

## Efficacy of Carbetocin versus Oxytocin and Ergometrin in Prevention of Postpartum Hemorrhage after Cesarean Section

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### Abstract

Postpartum haemorrhage is defined as blood loss of 500 millilitres or more within 24 hours after a vaginal or c-section birth (WHO 2018). Hypovolemia occurs when more than 1,000mL of blood is lost in the first 24 hours after birth. A postpartum haemorrhage is defined as the loss of more than 1000 ml of blood after a caesarean operation. During and after caesarean surgery, the effectiveness and safety of intravenous carbetocin, an analogue of oxytocin, was compared against intravenous oxytocin and intramuscular ergometrine for the prevention of postpartum haemorrhage. Researchers used a randomised, prospective strategy for the study Researchers at Benha University Hospital's Obstetrics & Gynecology department worked from January 2020 to November 2021. A total of 120 people are taking part in the research. Group A received carbetocin 100g intravenously after the birth of their second child in this trial. Patients in Group B received oxytocin 10IU intravenously and ergometrine 0.02 mg intramuscularly as a combination treatment for 60 patients. Results: Estimated blood loss was significantly different between groups given carbetocin. Carbetocin, rather than oxytocin and ergometrine, is more likely to prevent atonic postpartum haemorrhage in a woman who has had several pregnancies and is undergoing a caesarean section.

**Key words:** Carbetocin, Oxytocin and Ergometrin, Prevention of Postpartum Hemorrhage, Cesarean Section.

### 1. Introduction

The most common cause of maternal mortality is obstetric bleeding [1]. Obstetric haemorrhage is responsible for 27.1% of all maternal fatalities. Postpartum haemorrhage accounts for 72% of all obstetric haemorrhages [2].

Approximately 80% of instances of PPH are attributed to uterine atony. Complications of numerous pregnancies include caesarean delivery, fibroids, uterine overdistention, macrosomia of the foetus, and polyhydramnios. Chorioamnionitis is linked to atonic PPH [3].

There has been a rise in the number of women undergoing caesarean sections since 1990. The greatest increases were seen in Eastern Asia (34.7 percent) and Northern Africa (31.5 percent). According to the most current figures from 2010-2018, worldwide rates of caesarean sections varied from 5% in Sub-Saharan Africa to 42.8% in Latin America and the Caribbean [4].

According to a study that ranked Egypt third in the world, the caesarean section rate in Egypt in 1992 was 4.6%; in 1995, it was 6.7%; in 2000, it was 10.3%; and in 2014, it was 51.8 percent [5].

Multiple pregnancies have increased in recent decades due to assisted reproductive technologies, and they now account for 3% of all worldwide births [6]. Between 1980 and 2009, the number of twins born in the United States increased by 75%. [7].

The most common cause of postpartum bleeding is uterine atony [8]. Third-stage labour should be actively managed rather than passively managed, according to WHO 2018's new recommendations.

To avoid postpartum haemorrhage, this is the goal. Several pharmacological drugs have achieved these goals (uterotonics). It is now legal in the UK to administer Carbetocin during caesarean procedures to avoid PPH. Uterotonics were not needed as often in those who gave birth by caesarean section as they were in those who gave birth vaginally [9].

According to the WHO and other professional organisations, third-stage labour should be actively managed to prevent PPH. The umbilical cord may also be manipulated using non-pharmacological methods like as controlled cord traction and delayed cord clamping. If the third stage of labour is effectively managed, it is possible to reduce postpartum blood loss by 3-16.5 percent [1].

After a vaginal delivery, there is limited evidence that carbetocin may prevent postpartum haemorrhage (PPH), and the drug is prohibitively costly [10].

To mimic the effects of oxytocin, carbetocin was created and has the same affinity for the myometrium receptors as the original oxytocin [11].

Carbapenem 100g intravenously diluted in normal saline 10ml and delivered slowly over 30-60 seconds, as well as Oxytocin 10iu and Ergometrine 0.2mg intramuscularly after the births of the second and third children, will be compared by the researchers after both the second and third childbirth.

### 2. Patients and Methods

A randomised controlled trial was conducted. Informed permission was obtained to all participants before to the start. A total of 120 patients are being studied. From January 2020 to November 2021, researchers worked at the Obstetrics & Gynecology department at Benha University Hospital.

