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# Carbetocin versus Oxytocin: A Comparative Study to Prevent Postpartum Hemorrhage in Pre-eclamptic Women Delivered by Caesarean Section

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## ABSTRACT

**Background**: Postpartum hemorrhage and hypertensive disorders are the greatest contributors to maternal death in developing countries accounting for more than 50% of direct causes.

**Objective:** This study aimed to improve the clinical outcomes of carbetocin versus oxytocin in preventing postpartum hemorrhage in women with pre-eclampsia during C
aesarean Section (CS).

**Patients and methods**: This study included 120 pre-eclamptic pregnant women and were randomized (by alternation) into two groups of 60 patients: Group A received a single dose of carbetocin (100μg) diluted in 100ml 0.9% Nacl administered slowly over (30-60 seconds) intravenously after the delivery of the baby, while Group B received oxytocin (40 IU diluted in 100ml of 0.9% Nacl run at 25 ml per hour over 4 hours) intravenously after the delivery of baby.

**Results**: Regarding preoperative hemoglobin and HCT, there was no statistically significant difference between the 2 studied groups. There were statistical significant differences between the 2 groups in postoperative hemoglobin and HCT with higher levels among Group A compared with Group B. There was significant increase in frequency of blood transfusion and need of other uterotonic drugs in oxytocin group compared with carbetocin group. No significant difference was observed between the 2 studied groups in frequency of headache, but there were statistically significant increase in frequency of nausea, vomiting, abdominal pain and oligourea in oxytocin group compared to carbetocin group. There was significant increase in frequency of elevated temperature in carbetocine group compared to oxytocin group. **Conclusion:** Carbetocin has a superior effect on oxytocin for prevention of postpartum hemorrhage in women with pre-eclampsia.

**Keywords:** Carbetocin, Oxytocin, Postpartum hemorrhage, Pre-eclampsia, Cesarean section.

## INTRODUCTION

Primary postpartum hemorrhage (PPH) and hypertensive disorders are the greatest contributors to maternal death in developing countries, accounting for more than 50% of direct causes [(1)]. In developed countries both pathologies, together with embolism, are the main reasons women die during pregnancy. Any potential for improvement in management of these two disorders should be investigated [(2)].

Definition of PPH is the loss of 500 ml of blood in vaginal delivery or 1000 ml in Caesarean Section (CS) from the genital tract within 24 h of the delivery of the baby [(3)]**.** It is classified as: Minor PPH (blood loss 500–1000 ml) and major PPH (more than 1000 ml). Almost 500,000 women die due to this preventable cause each year, especially hemorrhage that occurred at time of delivery [(4)]. Other nonfatal complications may occur as Sheehan's syndrome (Pituitary infarction), coagulopathy, and organ damage due to hypotension, shock, and risk of hysterectomy [(5)].

Uterine atony is the first cause of hemorrhage at time of delivery; therefore, active management is better than expectant management of the third stage of labor. Third stage of labor is the period that following the delivery of a baby till placental delivery [(6)].

For many years, pharmacological options for the prevention of postpartum hemorrhage have been explored, among them is the oxytocin agonist carbetocin [(7,8)].

Uterotonic agents as oxytocin (10 IU) intramuscularly usually prevent PPH in low-risk vaginal and caesarean deliveries, or intravenous infusion (20–40 IU in 1000 ml, 150 ml/h) which is another alternative because of its short duration (its half-life is approximately 3.5 min) [(9)].

Carbetocin is a long-acting synthetic oxytocin analogue (1-deamino-1-monocarba-(2-O-methyltyrosine)-oxytocin that binds to oxytocin receptors with higher affinity), with a half-life of 40 minutes. Within two minutes of intravenous administration, it has the capacity to generate tetanic uterine contractions that last for six minutes. These tetanic contractions are followed by more rhythmic ones for approximately one hour [(10)].

Carbetocin has half-life of 40 min (4–10 times longer than oxytocin). Thus, it is given as single IV bolus following the delivery of baby at elective or emergency cesarean section and if further uterine stimulation is needed, treatment with other uterotonic drugs should be used. Carbetocin has also been shown to stimulate milk letdown due to its action on oxytocin receptors on the myoepithelial cells and there is not a significant amount of it in breast milk. Side effects are nausea, vomiting, chest pain, tachycardia, hypotension and respiratory distress [(11)].

Considering its potential advantages over oxytocin (more rapid and longer duration of effect,



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lower volumes to administer), it is imperative to evaluate this drug in women with pre-eclampsia.

This study aimed to improve the clinical outcomes of carbetocin versus oxytocin in preventing postpartum hemorrhage in women with pre-eclampsia during CS.

