



# The Effect of Carbetocin versus Misoprostol versus Ergometrine for Controlling Bleeding after Cesarean Section in Primigravidae

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** Women undergoing cesarean section have a high risk of blood loss and so are more likely to need a blood transfusion. The aim of this work was to compare the effectiveness of using carbetocin versus misoprostol versus ergometrine for controlling bleeding after cesarean section in primigravidae.

**Methods:** This prospective randomized clinical trial was conducted on 150 patients aged from 18-35 years old, primigravidae with singleton pregnancy undergoing elective cesarean section. Participants were divided into three equal groups: carbetocin group (group C) received a single 1-ml ampoule of carbetocin (100 µg/mL) added to 10 cm saline intravenously following the delivery of the neonate, misoprostol group (group M) received misoprostol 400ug per rectum immediately after induction of anesthesia in operating theater and ergometrine group (group E) received 0.2 mg of ergometrine intramuscularly in the first minute after delivery of the baby.

**Results:** The amount of blood in suction jar, amount of blood loss, Hb change and HTC change were significantly higher in the misoprostol group and ergometrine group than in the carbetocin group ( $p < 0.05$ ) and in the ergometrine group than the misoprostol group ( $p < 0.001$ ). Post-operative Hb in the ergometrine group was significantly lower in the carbetocin group ( $p = 0.001$ ).

**Conclusions:** Carbetocin can be considered a superior choice to misoprostol and ergometrine in reducing blood loss during CS in primigravidae.

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**Keywords:** Carbetocin; misoprostol; ergometrine; cesarean section; primigravidae.

## 1. INTRODUCTION

“Cesarean delivery is one of the most frequently performed major surgical procedures worldwide” [1]. “Compared with women who deliver vaginally, women undergoing cesarean section have a high risk of blood loss and so are more likely to need a blood transfusion” [2].

“The global increase in the incidence of cesarean delivery in the past decade has contributed to the appearance of postpartum hemorrhage (PPH)” [3]. “The risk of postpartum hemorrhage is further increasing in the presence of risk factors such as multiparity, polyhydramnios, grand multiparity, severe pre-eclampsia, antepartum hemorrhage, prolonged and obstructed labor, augmented labor, obesity, and anemia” [4].

“The currently accepted definition is to consider post-partum hemorrhage as blood loss of more than 500 mL regardless the type of delivery and severity as blood loss more than 1000 mL” [5]. “The American College of Obstetricians and Gynecologists considered that a decline in hematocrit of a rate of 10% or more constituted post-partum hemorrhage” [6].

“The aim of the treatment of postpartum hemorrhage is to restore myometrium contraction. For that, the following therapeutic options are used, alone or in combination: stimulation of uterine contractility with manual massage of the uterus; administration of oxytocin, misoprostol, ergometrine. Note also that the increased sensitivity of the gravid uterus to these drugs contributes to their therapeutic efficiency” [7].

Accordingly, “the administration of uterotonic agents during cesarean section (CS) and vaginal delivery has become crucial to diminish the risk of post-partum hemorrhage and improve maternal safety” [8].

“Oxytocin is considered as the gold standard uterotonic drug but has a short half-life of 4–10 min; hence, at cesarean section oxytocin must be ordered as a continuous intravenous infusion to achieve continuous uterotonic activity during the surgical procedure and the direct postpartum period. Misoprostol is a prostaglandin E1 analog supported in several randomized controlled trials to be efficient in preventing PPH because of its strong uterotonic effect” [8].

In addition, “misoprostol is low-cost, stable at room temperature, and easily administered. misoprostol has been widely studied in the prevention and treatment of post-partum hemorrhage after vaginal delivery; however, its usage in conjunction with cesarean section has not been studied as much” [9]. “The sublingual route is known as having the greatest benefit due to its rapid uptake, long-acting effect, and great bioavailability compared with other routes of intake” [10].

“Carbetocin, a long-acting oxytocin analogue, has been described to decrease the requirement for additional uterotonics during cesarean section in comparison with oxytocin. A 100- $\mu$ g dose of carbetocin has been recommended for preventing Post-partum hemorrhage. Carbetocin has been recommended for post-partum hemorrhage prevention after elective cesarean deliveries. Advantages of carbetocin over oxytocin is that owed to its long action and half-life, it is administrated as a single intravenous dose, while oxytocin necessitates frequent administration or continuous infusion over several hours, with differences in doses” [11].

“In comparison to Oxytocin, the administration of Ergometrine results in a sustained tonic uterine contraction through stimulation of myometrial  $\alpha$ -adrenergic receptors. Both uterine segments are thus stimulated to contract in a tetanic way. Intramuscular injection of the usual 0.25 mg dose effects in an onset of action of 2–5 minutes” [12].

The aim of this work was to compare the effectiveness of using carbetocin versus misoprostol versus ergometrine for controlling bleeding after cesarean section in primigravidae.