#### 2.1. Inclusion criteria:

- Patient with multiple pregnancies undergoing cesarean delivery under regional anesthesia.
- No evidence of maternal or fetal distress
- Gestational age of greater than 34 weeks: the gestational age will be determined based on the first day of the last menstrual period and confirmed by ultrasound scan during the first trimester.
- Agreed to participate in the study

## 2.2. Exclusion criteria:

- Traumatic postpartum hemorrhage.
- Placenta praevia.
- Placental abruption.
- Pregnancy-induced hypertension.
- Cardiac disease.
- Diabetes mellitus.

## Patients included in the study were divided into two groups:

- Group (A): included 60 patients who received 100µg of carbetocin, diluted in 10ml normal saline and injected slowly (over 30-60 seconds) I.V after delivery of the second fetus.
- Group (B): included 60 patients who received a combination of 10iu of oxytocin and ergometrine, diluted in 10ml normal saline and injected slowly over (30-60 seconds) IV and 0.2mg of ergometrine intramuscular after delivery of the second fetus.
- Every patient was subjected to Careful and detailed history taking, which included general examination, abdominal examination, vaginal examination, and lab investigations: complete blood count Rh typing coagulation profile ( prothrombin time, partial thromboplastin time, INR), liver function tests, and renal function tests.

Ultrasound scan: using a trans-abdominal scan to assess gestational age.

Assess any risk factors for postpartum hemorrhage as placenta previa.

For all cases, consent approved by the Ethics committee has been taken. Information sheet completed included Age, Parity, Gestational age at delivery, Blood pressure, Pulse, Temperature, and Hemoglobin concentration hematocrit value noted before cesarean sections and 24 hours postpartum. The differences between pre-and-post C.S. values were calculated in each group.

The uterine tone and size were evaluated by palpating the fundus and anterior wall of the uterus. A boggy uterus with heavy vaginal bleeding or increasing uterine size can suspect a diagnosis of uterine atony.

The need for the additional uterotonic drug in each group population was reported and tabulated.

Incidence of postpartum hemorrhage was reported

and tabulated.

## 2.3 Study drug administration:

After the second baby's birth during C.S, the study medication (carbetocin 100µg and oxytocin 10iu) was diluted in 10ml of normal saline and injected slowly (over 30-60 seconds) intravenously. And ergometrine 0.2mg was injected intramuscularly by the anesthetist. The slow injection has been shown to reduce the potentially harmful hemodynamic effects of oxytocin and presumably carbetocin [12].

## 2.4 Blood loss will be estimated by

The hematocrit value will be measured immediately before delivery and 24 hours after, for more objective of blood loss, Assessment will be done according to the following formula:

Estimated blood loss (EBL) = estimated blood volume (EBV) X [preoperative hematocrit (preop Hct) – postoperative hematocrit (postop Hct) / preoperative hematocrit (preop Hct)].

The patient's estimated blood volume (EBV) will be calculated as follows: woman's weight (in kilograms) X 85.

$$EBL = EBV \times (preop\ Hct - postop\ Hct) / preop\ Hct$$

The side effects of each drug, as nausea, vomiting, shivering, and headache, or others, were noted.

## 2.5 Statistical methodology

The data was collected, coded, and entered into the computer. The data were analyzed with the program (SPSS) statistical package for social science version 17.

## 2.6 Statistical tests used in this thesis were

- Description of qualitative variables by frequency and percentage.
- Description of quantitative variables in the form of mean and standard deviation (mean ± S.D.).
- Chi-square (x<sup>2</sup>) test was used for the comparison of qualitative variables with each other.
- Comparison between quantitative variables was carried by using:
- Student t-test of two independent samples.

## 3. Results

Table (1) Demographic data of the patients

Group	Carbetocin	Oxytocin & Ergometrine	P-value
Maternal age	25.51 ± 5.1	26.10 ± 6.23	0.57
Gestational age	35.53 ± 0.91	35.63 ± 0.61	0.39
Parity	1.81 ± 0.68	1.56 ± 0.89	0.08
BMI	25.4 ± 6.1	26.1 ± 4.7	0.48

Data are presented as mean±SD

Non-significant difference between Carbetocin group and oxytocin and ergometrine group as regarding age, Bodyweight (BW), parity, and gestational age at cesarean section time.

