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## Comparative study between the effect of carbetocin *versus* oxytocin plus sublingual misoprostol and oxytocin in the management of postpartum blood loss > 500 ml after vaginal delivery: a randomized controlled trial

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### ABSTRACT

**Objective.** In comparison to oxytocin alone, researchers wanted to examine how carbetocin and oxytocin plus sublingual misoprostol influenced the estimated and measured amount of blood loss following vaginal birth in women who had blood loss > 500 ml.

**Patients and Methods.** 135 women with blood loss greater than 500 ml after vaginal delivery were recruited in the current randomized open-label clinical trial at a tertiary university hospital between April 2019 and December 2022 (NCT03870503), after receiving standard treatments for managing the third stage of labour and signing an informant consent. They were separated into three groups: group 1 received 100 µg of carbetocin (Pabal Ferring, UK), group 2 received 400 µg of sublingual misoprostol with 20 IU of oxytocin (Syntocinon, Novartis, Switzerland), and group 3 received just 20 IU of oxytocin. Blood loss of 500 millilitres or less following postpartum haemorrhage therapy was the main goal.

**Results.** When compared to the carbetocin and oxytocin plus misoprostol groups, the oxytocin group had a substantial drop in haemoglobin concentration and a significant increase in estimated blood loss ( $p = 0.0001$ ;  $0.0001$ , respectively). The estimated blood loss in the oxytocin plus misoprostol group was significantly lower than in the carbetocin group ( $p = 0.004$ ). When comparing the carbetocin (13.3%) to the oxytocin plus misoprostol group (11.1%) and the oxytocin (24.4%), the incidence of postpartum blood loss > 1,000 ml was higher in the oxytocin group ( $p = 0.0001$ ).

**Conclusions.** Oxytocin plus misoprostol is more effective than oxytocin and carbetocin in the management of post-partum blood loss > 500 ml after vaginal delivery.

### INTRODUCTION

Postpartum haemorrhage (PPH) is defined as bleeding lasting quite 500 millilitres after vaginal delivery, but the American College of Obstetrics and Gynecology (ACOG) revised the definition in 2017, and therefore the current definition is cumulative blood loss

greater than 1,000 millilitres with signs and symptoms of hypovolemia within 24 hours, no matter delivery method [1, 2]. While this adjustment was made with the understanding that blood loss at the time of birth is usually underestimated, blood loss of quite 500 ml during vaginal delivery should be considered abnormal and should require medical attention [3].

The failure of the uterus to contract and retract after childbirth has been recognized because the most dramatic explanation for PPH for millennia, and it complicates up to 10% of pregnancies worldwide. PPH is liable for one maternal fatality every seven minutes in the underdeveloped world [4].

By stimulating uterine contractions and avoiding uterine atony, active treatment of the third stage of labour aims to assist placenta delivery and prevent primary postpartum haemorrhage (PPH). After the placenta is delivered, the customary elements include, if necessary, the administration of uterotonic drugs, controlled cord traction, and uterine massage [5].

Oxytocin must be kept and transported at 2-8 °C. In low-resource countries, the cold chain isn't commonly available. A heat-stable uterotonic medication would be highly helpful since it might not only reduce storage and shipping costs and logistical problems but might also prevent atonic PPH deaths caused by denatured and useless oxytocin [6]. Carbetocin has the potential to be a newer long-acting oxytocin analogue [7].

Continuous contractions last 11 minutes and rhythmic contractions last 120 minutes after carbetocin is run into the uterus [8]. A heat-stable carbetocin is currently available [9]. The World Health Organization (WHO) authorized carbetocin for the prevention of PPH altogether births in December 2018 when the value was like other effective uterotonics [3].

The main disadvantage of carbetocin is that it's significantly more costly than oxytocin and isn't widely available, particularly in low-resource countries [8]. Misoprostol is especially useful in these conditions since it's inexpensive, temperature-resistant, and readily available in resource-poor countries [10]. The exciting possibility that misoprostol might be employed by traditional birth attendants, or self-administered, for births occurring far away from health services and health personnel, where women are most in danger of the rapidly fatal effects of severe PPH, raised the likelihood that it might be employed by traditional birth attendants, or self-administered [11]. When oxytocin is unavailable or the standard of oxytocin can't be guaranteed, another injectable oxytocic (carbetocin) or oral misoprostol should be used instead.

