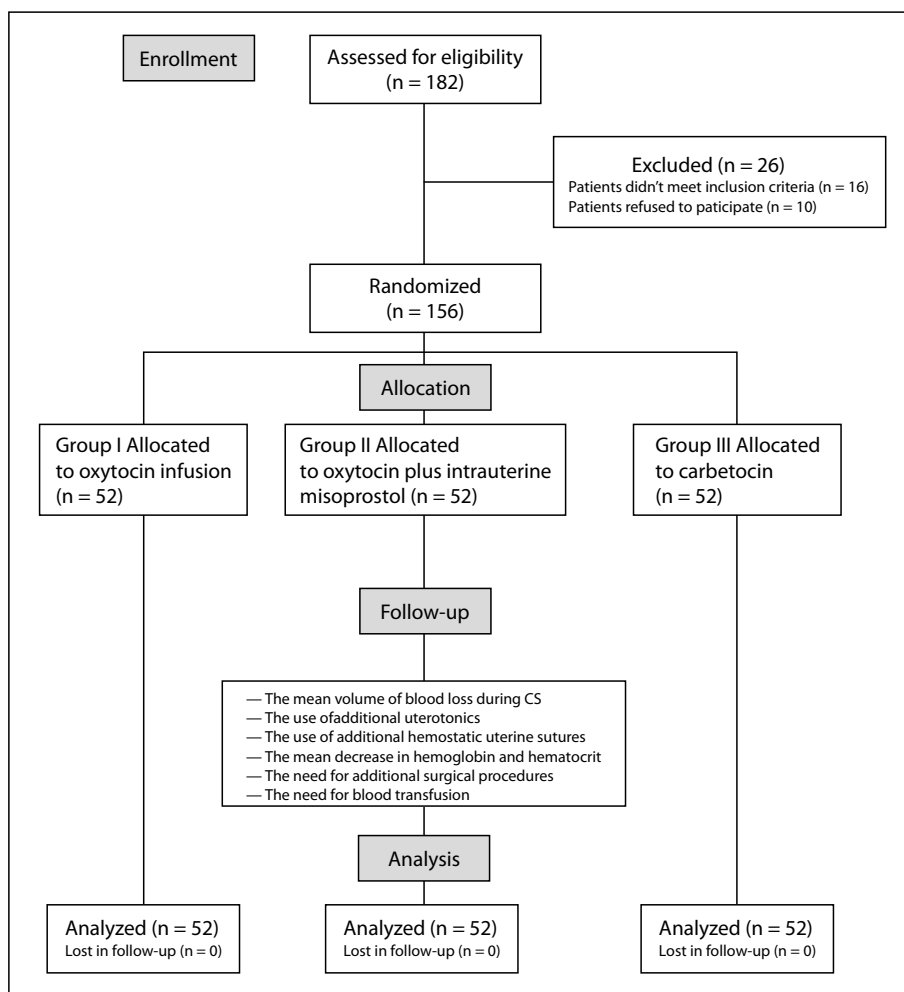
The same surgeons evaluated uterine tone in all cases, by palpating the uterine fundus (Pinar Özcan and Çağlar Çetin). Postpartum hemorrhage was diagnosed when the total blood loss reached 1000 mL or more or when there was evidence of blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after delivery, including any intrapartum loss. The primary outcome measures were: PPH to evaluate with the change between the concentrations of preoperative and postoperative hemoglobin and hematocrit and intraoperative blood loss. The secondary outcomes were additional number of intraoperative hemostatic uterine sutures, operating time, the requirement for extra uterotonics, and the necessity for blood transfusion.