**Table (2)** Hemoglobin levels before and after cesarean section.

Group	carbetocin	Oxytocin & ergometrine	P value
Pre-operative Hb (g/dl)	10.32 ± 1.12	10.16 ± 1.14	0.44
Postoperative Hb 24hrs (g/dl)	9.72 ± 1.04	9.20 ± 1.3	0.01
Hb drop (g/dl)	0.60 ± 0.08	0.96 ± 0.16	0.001

**Table (3)** Comparison between carbetocin group and oxytocin & ergometrine groups as regards estimated blood loss, hematocrit pre and postoperative.

Group	Carbetocin	Oxytocin & ergometrine	P value
Hematocrit pre-op	36.38 ± 5.19	35.63 ± 5.21	0.43
Hematocrit 24hrs postoperative	32.39 ± 5.21	30.1 ± 5.18	0.013
Hematocrit drop	3.99 ± 0.02	5.62 ± 0.03	0.001
Estimated blood loss	334.54 ± 99.6	467.23 ± 250.7	0.001

**Table (4)** Comparison of incidence of PPH between carbetocin group versus oxytocin & ergometrine group and hemodynamic changes.

group	carbetocin	Oxytocin & ergometrine	P-value
Post-partum hge	3 patients 5%	10 patients 16.6%	0.04
SBP pre-CS/mmHg	110.3 ± 5.53	110.21 ± 6.32	0.93
DBP pre-CS/mmHg	75.32 ± 3.63	76.1 ± 4.28	0.28
SBP post-CS/mmHg	111.65 ± 5.3	116.46 ± 9.39	0.01
DBP post-CS/mmHg	76.56 ± 3.7	81.37 ± 11.43	0.03

**Table (5)** Comparison between carbetocin groups versus oxytocin & ergometrine group as regards need for additional management.

Group	carbetocin	Oxytocin & ergometrine	P- value
Additional uterotonic doses	12 (20%)	19 (32%)	0.13
Blood transfusion	1 (1.6%)	4 (6.66%)	0.16
Uterine artery ligation	1(1.6%)	3(5%)	0.2
hysterectomy	(0.0)	(0.0)	

**Table (6)** Drug side effect.

group	carbetocin	Oxytocin & ergometrine	P -value
Nausea	6	4	0.5
Vomiting	7	4	0.34
Headache	12	4	0.03
Tachycardia	8	3	0.11
Palpitation	3	2	0.63
Dyspnea	2	1	0.56
Itching	2	0	0.15

#### 4. Discussion

This study found no statistically significant difference between the mean ages of mothers in the Carbetocin and oxytocin & ergometrine groups when comparing the two groups' mean ages of 25.515.1 years and 26.106.23 years in accordance with the inclusion criteria and the clinical outcomes of this investigation.

Carbetocin versus oxytocin & ergometrine groups did not differ substantially ( $P > 0.05$ ) based on gestational age, mother weight, and parity at the time of caesarean section.

Before and after surgery, hematocrit and haemoglobin levels were compared between the two groups, and a substantial difference was found.

Preoperative haemoglobin levels for women were found to be the same for both carbetocin (10.32 1.12 gm./dl) and oxytocin (10.16 1.14 gm./dl) in this study. There was a significant difference ( $P 0.01$ ) in 24-hour postoperative haemoglobin (9.72 1.04 vs. 9.20 1.3gm/dl) between the carbetocin and oxytocin groups. The carbetocin and oxytocin groups showed a statistically significant difference ( $P 0.01$ ) in the 24-hour drop in haemoglobin concentration. Preoperative hematocrit levels were compared in this study, and carbetocin was shown to be superior than oxytocin ( $p = 0.043$ ). In the carbetocin group, the average drop in hematocrit was 3.99 0.02 percent and 5.62 0.03 percent in the oxytocin group, with a statistically significant difference ( $P 0.01$ ).

favouring the carbetocin group when comparing the 24-hour postoperative hematocrit values (32.39 5.21 percent versus 30.1 5.18 percent).

The carbetocin group had a mean blood loss of 334.54 ml compared to 467.23 ml for the oxytocin group, which was statistically significant ( $p < 0.001$ ). Table (1).

This analysis corroborated the results of Askar et al [13]. According to the findings, postpartum haemoglobin levels differed significantly between the carbetocin and syntometrin groups (10.9 g/dl in the carbetocin group and 10.6 g/dl in the syntometrine group) ( $P < 0.05$ ). It decreased in the carbetocin group by 0.8 g/dl, whereas it decreased in the syntometrine group by 1.1%. This discrepancy was substantial on a statistical basis ( $P < 0.01$ ). The syntometrine group lost 81.5 ml more blood than the carbetocin group, a result that was statistically significant in terms of the estimated mean blood loss.