Despite the utilization of a uterotonic drug as a preventative measure, PPH remains a frequent complication, accounting for one-quarter of all maternal fatalities worldwide. When prophylaxis fails and PPH develops, it's advised that uterotonic

medicines be used as "first line" therapy. However, it's unclear whether a uterotonic drug is best for treating PPH as a "first line" therapy [10].

Oxytocin, carbetocin, ergometrine, misoprostol, injectable prostaglandins, and combinations of those medications are among the uterotonic therapies available, with varying degrees of efficacy and adverse effects.

The purpose of this study is to evaluate the efficacy of oxytocin plus sublingual misoprostol against carbetocin and oxytocin alone within the treatment of blood loss greater than 500 ml following standard active third-stage labour management.

## MATERIALS AND METHODS

### *Study type, setting, and duration*

From April 1, 2019, to December 30, 2022, we performed an open label randomized controlled study on 135 pregnant women attending the labour wards at Aswan University Hospital in Aswan, Egypt. After the research protocol was approved by the institutional review board (Aswu/280/7/18), we prospectively filed it at clinicaltrials.gov (NCT03870503). We offered each participant a thorough description of the study's purpose and methods. Before the trial began, eligible patients who were invited to participate in the study in case they develop PPH gave written informed consent. This manuscript conforms to the enhancement, quality, and transparency of health research (EQUATOR) network guidelines.

### *Study participants*

Only women who signed informed consent papers were included in the research. In all the cases, PPH was defined as vaginal haemorrhage > 500 ml following vaginal delivery and uterine atony confirmed by abdominal palpation. Women who met the following criteria were not permitted to participate: < 37 weeks of pregnancy, genital tract injuries, coagulation deficit, hypertension, preeclampsia, cardiac, renal, or hepatic disease, epilepsy, and carbetocin or oxytocin hypersensitivity are all risk factors.

### *Randomization and allocation*

135 women with atonic PPH were divided into three equal groups using computer-generated random numbers. An independent individual created the

allocation sequence, and all medicines were tagged, packed, and stored in the labour ward before recruitment. By using opaque sealed packets with sequentially numbered medication codes, the allocation was hidden. Each lady was issued an order, and the medication was provided to her with a code that linked to her envelope number. In addition to normal treatment, we randomly allocated women to receive oxytocin alone, oxytocin with misoprostol, or carbetocin.

### *Intervention*

All women underwent routine active management of the third stage of labour with standard uterotonics, controlled cord traction after the delivery of the baby, and gentle uterine massage after the delivery of the placenta. At the delivery of the anterior shoulder of the baby, one of two uterotonic regimens was administered: intravenous 10 IU of oxytocin given either intramuscularly or intravenously. Immediately after the delivery of the baby, blood loss was collected by placing a clean fracture bedpan directly under the woman's buttocks for a minimum of one hour [1, 3].

Markings were written onto the bedpan to show when 500 ml had been reached. Women losing less than 500 ml were not entered into the trial.

Women losing 500 ml, or more were enrolled in the trial, and a clean bedpan was placed underneath their buttocks to collect blood lost after PPH diagnosis. A fresh, large perineal pad with plastic backing was positioned just below the bedpan to capture any spattering blood. Once the delivery attendant considered active bleeding to have stopped, the blood was transferred to a calibrated jar for measurement. Two 14-gauge cannulas were placed, and a crystalloid intravenous (i.v.) infusion was begun when atonic PPH occurred. An oxygen concentration of 10 L/min was given through a face mask. A Foley catheter was placed, and a fluid balance chart was recorded after the fundus was massaged. Every 15 minutes, the patient's pulse and blood pressure were recorded, and venipuncture was performed for cross-matching four units of blood, a full blood count, a coagulation screen, and urea and electrolytes testing.

To rule out retained products of conception and genital tract damage, an ultrasound scan and examination of the genital tract were performed.

Eligible participants were assigned to one of three study groups after diagnosis of blood loss of more

than 500 ml due to uterine atony: group I (carbetocin group) (45 patients received 100 µg carbetocin (Pabal Ferring, UK)), group II (oxytocin plus misoprostol group) (45 patients received 400 µg sublingual misoprostol (Cytotec Pfizer, New York, USA) plus 20 unit of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h (Syntocinon, Novartis, Switzerland), group III oxytocin group) (45 patients received 20 unit of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h) [1, 3].

The uterine tone and quantity of bleeding were evaluated 5 minutes after the medication was given, and the necessity for more uterotonic drugs and blood transfusion was decided.