### Interventions in groups

All participants were randomly assigned to one of three groups using a computer-based randomization number program (Fig. 1). Group I (n = 52) — oxytocin only (Synpitan forte®; Deva Pharma, İstanbul, Türkiye) (following the clamping of the umbilical cord, oxytocin was infused at a rate of 125 mL/h as 20 IU dissolved in 500 mL of normal 0.9% NaCl); Group II (n = 52) — the combination of oxytocin plus intrauterine misoprostol (Cytotec®; ARIS, İstanbul, Türkiye) (the oxytocin infusion was infused as previously described, and a 400 mg misoprostol tablet was inserted into the uterine cavity, at the fundal surface, after delivery of the placenta); Group III (n = 52) — carbetocin only (Pabal; Ferring Pharma, İstanbul, Türkiye) (immediately after delivery of the baby, 100 mg carbetocin was intravenously administered). Two surgeons (Pinar Özcan and Çağlar Çetin) performed all the surgeries.

### Statistical analysis

When we take the difference in the variable “Reduction in hemoglobin” between the two groups as 0.74 (with a standard deviation of 1.39) with a 95% confidence level



**Figure 1.** Study flowchart; CS — cesarean section

and 80% test power, we should include a minimum of 52 people in each group [12]. Variables were presented as mean ± standard deviation, number or percentage. The Pearson chi-square test and Fisher’s exact test were used to compare categorical variables. Distribution of variables were tested by the Shapiro–Wilk test and histogram. For normally distributed variables, the Student t test was used to compare two independent groups in terms of the means. For non-normally distributed variables, the Mann-Whitney U test was used to compare two independent groups in terms of the means. The relative risk (RR), the relative risk reduction (RRR), the absolute risk reduction (ARR) and the number needed to treat (NNT) were calculated. In all cases,  $p < 0.05$  was considered significant. All data were analysed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 182 patients were initially enrolled in the study. However, 26 women were excluded from the study before

randomization for various reasons: 16 did not meet the inclusion criteria, and 10 declined to participate. As a result, the analysis was performed on data from 156 women divided equally into three groups: 52 patients in Group I, 52 in Group II, and 52 in Group III. No patients were excluded after randomization. The flowchart of our study and the patient requirements are presented in Figure 1. The baseline demographic and obstetric characteristics of the patients in all groups are presented in Table 1. No statistically significant differences were observed among the groups concerning BMI, age, gestational age at birth, gravida, parity, and the indication for cesarean section.

The comparison of primary outcomes; intra-operative, post-operative and hemorrhage characteristics between groups are presented in Table 2. The blood loss characteristics, including the change in hemoglobin and the change in hematocrit concentration, intraoperative blood loss, intraoperative additional hemostatic uterine sutures and the requirement for additional uterotonics, were lowest in

**Table 1. Baseline obstetric and demographic characteristics of groups**

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
Age [years]	30.37 ± 4.87	31.94 ± 5.01	32.29 ± 5.78	0.15
Body mass index [kg/m <sup>2</sup> ]	29.28 ± 4.24	31.24 ± 6.29	29.59 ± 4.56	0.24
Gravida	2.17 ± 1.26	2.04 ± 1.02	2.12 ± 1.33	0.9
Parity	0.75 ± 0.9	0.6 ± 0.77	0.79 ± 1.14	0.65
Gestational age at birth [day]	268.67 ± 7.83	269.13 ± 6.8	269.56 ± 7.65	0.83
<b>Indication of CS</b>				
Previous CS	50% (26)	42.3% (22)	40.4% (21)	0.33
Fetal Distress	19.2% (10)	11.5% (6)	7.7% (4)	
Malpresentation	9.6% (5)	9.6% (5)	19.2% (10)	
Macrosomia	3.8% (2)	5.8% (3)	5.8% (3)	
Failure to progress	0% (0)	9.6% (5)	5.8% (3)	
Others	17.3% (9)	21.2% (11)	21.2% (11)	

Values are reported as mean ± standard deviation; p < 0.05, statistically significant difference; CS — cesarean section

