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Adjuvant Intravenous Tranexamic Acid Increases the Efficacy of Sublingual Misoprostol Compared with Carbetocin to Reduce the Amount of Blood loss During Cesarean Delivery: A Randomized Clinical Trial

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ABSTRACT

Background & Objective: To determine the safety and adequacy of intravenous (IV) carbetocin compared to IV tranexamic acid (TA) plus sublingual misoprostol in reducing hemorrhage during and following cesarean delivery (CD) in women with at least one risk factor for postpartum hemorrhage.

Materials & Methods: This clinical study was randomized. We randomly assigned 400 term pregnant women who were candidates for elective CD to receive either a 100 µg intravenous infusion of carbetocin or 1gm. IV TA along with 400 µg of sublingual misoprostol after delivery. Comparing the quantity of blood loss at and six hours following a CD was the primary result. We also disclosed the necessity for any extra medications and any adverse drug reactions.

Results: When compared to the misoprostol plus tranexamic acid group, the carbetocin group's total mean blood loss was considerably higher (829.7 293.3 mL vs. 609.33 211.5 mL; P = 0.0001). Following the administration of carbetocin and misoprostol with TA, respectively, 9.5% and 26.5% of patients required further uterotonics treatment (P = 0.0001). When compared to the carbetocin group, the misoprostol group's side effects, such as a bad taste in the mouth and fever, were much greater (P = 0.0001).

Conclusion: When it comes to minimizing overall blood loss during and after CD, IV tranexamic acid combined with sublingual misoprostol is superior to IV carbetocin.

Keywords: Carbetocin, Misoprostol, Postpartum hemorrhage, Tranexamic acid

Introduction

Despite major advancements in obstetric care, Postpartum hemorrhage (PPH) continues to be the most common complication seen in about one-fifth of cases and is associated with about one-quarter of maternal deaths globally, leading to increased maternal morbidity and mortality **(1)**. Primary PPH is estimated to occur in 2–6% of all births worldwide **(2-4)**.

To prevent PPH and its morbidity or mortality, various types of medications, such as oxytocin, misoprostol, and tranexamic acid, may be administered to a parturient. The gold-standard medication for PPH prophylaxis is oxytocin **(2)**.

However, oxytocin is not the perfect agent because of its short half-life of 4–10 min. The latent phase lasts two to five minutes when administered intramuscularly, however, the uterine activity can last two to three hours. Oxytocin, on the other hand, cannot be taken orally. It necessitates the use of a cold chain for storage and transportation. It should not be administered as a large bolus intravenously because it can cause severe hypotension. It might not be suitable, particularly for vulnerable individuals with preeclampsia, heart conditions, or protracted labor **(5)**.

Misoprostol taken sublingually is easier to give and less expensive than an oxytocin infusion. Additionally, it probably suits the lady better because it removes the limitations that an infusion line places on her. It is thermostable and works when administered orally, buccally, sublingually, vaginally, or rectally **(6)**.

TA is an inexpensive, readily accessible medication that has been demonstrated to lessen bleeding during surgery and lower the risk of mortality in patients with bleeding injuries **(7)**. It follows that the interest in its function in preventing PPH is not surprising **(8)**.

Carbetocin has been linked to a lower need for further uterotonic medications and a significant decrease in PPH incidence following CD when compared to oxytocin **(1, 9)**.

To reduce blood loss after CD in women with risk factors for PPH, the current study evaluates the effectiveness of TA with sublingual misoprostol and IV carbetocin.

Methods

We conducted a randomized study at the Obstetrics unit, Faculty of Medicine, Aswan University, Aswan, Egypt, from September 2019 to June 2022. On clinicaltrials.gov, we formally reported the study. (NCT03710317), for which we obtained ethical approval from the scientific departmental committee (Aswu/353/3/19). All women who were willing to participate signed informed written consent after receiving an in-depth explanation of the study medications, possible side effects, and complications.

Patients who had elective CD and had one or more of the following were eligible to participate: twin pregnancy, polyhydramnios, grand multipara, atonic PPH in the past, large fetus (over 4 kg), and maternal anemia (>7 g/dL hemoglobin).

We excluded women with the following conditions: patients with cardiac diseases, preeclampsia, renal, hepatic, or thromboembolic diseases, patients with placenta previa or accreta, and patients who had an allergy to the study medications. 470 patients were approached for participation; 70 were turned away, 45 did not match the requirements, and 25 declined. The research thus covered the remaining 400 patients. Prior to the abdomen ultrasound examination, all participants got thorough history, general, and obstetric exams. Weight, height, and preoperative hemoglobin levels were also completed for each participant (Figure 1).