The amount of blood lost was calculated by weighing the swabs and utilizing graphical charts. The haemoglobin level in the blood was measured 24 hours after birth: oxytocin (Syntocinon, Novartis, Switzerland) infusion 40 IU in 500 ml lactated ringer's solution 125 ml/h, misoprostol (Cytotec Pfizer, New York, USA) 600 µg rectally, insertion of an intrauterine Bakri balloon, laparotomy, and B lynch stitch, bilateral uterine artery ligation, hysterectomy.

Nausea, vomiting, tachycardia, diarrhoea, fever, and tachycardia were all noted as potential consequences.

### *Study outcomes*

The primary endpoint was measured as excessive bleeding blood loss  $\geq 500$  mills after PPH treatment; secondary outcomes included change in haemoglobin, side effects, need for additional interventions including blood transfusion, additional uterotonics, balloon tamponade, hysterectomy, and mean blood loss  $> 1,000$  ml.

### *Sample size*

The primary outcome measure was used to calculate the sample size. To detect a 100-ml difference in additional average blood loss after enrolment at a 5% significance level with 80 percent power (assuming mean additional blood loss of 400 ml in the carbetocin group and 300 ml in the oxytocin plus sublingual misoprostol, and a standard deviation of 200 ml in both groups), 45 women per group were needed. Epi-Info 6.0 was used to double-enter, verify, and clean data, and Stata 7.0 was used to analyse it (Stata, Texas, USA).

### Statistical analysis

The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) version 16 was used to enter data and perform statistical analysis. Numbers and percentages were used to describe qualitative data. The Chi-square test and the Monte Carlo test were employed to compare groups when needed. Quantitative data were expressed as means (SD) or medians, depending on the situation. The Kolmogorov-Smirnov test was used to determine their normalcy. A one-way ANOVA test with LSD *post-hoc* multiple comparisons were performed for comparison between groups in the normally distributed variables, if applicable. The Mann Whitney test and the Kruskal-Wallis test were employed to compare groups in non-normally distributed data, where applicable. We estimated odds ratios and their 95% confidence intervals. The statistical significance of P-value 0.05 was established.

### RESULTS

A total of 5,349 women were approached about taking part in the study. A total of 5,214 women were removed from the study: 39 women were found to be ineligible, 213 women declined to participate, and 4,962 women did not develop postpartum haemorrhage. The remaining 135 women were divided into three research groups at random (Figure 1). There were no significant differences in age, weight, height, BMI, parity, gestational age, first haemoglobin, blood pressure, or temperature between the three groups (Table 1).

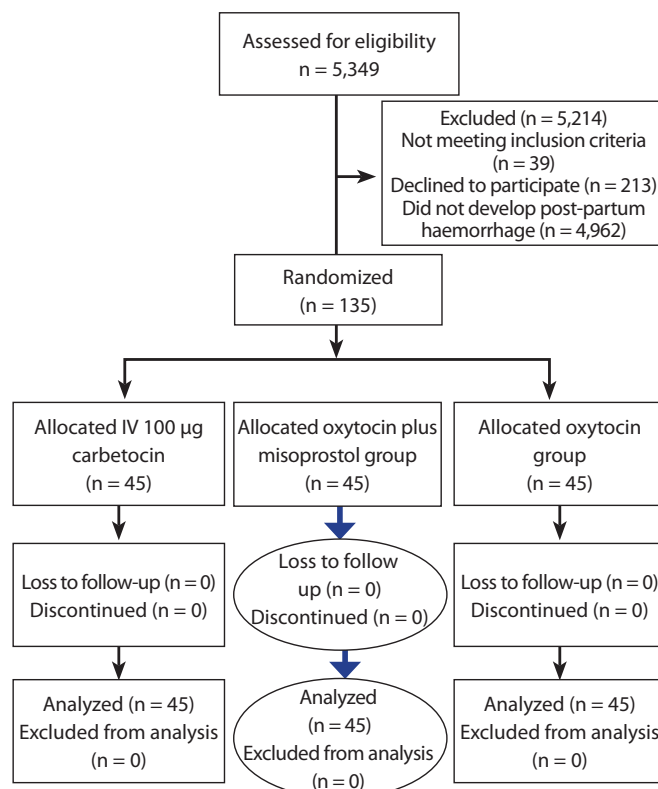


Figure 1. Consort flowchart showing enrolment of participants.

The oxytocin group had a statistically significant higher post-delivery pulse rate than the carbetocin group ( $p = 0.0001$ , 95%CI 2.68-7.86) and the oxytocin plus the misoprostol group ( $p = 0.0001$ , 95%CI 3.80-8.99).