## PATIENT AND METHODS

A randomized controlled clinical trial was conducted on 120 pre-eclamptic women undergoing lower segment CS in the Obstetrics and Gynecology Department in Zagazig University Hospitals, Emergency Unit during the period from December 2021 to June 2022.

**Inclusion criteria:** Pre-eclampsia women with a singleton pregnancy. Undergoing elective or emergency caesarean section. Gestational age is more than 28 weeks.

**Exclusion criteria:** Women with multiple gestations. HELLP syndrome. Gestational age less than 28 weeks. Women with placenta previa or placental abruption. Women with current or previous history of significant disease including heart disease, liver, renal disorders or known coagulopathy. Hypersensitivity to carbetocin or oxytocin.

Patients were randomly assigned into two groups by closed envelope technique. Group A: Patients received a single dose of carbetocin (100μg) diluted in 10 mL 0.9% Nacl, administered slowly over (30 - 60 seconds) IV after the delivery of the baby. Group B: Patients received oxytocin (40 IU diluted in 100 mL of 0.9% Nacl run at 25ml per hour over 4 hour) IV after the delivery of the baby.

All patients were in stable condition (no evidence of maternal hemodynamic instability or fetal distress) before randomization, all patients were evaluated hourly and received magnesium sulphate to prevent eclampsia before CS and for 24 hours postpartum.

All women in this study were subjected to full history through clinical and obstetric examination, Vital signs, including heart rate (HR), respiratory rate (RR), blood pressure (BP), temperature, were checked immediately after placental delivery, for 24 hours. The blood pressure was measured; immediately after delivery and every hour after delivery for 24 hour. Side effects of the drugs such as headache, nausea, dizziness, hypotension, flushing, chest pain, and dyspnea were recorded.

Laboratory investigations included: Blood group and RH type. Complete blood picture (Hb level and Hct). Coagulation profile, PTT, PT, and INR. Renal function tests. Liver function tests. Urine analysis for protein by dip-sticks. Urine collection 24 hours after CS.

Trans abdominal ultrasonography assessed gestational age and site of the placenta and fetal weight, CFMF, AFI, fetal presentation.

The primary outcome measure was development of PPH that requires use of additional uterotonics.

Secondary outcomes were incidence and amount of blood transfusion, hemoglobin and hematocrit changes pre-and post-delivery, vital signs during and after delivery, time of discharge from hospital, complications post-delivery (fever, disseminated intravascular coagulation), maternal infection, ICU admission, cesarean hysterectomy, and adverse effects.

**Ethical considerations:**

**An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

### *Statistical analysis*

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered, and analyzed using Microsoft Excel software. Data was then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative represented as numbers and percentages, while quantitative data represented by mean ± SD. Chi-square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Independent samples t-test was used to compare between two independent groups of normally distributed variables. P-value was set at $\leq 0.05$ for significant results, and $\leq 0.001$ for highly significant results.

## RESULT

There was no statistically significant difference between two groups in all items (Table 1).

**Table (1): Basic data of the two studied groups (No=120)**

| Variable | Group A No. (60) | Group B No. (60) | t-test | P-value |
|---|---|---|---|---|
| **Age (years)**<br>Mean ± SD<br>(Range) | 29.7 ± 4.9<br>(19-38) | 31.3 ± 6.1<br>(20-41) | 0.5 | 0.6 |
| **BMI**<br>Mean ± SD<br>(Range) | 28.4 ± 4.6<br>(20-34) | 28.6 ± 5.7<br>(19-36) | 0.4 | 0.7 |
| **Gravidity**<br>Mean ± SD<br>(Range) | 2.8 ± 0.3<br>(1-4) | 2.6 ± 0.2<br>(1-5) | 0.3 | 0.6 |
| **Parity**<br>Nulliparous<br>Multiparous | 40 (33.3%)<br>20 (66.7%) | 35 (58.3%)<br>25 (41.7%) | 0.7 | 0.9 |
| **Gestational age (weeks)**<br>Mean ± SD<br>(Range) | 34.4 ± 3.5<br>(28-40) | 35.3 ± 3.6<br>(28-40) | 1.37 | 0.12 |
| **Previous CS**<br>Median(range) | 3 (1-6) | 2 (1-4) | 0.706 | 0.48 |
| **Abortion**<br>Median(range) | 2 (1-7) | 1 (1-4) | 1.421 | 0.15 |

Table 2; there was no statistical differences between the two groups regarding pre-operative and 24 hours postoperative pulse rate, respiratory rate, systolic and diastolic blood pressure