## 2. PATIENTS AND METHODS

This prospective randomized clinical trial was conducted on 150 patients aged from 18-35 years old, BMI (18.5 – 29.9) primigravidae with singleton pregnancy undergoing elective cesarean section at The Department of obstetrics and gynecology, Tanta university hospitals, Egypt 1st of February 2020 to 31st of January 2021.

Exclusion criteria were hypersensitivity to Ergometrine, Carbetocin, prostaglandins or 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 and PPH due to causes other than uterine atony.

All patients were subjected to: history taking, clinical examination, investigational studies such as pelvi-abdominal ultrasound and preoperative and postoperative hemoglobin.

Eligible and consenting participants were randomized via a computer-generated random number sequence into one of three groups of 50 each.

The carbetocin group (group C) received a single 1-ml ampoule of carbetocin (100 µg/mL) added to 10 cm saline that was administered intravenously following the delivery of the fetus.

The misoprostol group (group M) received misoprostol 400ug per rectum immediately after induction of anesthesia in the operating theater.

The ergometrine group (group E) received 0.2 mg of ergometrine intramuscularly in the first minute after delivery of the baby.

The primary outcomes were the measured intraoperative and postoperative (end of cesarean delivery to 8 hours postpartum) blood loss. The secondary outcomes were postoperative change in hemoglobin (24 hours after delivery), need for additional oxytocics (over 24 hours), and drug-related side effects. The volume of blood in the suction bottle and blood-

soaked sponges was measured. Hemoglobin values were determined both before surgery and 24 h following surgery. The need for additional oxytocic therapy, need for blood transfusion (until discharge), and side effects of study drugs, cost of the drugs used, and any significant puerperal morbidity were also recorded.

### 2.1 Statistical Analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing ANOVA (F) test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

### 3. RESULTS

As regard of socio-demographic data (age and BMI), gestational age and indications of CS (infertility, abnormal Presentation, low-lying placenta, abnormal Liquor, fetal macrosomia and CPD), there was no statistically significant difference between the three groups. Table 1.

The amount of blood in suction jar, amount of blood loss, Hb change and HTC change was statistically significantly higher in the misoprostol group and ergometrine group than in the carbetocin group (p <0.05) and was statistically significantly higher in the ergometrine group than the misoprostol group (p <0.001). Post-operative Hb in the ergometrine group was statistically significantly lower in the carbetocin group

**Table 1. Comparison between study groups as regard of socio-demographic data, Gestational age and indications of CS**

	<b>Carbetocin group (n= 50)</b>	<b>Misoprostol group (n= 50)</b>	<b>Ergometrine group (n= 50)</b>	<b>P value</b>
<b>Age (years)</b>	27.38 ± 4.827	27.58 ± 4.380	26.38 ± 4.237	0.361
<b>BMI (kg/m2)</b>	26.43 ± 2.067	26.31 ± 2.778	26.20 ± 2.408	0.896
<b>Gestational age (weeks)</b>	36.80 ± 1.578	37.22 ± 1.447	36.88 ± 1.599	0.354
<b>Infertility</b>	0.0% (0)	10.0% (5)	8.0% (4)	0.268
<b>Abnormal Presentation</b>	66.0% (33)	58.0% (29)	70.0% (35)	
<b>Low-lying placenta</b>	14.0% (7)	24.0% (12)	12.0% (6)	
<b>Abnormal Liquor</b>	10.0% (5)	4.0% (2)	4.0% (2)	
<b>Fetal macrosomia</b>	6.0% (3)	2.0% (1)	4.0% (2)	
<b>CPD</b>	4.0% (2)	2.0% (1)	2.0% (1)	

Data are presented as mean ± SD or percentage (frequency). CPD: Cephalopelvic disproportion

**Table 2. Duration of surgery, amount of blood loss, basal and post-operative hemoglobin and hematocrit values, need for blood transfusion, additional oxytocic and total hospital stay in studied groups**

	<b>Carbetocin group (n= 50)</b>	<b>Misoprostol group (n= 50)</b>	<b>Ergometrine group (n= 50)</b>	<b>P</b>	<b>P1</b>	<b>P2</b>	<b>P3</b>
Operative duration (minutes)	46.10 ± 7.712	48.70 ± 9.357	48.90 ± 7.712	0.174	0.358	0.281	1
Blood in suction jar (ml)	273.50 ± 44.150	327.50 ± 54.691	413.50 ± 54.213	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Estimated blood loss (ml)	694.00 ± 70.992	749.00 ± 54.856	875.00 ± 75.930	< 0.001*	< 0.001*	< 0.001*	< 0.001*
Basal Hb (gm/dl)	11.43 ± 0.823	11.33 ± 0.781	11.32 ± 0.712	0.718	1	1	1
Post-operative Hb (gm/dl)	10.05 ± 0.766	9.83 ± 0.677	9.55 ± 0.633	0.002*	0.336	0.001*	0.132
Hb change (gm)	-1.38 ± 0.207	-1.50 ± 0.220	-1.78 ± 0.257	< 0.001*	0.037*	< 0.001*	< 0.001*
Basal Hct (%)	39.13 ± 39.164	33.43 ± 2.030	33.44 ± 1.799	0.352	0.632	0.634	1
Post-operative Hct (%)	31.29 ± 1.819	30.96 ± 1.942	30.57 ± 1.667	0.145	1	0.150	0.874
Hct change (%)	-2.26 ± 0.313	-2.48 ± 0.299	-2.87 ± 0.376	< 0.001*	0.005*	< 0.001*	< 0.001*
Need for transfusion	6.0% (3)	6.0% (3)	8.0% (4)	0.898	> 0.05	> 0.05	> 0.05
Need for additional oxytocic	12.0% (6)	22.0% (11)	28.0% (14)	0.136	> 0.05	> 0.05	> 0.05
Hospital stay (hours)	30.96 ± 8.430	29.52 ± 11.165	27.84 ± 10.124	0.296	1	0.359	1