A considerable difference in mean blood loss was seen between the oxytocin and Carbetocin groups, however the difference was statistically insignificant [14].

According to another study, carbetocin is associated with less blood loss than oxytocin and ergometrine in the prevention of PPH [15].

HB investigations by Kansouh et al. [16] and Seow et al. [17] found that the oxytocin group had a larger estimate of blood loss than the control group before and after surgery [17]. The H.B. levels in this group dropped significantly. This is in accordance with current study results.

A network meta-analysis of accessible pharmacological drugs, which comprised 46 trials and 7368 people, contradicts our results. There was a clinically insignificant quantity of blood loss (54.83 mL; 95 percent confidence interval, 26.48–143.78) in favour of carbetocin over oxytocin, but this difference was not statistically significant [18].

Contrary to popular belief, PPH (defined as more than 1000 ml. The oxytocin concentration was higher than the carbetocin concentration. As said, there were no significant differences in blood pressure between the two groups before and after caesarean birth ( $P > 0.05$ ), although this was no longer the case after caesarean delivery ( $P < 0.05$ ) ( $P < 0.04$ ).

In a study including 694 women who had elective caesareans, the researchers administered carbetocin (100 mcg IV bolus) or oxytocin (25 iu per hour, 1000 mL of Ringer's lactate) during an 8-hour continuous infusion, and the researchers evaluated the incidence of PPH in women who got either drug. As a result of the carbetocin treatment, there was a decrease in PPH and an increase in the use of therapeutic oxytocin.

The hemodynamic effects of oxytocin and carbetocin were compared, and the efficacy of these two drugs was evaluated in terms of blood loss and the additional uterotonic needed following caesarean section at high risk of primary postpartum haemorrhage (Larciprete et al.,) [20]. There was no significant difference in estimated blood loss or haemoglobin levels

( $p > 0.05$ ) between oxytocin-treated and non-oxytocin-treated women. The findings of this investigation were at conflict with our own.

Carbetocin was shown to have less postpartum blood loss, lower incidence of atonic PPH (0.3% vs. 6.3%), and lower requirement for additional uterotonic medicines (9.1%) than oxytocin in the research by Amornpetchakul and colleagues [21]. There were no significant differences in side effects across the groups.

There was reduced need for blood transfusions and the usage of additional uterotonic medicines. The carbetocin and oxytocin groups did not vary significantly ( $P > 0.05$ ).

A randomised, double-blind experiment was carried out by Boucher et al. [22] at two institutions. In terms of demographics and risk factors for PPH, both groups were similar. The number of women requiring additional uterotonic medications did not alter much, according to the research.

In their double-blind randomised study, Attilakos et al. [23] found that women in the oxytocin group needed significantly more additional oxytocics (45.5 percent vs 33.5 percent, Relative risk 0.74, 95 percent CI 0.57-0.95). Relative risk 0.74, 95% CI 0.57-0.95), 45.5 percent to 33.5 percent. Carbetocin has been linked to a reduction in the need of extra oxytocins. PPH and blood transfusion rates have not been studied to see whether this reduces the rate of PPH or not. A comparison of mothers in the Carbetocin and oxytocin & ergometrine groups indicated no statistically significant difference in mean age between the two groups, which were both 25.515.1 years old, in agreement with the inclusion criteria and the clinical results of this trial.

There was no significant difference between the groups in terms of gestational age, mother weight, and the number of pregnancies at the time of caesarean section ( $P > 0.05$ ).

Comparisons of hematocrit and haemoglobin levels between the two groups before and after surgery showed that the two groups differed significantly.

There was no statistically significant difference between carbetocin (10.32 1.12 gm/dl) and oxytocin (10.16 1.14 gm/dl) in women's preoperative haemoglobin levels, according to this study. After 24 hours of follow-up, haemoglobin levels were significantly different between the carbo-oxytocin and the oxytocin groups ( $P < 0.01$ ). In the 24-hour drop in haemoglobin concentration, carbetocin and oxytocin groups differed significantly ( $P < 0.01$ ). For pre-operative hemostasis, carbetocin outperformed oxytocin ( $p = 0.043$ ) in this study, according to the findings. Carbetocin had a statistically significant advantage ( $P < 0.01$ ) over oxytocin in the comparison of 24-hour postoperative hematocrit values (32.39 5.21 percent against 30.1 5.18 percent), with a mean reduction in hematocrit of 3.99 0.02 percent and a 5.62 0.03 percent in the oxytocin group.