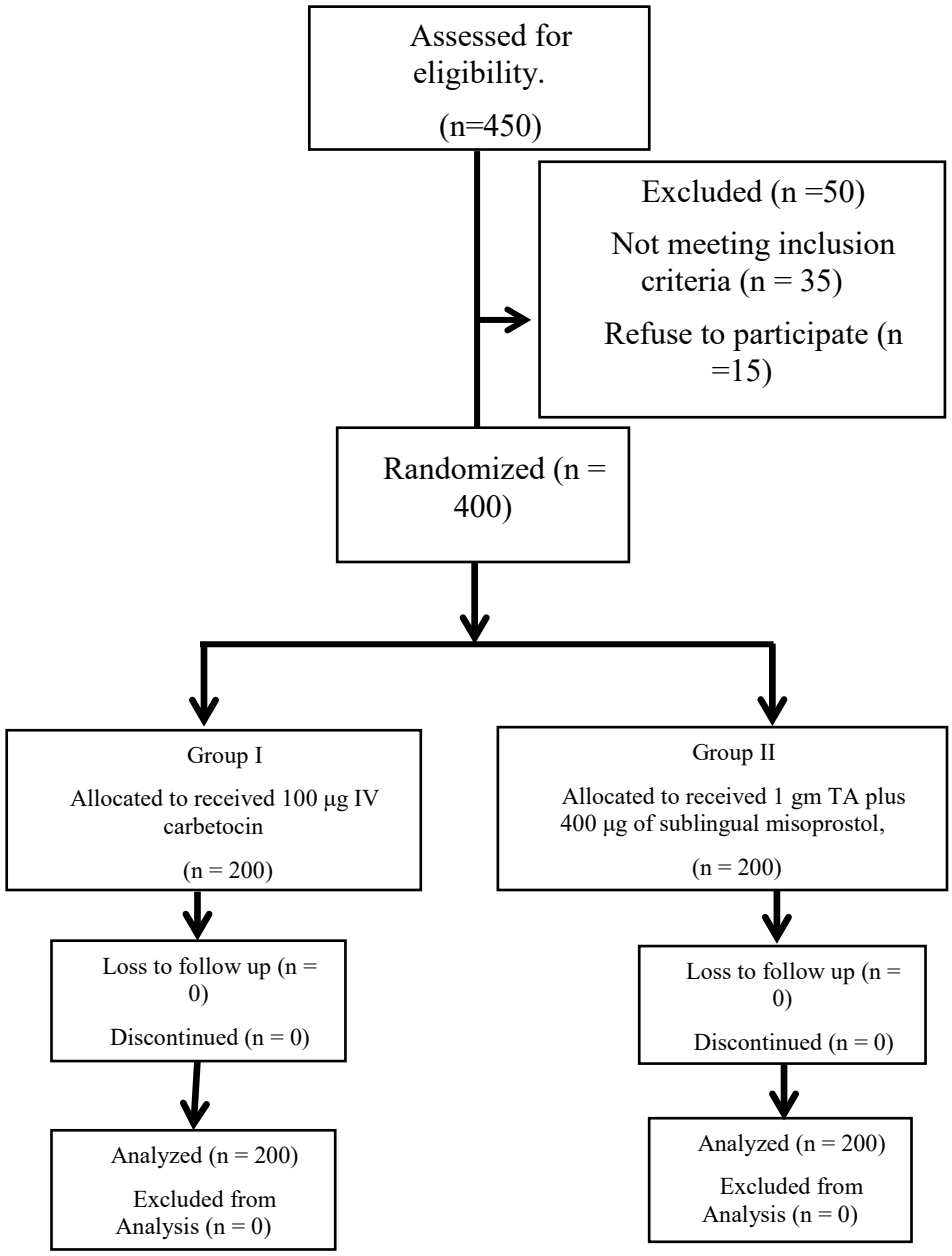

Figure 1. Consort flowchart showing enrollment of participants

A table of randomly produced integers by a computer was used to assign participants to carbetocin and TA plus buccal misoprostol groups in a 1:1 ratio. The allocation sequence was created by a medical chemist who did not participate in carrying out the intervention or reviewing the results. The computerized randomization list was prepared by a statistician who was only indirectly involved in the trial and kept the key for group allocation hidden from the investigators until the study was completed. The experimental medications were created by a medicinal chemist, who administered them in sequentially opened, opaque packages that were serially numbered and sealed before anesthetic induction, with the group allocation sequence kept secret.