**Table 2. Comparison of operative characteristics, hemorrhage and post-operative characteristics between groups**

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
The pre-operative hemoglobin concentration [g/dL]	11.81 ± 1.24	12.05 ± 1.29	11.9 ± 1.21	0.600
The pre-operative hematocrit concentration [%]	35.60 ± 3.63	36.25 ± 3.4	35.94 ± 3.3	0.630
The changing of the hemoglobin concentration [g/dL]	1.05 ± 0.93	1.08 ± 0.89	0.97 ± 0.88	0.640
The changing of the hematocrit concentration [%]	3.33 ± 3.41	3.13 ± 2.78	2.9 ± 2.89	0.590
Operating time [min]	49.65 ± 17.05	46.00 ± 12.14	44.13 ± 12.71	0.120
Intraoperative blood loss [mL]	721.96 ± 370.06	810.60 ± 556.18	755.52 ± 533.3	0.840
Intraoperative additional hemostatic uterine sutures	9.6% (5)	15.4% (8)	19.2% (10)	0.379
Need for additional uterotonics	21.2% (11)	28.8% (15)	11.5% (6)	0.090
Need for blood transfusion	0% (0)	1.9% (1)	0% (0)	1

Values are reported as mean ± standard deviation; p < 0.05, statistically significant difference

group III, although all groups were comparable in terms of blood loss parameters. According to these parameters, a trend towards decreased intraoperative hemorrhage was observed in group III. However, 21.1% (11) of Group I, 25% (13) of Group II and 26.9% (14) of Group III had blood loss > 1000 mL, while all groups were similar in terms of blood loss (p = 0.78). Group III exhibited the highest proportion of blood loss exceeding 1000 mL. In Group III, only one case necessitated additional surgical intervention, specifically uterine artery ligation, due to intraoperative bleeding. In contrast, only one case in Group II required a blood transfusion. 13 (25%) in Group II and 14 (26.9%) in Group III have PPH while 11 (21.2%) in the control group have PPH (p = 0.6 and p = 0.4, respectively). For the combination of Oxytocin and intrauterine misoprostol, The ARR was 3.8% (95% CI: 20.02–12.33) with RR of 1.18 (95% CI: 0.58–2.39) and NNT 26 (95% CI: 8.1–4.9) and for carbetocin, The ARR was 5.8%

(95% CI: 22.15–10.61) with RR of 1.27 (95% CI: 0.63–2.53) and NNT 17 (95% CI: 9.41–4.51) (Tab. 4).

No drug adverse effects were observed in any of the groups, and there were no major postoperative complications in any of the groups. The neonatal outcomes of the groups are shown in Table 3. All three groups showed comparable Apgar scores at 1 and 5 minutes after birth, and there were no significant differences in neonatal intensive care unit (NICU) admissions among the groups.

## DISCUSSION

Researchers have generally focused on determining the best choice of either pharmacological or non-pharmacological interventions by achieving favourable uterine contractions during CS, because of the significance of PPH in terms of its mortality and morbidity. Every evaluation of the choices, in terms of efficacy, potential adverse events

**Table 3. The neonatal outcomes of the study**

Characteristics	Group I (n = 52)	Group II (n = 52)	Group III (n = 52)	p value
Birth weight [g]	3203.37 ± 606.56	3308.65 ± 405.44	3235.87 ± 522.45	0.341
Apgar score at 1 minute	7.9 ± 0.95	7.85 ± 1.22	8.06 ± 1.14	0.390
Apgar score at 5 minute	9.33 ± 0.61	9.35 ± 0.81	9.48 ± 0.72	0.290
NICU admission	11.5% (6)	71.9% (1)	3.8% (2)	0.084

Values are reported as mean ± standard deviation; p < 0.05, statistically significant difference; NICU — neonatal intensive care unit