In addition, there was no significant difference in post-delivery pulse rate between the oxytocin plus misoprostol and carbetocin groups ( $p = 0.692$ , 95%CI -1.47 to 3.72).

The oxytocin group had a statistically significant lower post-delivery SBP and DBP than the carbetocin

Table 1. Baseline characteristics of pregnant women in the study groups.

Parameters	Group I (n = 45)	Group II (n = 45)	Group III (n = 45)	P-value
Age (year)	29.5 ± 2.42	29.6 ± 2.68	29.83 ± 2.85	0.854
Weight (kg)	69.25 ± 7.76	69.43 ± 7.18	69.4 ± 7.77	0.994
Height (cm)	162.45 ± 4.19	163.58 ± 4.38	163.52 ± 4.6	0.436
BMI (kg/m <sup>2</sup> )	26.2 ± 2.55	25.96 ± 2.74	25.94 ± 2.71	0.888
Parity (median) (minimum-maximum)	3 (0-4)	2 (0-5)	3 (0-5)	0.866
Gestational age (weeks)	38.4 ± 1.45	38.55 ± 1.34	37.5 ± 1.22	0.878
Initial haemoglobin	10.97 ± 0.624	10.98 ± 0.623	10.83 ± 0.622	0.905
Duration of first stage (h)	9.78 ± 2.91	9.81 ± 2.06	9.92 ± 1.06	
Duration of second stage (mins)	64.72 ± 16.12	63.72 ± 17.13	63.72 ± 13.16	
Duration of third stage (mins)	4.42 ± 1.2	4.73 ± 2.3	4.23 ± 1.3	0.965
Birth weight (g)	3,176 ± 376.64	3,182 ± 35.21	3,182 ± 35.25	

BMI: Body Mass Index; CS: caesarean section; CPD: cephalopelvic disproportion; variables are presented as mean and standard deviation, median (minimum-maximum) and number (percentage).

**Table 2.** Post-delivery variables in the three groups.

Blood loss	Group I (n = 45)	Group II (n = 45)	Group III (n = 45)	P-value
Amount of bleeding (ml)	811 ± 525.66	722 ± 312.77	910 ± 389.17	0.007* 0.03*/0.04*/0.0001*
PPH > 1,000 ml (%)	6 (13.3 %)	5 (11.1%)	11 (24.4 %)	0.0001* 0.326/0.0001*/0.0001*
Temperature	36.91 ± 0.07	37.45 ± 0.64	36.95 ± 0.43	0.0001* 0.0001*/0.12/0.0001*
Pulse (30 minutes after delivery)	94.46 ± 7.5	93.99 ± 9.7	96.99 ± 9.7	0.692 0.721/0.692/0.126
Hb 24 h after delivery(g/dl)	9.98 ± 2.71	8.98 ± 4.21	9.93 ± 3.27	0.0001* 0.0001*/0.221/0.0001*
SBP (30 minutes after delivery)	119.09 ± 3.67	116.04 ± 7.23	103.04 ± 6.12	0.0001* 0.193/0.0001*/0.0001*
DBP (30 minutes after delivery)	86.32 ± 3.36	81.41 ± 5.15	73.41 ± 4.48	0.0001* 0.026*/0.026*/0.0001

\*Statistically significant difference (Group I versus Group II/Group I versus Group III/Group II versus Group III); variables are presented as mean and standard deviation, and number (percentage).

cin group (p = 0.0001, 95%CI -7.88 to -4.69) and the oxytocin plus misoprostol group (p = 0.0001, 95%CI -7.89 to -4.70).

When compared to both the oxytocin and carbetocin groups the oxytocin plus the misoprostol group, had a substantial rise in post-delivery temperature (p = 0.0001).

When compared to the carbetocin and oxytocin plus the misoprostol groups, the oxytocin group had a statistically significant lower haemoglobin level and greater blood loss (p = 0.0001). The TA + oxytocin group had a statistically significant higher haemoglobin level and less blood loss than the carbetocin group (p = 0.004 and 0.043, respectively) (Table 2).

PPH was more common in the oxytocin group (9.1%) than in the carbetocin group (2.5%) or the oxytocin plus the misoprostol group (0.83%) (p = 0.0001).

There was no significant difference in the incidence of PPH between the carbetocin group and the oxytocin plus misoprostol group (p = 0.298), therefore the oxytocin group used more extra uterotonics than the other two groups. Only 14 (10.8%) women in the oxytocin group required blood transfusion.