All researchers, operators, outcomes evaluators, and anesthetists were kept in the dark about the participants' allocation until the trial's conclusion.

CD was performed by two members of our study team, both of whom were obstetrician consultants with at least 10 years of relevant experience.

Following the onset of spinal anesthesia and the delivery of the infant, eligible patients were randomly assigned to each of the two teams.

The carbetocin cohort (group 1) got 100 µg of IV carbetocin immediately following the delivery, along with a placebo to sublingual misoprostol in the form of two ranitidine tablets, and a placebo to TA (110 normal saline) by slow injection at a rate of roughly 1 mL per minute.

Group 2 received 1 g of TA (10 ml) in 100 ml of saline infusion by slow injection at an approximately 1 mL per minute rate, along with 400 µg of sublingual misoprostol, as well as a placebo to carbetocin.

After delivering the placenta, the surgical obstetrician assessed the womb tonality on a 5-point Likert scale (0 floppies, 4 rock hard) and then every 5 minutes until abdominal closure started. If the uterine tone was insufficient or the CD became hemorrhagic, further oxytocic treatment was administered.

Intraoperative blood loss was calculated using the weight (in grams) difference between the dry and soaked operating room linens and towels (1 gram = 1 ml). The calculation of post-operative blood loss by vaginal blood loss during the first six hours after CD was done using the weight (in grams) differential between the dry and saturated vaginal pads (1 gram = 1 ml). After that, the sum of intraoperative and postoperative blood loss was calculated **(10, 11)**.

Estimating blood loss during and after a CD served as the main goal. The secondary outcome indicators included the need for any extra oxytocic medications, postoperative hemoglobin concentration, the frequency of postpartum hemorrhage, operating time, and the frequency of side effects (unpleasant taste, fever, shivering, nausea, vomiting, and diarrhea). The sample size was determined to support the first outcome (blood loss in women following CD), with a mean blood loss of 663 mL and a usual deviation of 225 mL for the use of carbetocin (**12**). If TA with buccal misoprostol is more effective than oxytocin at lowering blood loss by 125 mL, 200 individuals in each group will have > 85 percent power to detect such a difference at a 5% significance level (Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

We used SPSS software, version 20 (IBM, USA) to examine the data. The proper means (SD) or medians were used to characterize quantitative data. The Kolmogorov-Smirnov test was used to determine their normalcy. Using an independent sample t-test, groups were compared within the normally distributed variables. For group comparisons within the non-normally distributed variables, the Mann-Whitney test was applied. To compare the groups, a Chi-square test was utilized. Odds ratios were computed along with their 95% confidence interval. It was statistically significant if the "P-value" was 0.05.

Results

There was no discernible difference between the two groups in terms of age, weight, height, BMI, parity, gestational age, beginning hemoglobin, or CD indication (Table 1).

When compared to the carbetocin group, the TA with sublingual misoprostol group significantly reduced intraoperative bleeding, postoperative blood loss, and total estimated blood loss (P=0.0001) (Table2).

The incidence of the need for additional uterotonics decreased significantly. TA plus buccal misoprostol group, 19 (9.5%) patients compared to the carbetocin group, 53 (26.5%) patients. (P=0.0001)

Additionally, there was a significantly lower incidence of PPH in the 13 (6.5%) patients in the TA + buccal misoprostol group compared to the 36 (18%) patients in the carbetocin group (P 0.0001). The number of patients who required further surgical treatment also decreased significantly in the TA plus buccal misoprostol group, from 23 (11.5%) to four (2%), respectively (P 0.0001). Additionally, 19 (9.5%) patients in the TA + buccal misoprostol group required a blood transfusion less frequently than the 37 (18.5%) patients in the carbetocin group (P = 0.0001). Post-operative hemoglobin, however, did not significantly differ between the two groups (P=0.0844).

There was no discernible difference between the two groups regarding the difference in operative time (P = 0.122) or the duration of hospitalization (P =0.186).

Finally, we found that the risk of pharmaceutical side effects, such as disagreeable taste and fever, was considerably greater in the group receiving TA with buccal misoprostol, where there were 18 (9%), 22 (11%) patients, as opposed to two (1%), eight (4%), in the group receiving carbetocin (P=0.0001, 0.008).