**Table 4. Incidence of postpartum hemorrhage**

Variables	Group II (n = 52)	Group III (n = 52)
Postpartum hemorrhage	13	14
Relative risk (RR)	1.18 (0.58–2.39)	1.27 (0.63–2.53)
Relative risk reduction (RRR)	18.2% (139.2–41.6%)	27.3% (153.7–36.19%)
Absolute risk reduction (ARR)	3.8% (20.02–12.33%)	5.8% (22.15–10.61%)
Number needed to treat (NNT)	26 (8.1–4.9)	17 (9.41–4.51)
p value	0.642	0.491

and cost-effectiveness, should be beneficial for the management and prevention of PPH. Possible agents used for the prophylaxis of PPH include tranexamic acid, oxytocin, methylergometrine, misoprostol and carbetocin. Oxytocin is the primary choice of uterotonic medication for preventing and treating uterine atony. Methylergonovine remains the secondary option for uterotonic treatment in preventing and managing PPH [14]. Methylergonovine is a synthetic alkaloid that induces powerful contractions of the myometrium. However, when administered parenterally, especially intravenously, it may lead to transient but significant elevation in blood pressure [15]. In our randomized controlled trial, we focused on the efficacy and potential adverse events of the three most used pharmacological uterotonics (oxytocin, misoprostol, which is highly cost-effective, and carbetocin, which is long acting and single dose) in women who underwent caesarean section, although oxytocin has routinely been suggested as the primary treatment option for the prevention of PPH, because of its efficacy and safety profile.

Oxytocin and the combination of oxytocin plus misoprostol are generally the two most used uterotonic agents in Türkiye. In the daily routine practice of our department, oxytocin is prophylactically used during CS to prevent PPH, as recommended. When an additional uterotonic is needed, we generally use misoprostol as the second agent. Carbetocin seems to be more expensive in Türkiye, compared to oxytocin and misoprostol. Thus, we would like to especially focus on the efficacy of carbetocin, to establish whether it has any superiority over the other drugs for the prevention

of PPH. Our results demonstrated that carbetocin has no overall advantage on other alternatives regarding prevention of PPH. Contrary to the literature, we did not report any severe adverse effects related to misoprostol, because we used intrauterine misoprostol, whereas other studies generally used sublingual misoprostol tablets. According to our results, the combination of misoprostol and oxytocin is no more effective than oxytocin alone.

A double-blind randomized controlled study including 263 women evaluated the efficacy and safety of oxytocin, misoprostol and carbetocin for the prevention of PPH. Their results demonstrated that carbetocin was similar to oxytocin (RR 0.41, 95% CI: 0.14–1.25) and superior to misoprostol (RR 0.21, 95% CI: 0.07–0.58) in terms of the prevention of uterine atony during elective CS. Moreover, the requirement for extra uterotonics was found to be less in the carbetocin group when compared to the other groups. They also showed that the ratio of adverse effects, such as abdominal pain resulting from uterine contractions, were lower with carbetocin. In this study, the misoprostol was used as a sublingual 400 µg misoprostol tablet following the caesarean delivery [16].

The results from misoprostol may be due to the use of sublingual tablets, as well as the use of misoprostol alone, as another trial including 380 women concluded that the combination of misoprostol with oxytocin was as effective as IV carbetocin [17].

The latter trial evaluated the prevention of PPH using a combination of oxytocin infusion and sublingual misoprostol versus IV carbetocin in high-risk women undergoing caesarean delivery. Another randomized controlled trial

including 300 women compared the use of the combination of oxytocin and intrauterine misoprostol versus oxytocin alone in terms of the incidence of PPH in women undergoing elective CS. Their results indicated that the combination of 400 µg intrauterine misoprostol tablets with oxytocin is safe and effective for the prevention of PPH in elective CS delivery (ARR 5.3%, 95% CI: 0.8–10.6, with RR 0.20, 95% CI: 0.05–0.90; 95% CI: 125–9, NNT 19) [12].

There was a trend towards the use of intrauterine misoprostol to prevent PPH after the publication by Quiroga Díaz et al. [11]. They reported good efficacy of intrauterine misoprostol (800 µg), with few adverse events in the prevention of PPH. A systematic review and meta-analysis including 17 studies (3174 women) assessed the efficacy and safety of use of prophylactic misoprostol to reduce blood loss during either intraoperative or postoperative haemorrhage in women undergoing CS, concluding that the combination of misoprostol with oxytocin appears to be more effective than oxytocin alone, based on a few trials with methodological limitations. It also reported a higher risk of pyrexia and shivering in women who receive misoprostol alone or the combination of misoprostol and oxytocin [18].