The oxytocin + misoprostol group had a higher rate of diarrhoea and increase temperature (6.6%) than the carbetocin group (0%) or the oxytocin group (0%). There were no significant differences in the incidence of nausea, vomiting, or diarrhoea across the three groups (Table 3).

**Table 3.** Adjuvant interventions and side effect measurements.

Variables	Group I (n = 45)	Group II (n = 45)	Group III (n = 45)	P-value
Additional uterotonics (%)	7 (15.5)	6 (13.3 %)	12 (26.6)	0.0001* 0.261 / 0.0001*/ 0.0001*
Bakri balloon (%)	1 (2.2)	1 (2.2)	3 (6.6)	0.132
B lynch stitch (%)	1 (2.2)	1 (2.2)	2 (2.2)	0.536
Uterine artery ligation (%)	/	/	1 (7.5)	/
Hysterectomy (%)	/	/	/	/
Need Blood Transfusion (%)	8 (50)	7 (12.5)	13 (7.5)	0.0001* 0.214 / 0.0001*/ 0.0001*
Tachycardia (> 100 b/min)	9 (20)	10 (22.2)	15(33.3)	0.0001* 0.672 / 0.0001*/ 0.0001*
Fever (%)	/	3 (6.6)	/	/
Nausea (%)	2 (4.4)	3 (6.6)	3(6.6)	0.906
Vomiting (%)	1 (2.2)	1 (2.2)	2 (4.4)	1.000
Diarrhoea (%)	1 (2.2)	1 (2.2)	3 (6.6)	0.620

\*Statistically significant difference (Group I versus Group II/Group I versus Group III/Group II versus Group III); variables are presented as mean and standard deviation and number (percentage).

## DISCUSSION

This research was designed to compare the efficacy of intravenous 100 µg carbetocin against 20 units of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h with 400 µg sublingual misoprostol, as well as 20 units of oxytocin infusion in 500 ml lactated ringer's solution 125 ml/h alone, in reducing blood loss in pregnant women who are having a vaginal birth and experience blood loss > 500 ml. Our research found that using oxytocin in combination with sublingual misoprostol or i.v. carbetocin reduces determined blood loss, the incidence of PPH, and hence the requirement for further uterotonics, compared to oxytocin alone.

In comparison to oxytocin, carbetocin dramatically reduced postpartum blood loss and reduced the need for extra uterotonics in women with atonic PPH, with no notable adverse effects or hemodynamic abnormalities. This is often thanks to carbetocin's longer half-life, which causes a greater uterine response in terms of frequency and amplitude of uterine contractions [10]. These findings were also the results of several studies published within the literature [12-15].

Our findings matched those of Samimi *et al.*, who gave carbetocin or syntometrine to 200 women undergoing childbirth to avoid PPH. The need for extra uterotonics was observed to be considerably reduced within the carbetocin group. Carbetocin was shown to be more efficient than syntometrine in preventing PPH [13].

Our findings matched those of one study, which randomly assigned 200 women who delivered vaginally and had at least two risk factors for atonic PPH to receive either 100 µg i.m. carbetocin or 5 IU i.m. oxytocin. The quantity of bleeding, the prevalence of PPH, and therefore the requirement for extra uterotonics were all shown to be considerably reduced within the carbetocin group. They concluded that carbetocin is a better alternative to conventional oxytocin for preventing PPH in women with at least two PPH variables, with fewer hemodynamic abnormalities and adverse effects [14].

Another study randomly assigned 100 women who delivered vaginally and had experienced atonic PPH to receive either 100 mcg i.m. carbetocin or 10 IU i.m. oxytocin. The quantity of bleeding and the requirement for additional uterotonics were all shown to be considerably reduced in the carbetocin group [15].

Boucher *et al.* recently published research in which they found that the carbetocin group needed substantially less uterine massage and other uterotonics,

which matched our findings. They administered carbetocin 100 µg i.m. or oxytocin 10 IU i.v. oxytocin infusion over 2 hours to 160 women with at least one risk factor for PPH who delivered delivery vaginally [16]. Carbetocin 100 g has all the earmarks of being as effective as oxytocin in decreasing PPH, according to Boucher *et al.* [16], Elbohuty *et al.* [17], Widmer *et al.* [18] and Fenix *et al.* [19]. Similarly, adding sublingual misoprostol to oxytocin improves the efficacy of oxytocin as compared to i.v. carbetocin in terms of determined blood loss in our study.

Evidence suggests that prior oxytocin exposure appears to desensitize oxytocin receptors, leading to poor oxytocin-induced uterine contractility [20].