Regarding nausea, vomiting, or diarrhea, there was no discernible difference between the two groups (P= 0.948, 1.000, and 1.000, respectively) (Table 3).

Table 1. Preoperative Characteristics of pregnant women in the study groups

Parameters	Group I (n = 200)	Group II (n = 200)	Significance
Age (year)	30.4 ± 4.9	31.03 ± 5.1	0.122
Weight (kg)	69.97 ± 6.79	69.8 ± 7.41	0.847
Height (cm)	163.18 ± 4.16	163.06 ± 4.23	0.866
BMI	26.08 ± 2.02	26.21 ± 2.2	0.874
Birth weight (grams)	3621.71 ± 650	3496.32 ± 742	0.637
Parity (median) (Minimum – maximum)	2 (0 – 6)	2 (0 – 6)	0.476
Gestational age (weeks)	38.5 ± 1.02	38.41 ± 1.2	0.813
Anemia	48(24)	46(23)	0.750
Polyhydramnios	33(16.5)	31(15.5)	0.891
Initial Hemoglobin	10.66 ± 0.78	10.65 ± 0.72	0.655
indication of CD (%)			
repeated cs	93(46.5)	95(47.5)	
breech	33(16.5)	32(16)	
twin	23(11.5)	25(12.5)	0.988
macrosomia	24(12)	23(11.5)	
patient request	27(13.5)	25(12.5)	

BMI (body mass index), CS (Cesarean Delivery),
 # Variables are presented as mean and standard deviation, median (minimum – maximum) and number (percentage).
Macrosomia =baby more than 4 kilogram

Table 2. Primary outcomes in the study groups: -

Blood loss	Group I (n = 200)	Group II (n = 200)	Significance
Intraoperative	665.5 ± 272.2	465.58 ± 191	0.0001*
postoperative	165.83 ± 36.59	143.75 ± 33.33	0.0001*
Total blood loss	829.7 ± 293.3	609.33 ± 211.5	0.0001*

*** Statistically Significant Difference**
 # Variables are presented as mean and standard deviation.

Table 3. operative and postoperative outcome in the study groups: -

Variables	Group I (n = 200)	Group II (n = 200)	Significance
Post hemoglobin	9.74 ± 0.64	9.75 ± 0.69	0.844
Operative time	78.21 ± 19.18	74.46 ± 17.1	0.122
Hospital stays	4.25 ± 0.6	4.25 ± 0.57	0.186
Post-partum hemorrhage (%)	36 (18)	13 (6.5)	0.0001*
Need Blood Transfusion (%)	37 (18.5)	14(7)	0.004*
Additional Uterotonics (%)	53(26.5)	19(9.5)	0.0001*
Extra surgical intervention (%)	23 (11.5)	4 (2)	
Uterine artery ligation	13(16.6)	3 (1.5)	0.0001*
b-lynch suture	10(5)	1(0.5)	

Variables	Group I (n = 200)	Group II (n = 200)	Significance
unpleasant taste **fever**	18(9%) 22(11%)	2(1) 8(4)	0.0001* 0.008*
Nausea (%)	14 (7.7)	13 (6.6)	0.948
Vomiting (%)	6 (3.3)	7(3.3)	1.000
Diarrhea (%)	9(3.3)	0 (3.3)	1.000

***Statistically Significant Difference # Variables are presented as mean and standard deviation and number (percentage).**
Post-partum hemorrhage= blood loss more than 1000 ml
Additional Uterotonics =ergonovine and 15-methyl prostaglandin $F_{2\alpha}$.

Discussion

The goal of this study was to compare the efficacy of intravenous carbetocin against intravenous TA plus sublingual misoprostol in minimizing blood loss in CD-affected pregnant women. According to our research, the combination of sublingual misoprostol with intravenous TA significantly reduced intraoperative and overall blood loss, CD-related blood transfusions, postpartum hemorrhage incidence, and the requirement for further uterotonics. Additionally, no occurrences of lung embolism or deep vein thrombosis were identified.

The degrees of plasminogen activators increased half an hour after the start of surgery, according to previous studies **(7)**. As a result, the speculative foundation might clarify the predicted effectiveness of TA for lowering loss for surgical operations with specific concern for CD and may be used as misoprostol in decreasing loss of blood during CD, especially in instances when oxytocin is not accessible.