A double-blind, randomised, single-centre study including 114 women who underwent non-elective CS under general anaesthetic compared the efficacy of carbetocin versus oxytocin [19].

Their results showed no significant differences regarding the change of haemoglobin concentration, estimated blood loss, the rates of PPH and blood transfusions. Based on this, they concluded that the efficacy of oxytocin and carbetocin is similar for haemoglobin drop, estimated blood loss, additional uterotonics and blood transfusions. They also showed that there was a trend towards the need for additional uterotonics in the carbetocin group, although this was not statistically significant. Finally, they concluded that carbetocin showed no superiority to oxytocin. Furthermore, a double-blinded RCT, which included 180 obese nulliparous women undergoing emergency CS, evaluated the efficacy and safety of carbetocin versus oxytocin to prevent PPH. They showed that carbetocin is more effective than oxytocin, with a similar safety profile, in the prevention of PPH while maintaining adequate uterine contractility in obese nulliparous women undergoing emergency CS [20]. A meta-analysis including seven studies involving 2012 women compared the efficacy of oxytocin and carbetocin to prevent PPH in CS [21]. According to the results of this meta-analysis, the use of carbetocin results in a significant reduction in PPH ( $p < 0.009$ , RR 0.79, 95% CI: 0.66–0.94), in the need for additional uterotonics ( $p < 0.001$ , RR 0.57, 95% CI: 0.49–0.65) and in the need for transfusion ( $p < 0.002$ , RR 0.31, 95% CI: 0.15–0.64) when compared to oxytocin.

They concluded that carbetocin is effective in reducing PPH, the need for transfusion and the need for additional uterotonics during CS. Meanwhile, they suggested a locoregional cost-effectiveness analysis before adopting carbetocin in routine prophylaxis, because of the disparity between the cost of oxytocin and the cost of carbetocin. A multicentre, double-blind, RCT from Canada including 694 patients undergoing elective CS assessed the efficacy of carbetocin with oxytocin to prevent uterine atony [22].

They demonstrated that carbetocin appears to be more effective when compared to continuous IV oxytocin infusion and has a similar safety profile.

One limitation of the present study is that there is no group involving misoprostol alone. This is because we would not prophylactically use misoprostol alone to prevent PPH in our department. If we had used misoprostol alone, carbetocin may have been superior, whereas the combination of both drugs (oxytocin and misoprostol) may have produced a comparable effect to the carbetocin. The strength of our study is that it is a RCT with power calculations. Additionally, there are no other current studies comparing carbetocin and intrauterine misoprostol.

## CONCLUSIONS

In conclusion, our findings indicate that carbetocin does not exhibit superiority in preventing postpartum hemorrhage in women undergoing cesarean section. Furthermore, a notable difference exists in the cost between oxytocin and carbetocin. Considering its efficacy, affordability, and favorable safety profile, oxytocin remains a highly effective option for preventing postpartum hemorrhage. We recommend maintaining the routine use of oxytocin in cesarean section procedures until substantial evidence of carbetocin's superiority over oxytocin is established. Oxytocin should remain the preferred option until such proof is demonstrated conclusively.

## Article information and declarations

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Ethics

This study was a prospective, randomized, controlled study (NCT05083910) conducted at the Department of Obstetrics and Gynaecology of Medical Faculty of Bezmialem Vakif University between July 2021 and January 2022.

### Conflict of interest

The authors declare that they have no conflict of interest.