*Data are presented as mean ± SD or percentage (frequency), \* is significant when < 0.05. P1: Carbetocin group & Misoprostol group. P2: Carbetocin group & Ergometrine group. P3: Misoprostol group & Ergometrine group. Hb: Haemoglobin, Hct: Hematocrit*

( $p=0.001$ ). Operative duration, basal Hb, basal Hct, post-operative Hct, need for transfusion, need for additional oxytocic, hospital stay were insignificantly different among the studied groups. Post-operative Hb was insignificantly different between carbetocin and misoprostol groups Table 2.

#### 4. DISCUSSION

In this study, there was no statistically significant difference between the three studied groups as regards the operation duration. This was comparable with a study conducted by Owonikoko et al. [13] who reported the insignificance of the operation time when they studied the effect of sublingual misoprostol versus intravenous oxytocin on reducing blood loss at CS in Nigeria.

In the current study, the amount of blood in a suction jar and the estimated blood loss were statistically significantly lower in the carbetocin group than the other two groups. The post-operative Hb in the ergometrine group was statistically significantly lower in the carbetocin group than the other two groups. Hb change and Htc change were statistically significantly lower in the carbetocin group than the other two groups.

The need for transfusion and the need for additional oxytocic were significantly lower in the carbetocin group. However, the hospital stay was higher in the carbetocin group than in the two other groups.

Many studies worldwide compared misoprostol to oxytocin [14,15] and carbetocin to oxytocin [11,16] in reducing blood loss during cesarean section. However, few studies compared carbetocin to misoprostol in reducing blood loss during cesarean section [17].

We found that carbetocin is superior to ergotamine in reducing blood loss in CS in primigravida. In the same line with our results, Su et al. [18,19] in the cochrane of 2007 regarding "oxytocin agonists for preventing postpartum hemorrhage" [18], and in the cochrane 2012 regarding "carbetocin for preventing postpartum hemorrhage" [19], conclude that the use of carbetocin is more effective than oxytocin for preventing PPH in women undergoing cesarean section, but the data and the evidence were still insufficient.

We found that misoprostol is superior to ergotamine in reducing blood loss in CS in

primigravida. In agreement with our results, Gupta et al. [20] found that misoprostol is effective as intramuscular oxytocin in reducing blood loss during cesarean section, however, it has more side effects as regarding transient pyrexia and shivering. Also, Adanikin Al et al. [21] who compared oxytocin infusion to 600ug rectal misoprostol after cesarean section in tropical climates where there is a little capability for refrigeration, found that Misoprostol is as effective as oxytocin infusion for the prevention of PPH.

On the contrary, Elbohoty et al. [22] reported that 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.

Additionally, some studies have demonstrated misoprostol 400–600- $\mu$ g to be as effective as oxytocin [14,15], and a combination of misoprostol 200  $\mu$ g with oxytocin has been demonstrated to reduce blood loss and the need for additional uterotonics [23].

We found that carbetocin is superior to misoprostol in reducing blood loss in CS in primigravida. In agreement with our study, Moustafa et al. [17] concluded that intravenous therapy infusion of 100 ug carbetocin is more effective in managing blood loss during CS than 600ug rectal misoprostol.

A previous Egyptian study that enrolled 380 patients compared a combination of 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 [24].

A systematic review [19] of 11 studies included four studies that compared carbetocin (100  $\mu$ g administered intravenously) with oxytocin in patients undergoing 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).

In the present study, the need for blood transfusion was significantly lower in the carbetocin group. This was in agreement with Ali et al. [25] and Moustafa et al. [17] who found that carbetocin decreases the need for blood transfusion after cesarean.

Overall, our data suggested the superiority of carbetocin over misoprostol in preventing PPH during CS in primigravidae.

## 5. CONCLUSIONS

Carbetocin was demonstrated to be superior to misoprostol in preventing PPH evident by a lower amount of blood in a suction jar and lower estimated blood loss as well as lower Hb and hematocrit deficit pre- and post-operatively. Consequently, it is suggested that carbetocin can be considered a superior choice to misoprostol and ergometrine in reducing blood loss during CS in primigravidae.

## CONSENT AND ETHICAL APPROVAL

The study was done after being approved by the Ethical Committee, Tanta University Hospitals. An informed written consent was obtained from all included subjects.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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