Mean blood loss in the carbetocin group was 334.54 millilitres, whereas the mean loss in the oxytocin group

was 467.23 millilitres. This was a statistically significant difference ( $p < 0.001$ ). Table (1).

According to this research, Askar et al results (13). According to the study, postpartum haemoglobin levels were significantly different between the carbetocin and syntometrin groups 24 hours after delivery (10.9 g/dl in the carbetocin group and 10.6 g/dl in the syntometrine group) ( $P < 0.05$ ). There was a 0.8 g/dl reduction in haemoglobin concentration in the carbetocin group and a 1.1 g/dl drop in the syntometrine group. There was a statistically significant difference between the two outcomes ( $P < 0.01$ ). Between the carbetocin and syntometrine groups, there was a statistically significant difference in mean blood loss, with the syntometrine group losing 81.5 ml more.

Although oxytocin and Carbetocin groups had significant differences in mean blood loss, the differences were statistically insignificant [14].

PPH is less likely to occur when a carbotocin-oxytocin combination is used, according to another study [15].

According to Kansouh and Seow's [16] and Kansouh and Seow's (9) research, there was an estimated larger amount of blood loss in the oxytocin group [17]. In this group, the H.B. decreased by a substantial amount. Based on the most recent studies, this is consistent with the results

According to a network meta-analysis of 46 trials and 7368 people, our findings are incorrect. Just 54.83 mL of predicted blood loss (95 percent confidence range: 26.48–143.78) was shown to be superior than oxytocin, which is clinically insignificant [18].

If we look at the frequency with which major PPH (more than 1000 ml. The concentration of oxytocin was higher in the oxytocin group than in the carbetocin group. When comparing the two groups before and after a caesarean section, no significant differences in blood pressure readings ( $P > 0.05$ ) were discovered between them. However, after the procedure ( $P < 0.05$ ), there was a significant difference between them ( $P < 0.04$ ).

A continuous 8-hour infusion of either carbetocin or oxytocin (25 iu. per hour, 1,000 millilitres of Ringer's lactate) was administered to 694 women who had elective caesarean sections, with the researchers then comparing how often they had postpartum haemorrhage (PPH). Carbetocin decreased the frequency of PPH and the need for therapeutic oxytocin (4.7 percent instead of 10.1 percent ;  $P = 0.01$ ).

Oxytocin and carbetocin hemodynamic effects were compared, and the efficacy of these two drugs was evaluated in terms of blood loss and the additional uterotonic necessary following caesarean section at high risk of primary postpartum haemorrhage (Larciprete et al., 20). There was no significant difference in estimated blood loss or haemoglobin levels ( $p > 0.05$ ) between oxytocin-treated and non-oxytocin-treated women (24.5%). Contrary to our expectations, the findings of this investigation were not what we expected.

Amornpetchakul et al. [21] found that carbetocin reduced postpartum blood loss, the incidence of atonic

PPH, and the requirement for additional uterotonic medicines in the carbetocin group compared to the oxytocin group. The groups did not differ significantly in terms of side effects.

There was reduced need for blood transfusions and other uterotonic medicines. The carbetocin and oxytocin groups had no statistically significant differences ( $P > 0.05$ ).

Randomized, double-blind trials were carried out in two hospitals by Boucher et al. [22]. Each group had a similar demographic profile and risk variables for PPH, which were statistically significant. There was no substantial difference in the number of women requiring additional uterotonic medications, according to the findings.

More women in the oxytocin group needed additional oxytocics, according to Attilakos et al. (23)'s double-blind randomised study (45.5 percent vs 33.5 percent , Relative risk 0.74, 95 percent CI 0.57-0.95). Relative risk 0.74, 95% CI 0.57-0.95), compared to 33.5 percent (45.5 percent). An increase in the use of carbetocin was shown to reduce the need of other oxytocics. PPH and blood transfusion rates have not been studied to see if this will reduce the rate of PPH or not.

## 5. Conclusion

In a caesarean birth with multiple pregnancies, carbetocin is more powerful and beneficial in avoiding atonic postpartum haemorrhage than the oxytocin-ergometrine combination.

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