## REFERENCES

- Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014; 2(6): e323–e333, doi: [10.1016/S2214-109X\(14\)70227-X](https://doi.org/10.1016/S2214-109X(14)70227-X), indexed in Pubmed: [25103301](https://pubmed.ncbi.nlm.nih.gov/25103301/).
- Wang CY, Chen YC, Lin CH, et al. Successful treatment with recombinant blood factor VIIa in severe postpartum hemorrhage-induced disseminated intravascular coagulation. *Taiwan J Obstet Gynecol*. 2016; 55(2): 301–302, doi: [10.1016/j.tjog.2014.11.027](https://doi.org/10.1016/j.tjog.2014.11.027), indexed in Pubmed: [27125421](https://pubmed.ncbi.nlm.nih.gov/27125421/).
- Alkış İ, Karaman E, Han A, et al. The fertility sparing management of postpartum hemorrhage: A series of 47 cases of Bakri balloon tamponade. *Taiwan J Obstet Gynecol*. 2015; 54(3): 232–235, doi: [10.1016/j.tjog.2014.03.009](https://doi.org/10.1016/j.tjog.2014.03.009), indexed in Pubmed: [26166332](https://pubmed.ncbi.nlm.nih.gov/26166332/).
- Purwosunu Y, Sarkoen W, Arulkumar S, et al. Control of Postpartum Hemorrhage Using Vacuum-Induced Uterine Tamponade. *Obstet Gynecol*. 2016; 128(1): 33–36, doi: [10.1097/AOG.0000000000001473](https://doi.org/10.1097/AOG.0000000000001473), indexed in Pubmed: [27275795](https://pubmed.ncbi.nlm.nih.gov/27275795/).
- World Health Organization WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva (Switzerland), 2012.
- Mavrides E, Allard S, Chandraran E, et al. Prevention and management of postpartum haemorrhage: Green-top Guideline No 52. *BJOG*. 2016; 358: 106–149.
- Sentilhes L, Vayssière C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol*. 2016; 198: 12–21, doi: [10.1016/j.ejogrb.2015.12.012](https://doi.org/10.1016/j.ejogrb.2015.12.012), indexed in Pubmed: [26773243](https://pubmed.ncbi.nlm.nih.gov/26773243/).
- Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. *Eur J Obstet Gynecol Reprod Biol*. 2009; 147(1): 15–20, doi: [10.1016/j.ejogrb.2009.06.018](https://doi.org/10.1016/j.ejogrb.2009.06.018), indexed in Pubmed: [19616358](https://pubmed.ncbi.nlm.nih.gov/19616358/).
- Leduc D, Senikas V, Lalonde AB, et al. CLINICAL PRACTICE OBSTETRICS COMMITTEE. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. *J Obstet Gynaecol Can*. 2009; 31(10): 980–993, doi: [10.1016/S1701-2163\(16\)34329-8](https://doi.org/10.1016/S1701-2163(16)34329-8), indexed in Pubmed: [19941729](https://pubmed.ncbi.nlm.nih.gov/19941729/).
- Hofmeyr GJ, Gülmezoglu AM. Misoprostol for the prevention and treatment of postpartum haemorrhage. *Best Pract Res Clin Obstet Gynaecol*. 2008; 22(6): 1025–1041, doi: [10.1016/j.bpobgyn.2008.08.005](https://doi.org/10.1016/j.bpobgyn.2008.08.005), indexed in Pubmed: [18786863](https://pubmed.ncbi.nlm.nih.gov/18786863/).
- Quiroga DR, Cantú MR, Tello GHE, et al. Misoprostol intrauterino para la prevención de la hemorragia postcesárea [Intrauterine misoprostol for the prevention of bleeding cesarean]. *Ginecol Obstet Mex*. 2009; 77(10): 469–474.
- Alalfy M, Lasheen Y, Elshenoufy H, et al. The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial. *J Matern Fetal Neonatal Med*. 2020; 33(9): 1459–1465, doi: [10.1080/14767058.2018.1519796](https://doi.org/10.1080/14767058.2018.1519796), indexed in Pubmed: [30176758](https://pubmed.ncbi.nlm.nih.gov/30176758/).