By preventing plasmin from acting enzymatically on fibrin, TA provides an option to sustain hemostasis. Tranexamic acid may improve outcomes for women with postpartum hemorrhage if it lowers surgical bleeding. According to our research, the estimated bleeding in the carbetocin group was significantly higher than in the TA plus sublingual misoprostol group (P = 0.0001). These outcomes also corroborated published results of several trials **(12-16)**.

In addition, our research was based on the findings of Nayak, Pradhan **(17)** Musa et al., Musa, Ijaiya **(18)**, Patil and Patted **(19)**, and Rajaei, Karimi **(20)** who discovered that 400 mg of sublingual misoprostol appeared to be just as effective as oxytocin in reducing blood loss during the third stage of labor.

Our study supports the hypothesis that intravenous TA increases the potency of sublingual misoprostol, making it more effective than carbetocin in decreasing the quantity of postpartum bleeding which extra women within the carbetocin group required more uterotonic medications. Misoprostol is appealing for use in the prevention and treatment of postpartum hemorrhage because of its extended shelf life outside the refrigerator and oral delivery, especially in low-resource settings where it is easy to store and distribute. In addition, it does not affect vital signs or induce bronchoconstriction; therefore, it is frequently used safely in pregnant women who have asthma **(5)**.

One study found that women who got carbetocin experienced considerably less blood loss throughout the third stage of labor and the postpartum period than women who received misoprostol, whether they delivered vaginally or via CD **(20)**.

Intense myometrial contractions, elevated platelet action, and a significant release of clotting elements all occur sequentially after delivery when the placenta separates from the uterine lining to minimize bleeding, but at the same time, fibrinolytic activity rises **(21)**. Administration of TA may be prepared to block the secondary mechanism, while misoprostol administration strengthens the main mechanism, facilitating the hemostatic process. Finally, a detailed correlation between lower fibrinogen levels and outcomes in PPH cases was found, which further implies that TA may be helpful in PPH **(22)**.

According to a recent Cochrane analysis, prompt TA administration to patients experiencing postpartum hemorrhage after delivery via any method led to lessened total blood loss as well as lower maternal death as a result of hemorrhage (relative risk RR 0.81; 95% C1: 0.65 - 1.00) **(6)**. These results corroborated the previous findings of maternal antifibrinolytic trials **(23-25)**.
Women taking misoprostol had adverse effects including shaking and a foul taste far more frequently than those taking carbetocin. These results are very similar to those of previous investigations **(15-17, 26)**.

The study had its limitations. First, we compared misoprostol plus TA with carbetocin and not with oxytocin, which represents the gold standard for the prevention of PPH. However, trials contrasting the effects of oxytocin and carbetocin in CD indicate that carbetocin is more effective in terms of bleeding reduction and the requirement for further medications **(27-31)**.

It was single-center research, and we didn't utilize the alkaline hematin technique, which is an established technique for reliable blood loss assessment, but instead employed a gravimetric approach to determine the quantity of bleeding. In the obstetric population undergoing cesarean delivery, however, Saoud et al., compared the two techniques for estimating surgical bleeding, concluding that measuring the quantity of bleeding using a gravimetric approach is an accurate and objective instrument for gauging the loss of blood **(32)**. However, larger multicenter trials are needed to prove that TA coupled with misoprostol is efficacious in avoiding postpartum hemorrhage in high-risk parturient.

Furthermore, blood loss has been linked to surgical problems that were not taken into account in our investigation. Furthermore, while there is a difference in uterine receptor responsiveness to carbetocin between 37 and 40 weeks, there is no statistically significant difference between the research groups in terms of gestational age at CD.

The fact that a double-blinded clinical study with adequate power was used to assess the effects of intravenous TA with oral misoprostol vs. intravenous carbetocin on perioperative bleeding was one of the study's merits.

The simplicity with which IV TA and sublingual misoprostol can minimize surgical bleeding by a clinically significant quantity is another highlight of the research.

Conclusion

The quantity of blood loss during and following CD can be decreased more effectively with IV TA with sublingual misoprostol than with IV carbetocin. The effectiveness of sublingual misoprostol to reduce bleeding during and after CD may be increased by the addition of tranexamic acid. Sublingual misoprostol with tranexamic may also be utilized in situations when oxytocin or carbetocin are not accessible or cannot be provided.

Compliance with ethical standards

Ethical Approval

The study protocol was approved by the Ethics Committee of the Aswan University Faculty of Medicine (Aswu/353/3/19). ClinicalTrials.gov identifier: NCT03710317

The study was in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Authors Contribution

NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation. HS: manuscript preparation.

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None.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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