In 2010, Winikoff *et al.* published the results of a single trial that compared the effectiveness of misoprostol *vs* traditional uterotonics in the absence of oxytocin prophylaxis [21]. In this study, 978 women were treated for PPH at four hospitals in Ecuador, Egypt, and Vietnam. Participants were randomly assigned to receive either 800-g sublingual misoprostol (n = 488) or 40 IU intravenous oxytocin (n = 490). Misoprostol, while being less effective than oxytocin, was able to stop active bleeding in 90% of women. As a result, the researchers concluded that it was effective enough to be utilized as a first-line treatment for PPH in the absence of oxytocin.

Blum *et al.* evaluated the effects of misoprostol and conventional uterotonics after delivery of 10 IU oxytocin prophylaxis in one of two studies [22]. PPH was treated in a total of 807 women. Participants were given either 800 g sublingual misoprostol (n = 407) or 40 IU intravenous oxytocin (n = 402) at random. When used for the management of PPH owing to uterine atony, the authors found that misoprostol is clinically comparable to oxytocin in women who had received oxytocin prophylaxis during the third stage of labour. Lokugamage *et al.* presented the results of research looking at the effects of misoprostol after oxytocin prophylaxis in 2001. When given to 64 women with PPH, they found that 800 g rectal misoprostol had a substantial benefit over a combination of syntometrine i.m. plus syntocinon i.v. for PPH therapy [23]. In favour of misoprostol, there was a 28.1% difference in the rate of bleeding cessation within 20 minutes (p = 0.01).

Despite continuing efforts, less competent health personnel attend births in low-resource countries, which can lower maternal mortality; as a result, the maternal death rate in developing countries remains high [1]. Preventing and treating PPH is particularly difficult in areas where most deliveries take place at pa-

tients' homes or in tiny clinics, and when obstetric care is limited [3]. Without skilled delivery attendants, sublingual misoprostol with oxytocin might be a one-of-a-kind combo, and it could potentially be the only medical option for treating PPH after births [17]. Misoprostol does not need to be kept at a certain temperature; thus, it can be used in the absence of skilled labour and delivery personnel or when injectable oxytocin is unavailable [10].

The findings of this trial, in agreement with other trials [23-27], add to the body of data on the safety of misoprostol for PPH therapy. In this trial, no serious side effects or safety issues were observed among women who used misoprostol for treatment as well as prevention.

There were several limitations to the study. First, the generalizability of our findings may be restricted since this was a single-centre study with a small number of women with PPH.

The comprehensive data collection that took place over a two-and-a-half-year period to document the use of carbetocin *versus* oxytocin plus misoprostol and oxytocin alone for the treatment of PPH is a significant strength of this study.

The randomized trial was sufficiently powered to evaluate the effects of intravenous TA with oral misoprostol *vs* intravenous carbetocin on the amount of blood loss, which was one of the study's merits.

The simplicity with which sublingual misoprostol and i.v. TA can reduce postpartum blood loss by a clinically significant amount is another highlight of the research.

### **Clinical implications**

This study demonstrates that utilizing oxytocin in conjunction with sublingual misoprostol and i.v. carbetocin alone lowers the occurrence of severe PPH and the need for further uterotonics when compared to using oxytocin alone. Compared to carbetocin, adjuvant sublingual misoprostol improves oxytocin's effectiveness. Misoprostol appeared to reduce blood loss more successfully when used in conjunction with oxytocin as secondary prophylaxis of postpartum haemorrhage.

## **CONCLUSIONS**

Oxytocin plus misoprostol is more effective than oxytocin and carbetocin in the management of

post-partum blood loss > 500 ml after vaginal delivery. Adjuvant sublingual misoprostol increases oxytocin's efficiency in comparison to carbetocin. When administered in conjunction with oxytocin as a supplementary prophylactic for postpartum haemorrhage, misoprostol seems to increase the efficacy of oxytocin to lessen blood loss more successfully.

## **COMPLIANCE WITH ETHICAL STANDARDS**

### **Authors contribution**

All authors contributed equally to this work.

### **Funding**

None.

### **Study registration**

It was a clinically registered randomized, double-blind, clinical trial (ClinicalTrials.gov: NCT03870503).

### **Disclosure of interests**

The authors declare that they have no conflict of interests.

### **Ethical approval**

The ethical review board approved the study by a grant number of (Aswu/280/7/18).

### **Informed consent**

Informed consent was received from the patient for the publication of this case report.

### **Data sharing**

Data are available under reasonable request to the corresponding author.

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