- Takmaz T, Özcan P, Sevkett O, et al. Less Blood Loss by Earlier Oxytocin Infusion in Cesarean Sections? A Randomized Controlled Trial. *Z Geburtshilfe Neonatol*. 2020; 224(5): 275–280, doi: [10.1055/a-1108-2017](https://doi.org/10.1055/a-1108-2017), indexed in Pubmed: [32120445](https://pubmed.ncbi.nlm.nih.gov/32120445/).
- Manrique Muñoz S, Munar Bauzá F, Francés González S, et al. [Update on the use of uterotonic agents]. *Rev Esp Anestesiol Reanim*. 2012; 59(2): 91–97, doi: [10.1016/j.redar.2012.02.019](https://doi.org/10.1016/j.redar.2012.02.019), indexed in Pubmed: [22480555](https://pubmed.ncbi.nlm.nih.gov/22480555/).
- Moertl MG, Friedrich S, Kraschl J, et al. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. *BJOG*. 2011; 118(11): 1349–1356, doi: [10.1111/j.1471-0528.2011.03022.x](https://doi.org/10.1111/j.1471-0528.2011.03022.x), indexed in Pubmed: [21668768](https://pubmed.ncbi.nlm.nih.gov/21668768/).
- Elboholy AEH, Mohammed WE, Sweed M, et al. Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery. *Int J Gynaecol Obstet*. 2016; 134(3): 324–328, doi: [10.1016/j.ijgo.2016.01.025](https://doi.org/10.1016/j.ijgo.2016.01.025), indexed in Pubmed: [27350226](https://pubmed.ncbi.nlm.nih.gov/27350226/).
- Elgafor el Sharkwy IA. Carbetocin versus sublingual misoprostol plus oxytocin infusion for prevention of postpartum hemorrhage at cesarean section in patients with risk factors: a randomized, open trail study. *Arch Gynecol Obstet*. 2013; 288(6): 1231–1236, doi: [10.1007/s00404-013-2896-7](https://doi.org/10.1007/s00404-013-2896-7), indexed in Pubmed: [23689739](https://pubmed.ncbi.nlm.nih.gov/23689739/).
- Conde-Agudelo A, Nieto A, Rosas-Bermudez A, et al. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2013; 209(1): 40.e1–40.e17, doi: [10.1016/j.ajog.2013.03.015](https://doi.org/10.1016/j.ajog.2013.03.015), indexed in Pubmed: [23507545](https://pubmed.ncbi.nlm.nih.gov/23507545/).
- Whigham CA, Gorelik A, Loughnan TE, et al. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial (J). *J Matern Fetal Neonatal Med*. 2016; 29(23): 3866–3869, doi: [10.3109/14767058.2016.1149564](https://doi.org/10.3109/14767058.2016.1149564), indexed in Pubmed: [26940081](https://pubmed.ncbi.nlm.nih.gov/26940081/).
- El Behery MM, El Sayed GA, El Hameed AA, et al. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. *J Matern Fetal Neonatal Med*. 2016; 29(8): 1257–1260, doi: [10.3109/14767058.2015.1043882](https://doi.org/10.3109/14767058.2015.1043882), indexed in Pubmed: [25946576](https://pubmed.ncbi.nlm.nih.gov/25946576/).
- Voon HY, Suharjono HN, Shafie AA, et al. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage: A meta-analysis of randomized controlled trials in cesarean deliveries. *Taiwan J Obstet Gynecol*. 2018; 57(3): 332–339, doi: [10.1016/j.tjog.2018.04.002](https://doi.org/10.1016/j.tjog.2018.04.002), indexed in Pubmed: [29880160](https://pubmed.ncbi.nlm.nih.gov/29880160/).
- Dansereau J, Joshi AK, Helewa ME, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol*. 1999; 180(3 Pt 1): 670–676, doi: [10.1016/S0002-9378\(99\)70271-1](https://doi.org/10.1016/S0002-9378(99)70271-1), indexed in Pubmed: [10076146](https://pubmed.ncbi.nlm.nih.gov/10076146/).