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**Table (2): Vital signs in two groups pre and post drugs administration**

| Vital signs | Group A<br>No. (60) | Group B<br>No. (60) | t-test | P-value |
|---|---|---|---|---|
| **Preoperative Pulse rate**<br>Mean ± SD | 76.1 ± 3.6 | 74.5 ± 4.5 | 0.9 | 0.1 |
| **Postoperative Pulse rate**<br>Mean ± SD | 85.6 ± 5 | 87.2 ± 8.1 | 1.1 | 0.2 |
| **Preoperative systolic blood pressure**<br>Mean ± SD | 153.38 ± 8.87 | 155.17 ± 14.3 | 1.4 | 0.08 |
| **Postoperative Systolic blood pressure**<br>Mean ± SD | 142.19 ± 10.3 | 140.33 ± 9.1 | 1.7 | 0.06 |
| **Preoperative diastolic blood pressure**<br>Mean ± SD | 95 ± 5.05 | 96.5 ± 6.68 | 1.1 | 0.3 |
| **Postoperative diastolic blood pressure**<br>Mean ± SD | 86.34 ± 5.46 | 87.2 ± 4.78 | 1.2 | 0.07 |
| **Preoperative RR(/min)**<br>Mean ± SD | 17.23 ± 1.24 | 16.9 ± 1.39 | 1.1 | 0.3 |
| **Postoperative RR(/min)**<br>Mean ± SD | 17.3 ± 2.01 | 17.1 ± 1.98 | 1.2 | 0.07 |

In table 3, there was significant difference between two groups in hemoglobin and HCT post operatively which higher among Group A than Group B. However, regarding preoperative hemoglobin and HCT, there was no significant difference between two groups.

**Table (3):** Comparing change in hemoglobin, HCT, pre and post-operative in two groups

| Variable | Time | | Group A No. (60) | Group B No. (60) | P# |
|---|---|---|---|---|---|
| **Hemoglobin (g/dl)** | **Pre** | Mean ± SD | 12.1 ± 2.5 | 11.8 ± 2.1` | 0.6 |
| | **Post** | Mean ± SD | 10.9 ± 07 | 9.1 ± 0.8 | 0.04* |
| | **P^** | | 6.7 | 5.5 | |
| **HCT** | **Pre** | Mean ± SD | 33.86 ± 2.3 | 33.67 ± 2.8 | 0.5 |
| | **Post** | Mean ± SD | 32.14 ± 3.7 | 31.38 ± 2.8 | 0.04* |
| | **P^** | | 5.6 | 4.7 | |

* Statistically significant difference (P ≤ 0.05). ^: Paired t test.

Table 4 showed that there was a significant reduction in frequency of blood transfusion and need of other uterotonic drugs in Group A compared with group B.

**Table (4): Blood transfusion and other drugs needed among two groups**

| Variable | Group A No. (60) | | Group B No. (60) | | $\chi^2$ | P-value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| **Needed Bl. transfusion:** | | | | | | |
| No | 56 | 93.3 | 50 | 83.3 | **4.02** | **0.04*** |
| Yes | 4 | 6.7 | 10 | 16.7 | | |
| **Needed other drugs:** | | | | | | |
| No | 60 | 100 | 45 | 75 | **17.78** | **<0.001**** |
| Yes | 0 | 0 | 15 | 25 | | |

$\chi^2$: Chi square test. *: Significant. **: Highly significant.

Table 5 showed that there were no significant differences between two groups in frequency of headache but there were statistically significant increase in frequency of nausea, vomiting, abdominal pain and oliguria in oxytocin group compared to carbetocin group while there was significant increase in frequency of elevated temperature in carbetocin group compared to oxytocin group.

**Table (5): Comparison between two groups regarding side effects of drugs**

| Side effects of drugs | Group 1 No. (60) | | Group 2 No. (60) | | $\chi^2$ | P-value |
|---|---|---|---|---|---|---|
| | No | % | No | % | | |
| **Headache:** | | | | | | |
| No | 39 | 65 | 34 | 56.6 | 1.04 | 0.31 |
| Yes | 21 | 35 | 26 | 43.4 | | NS |
| **Nausea:** | | | | | | |
| No | 55 | 91.7 | 48 | 80 | **14.22** | **<0.001**** |
| Yes | 5 | 8.3 | 12 | 20 | | |
| **Vomiting:** | | | | | | |
| No | 60 | 100 | 52 | 86.7 | **19.2** | **<0.001**** |
| Yes | 0 | 0 | 8 | 13.3 | | |
| **Abdominal pain:** | | | | | | |
| No | 56 | 93.3 | 50 | 83.3 | **4.63** | **0.03*** |
| Yes | 4 | 6.7 | 10 | 16.7 | | |
| **Oliguria:** | | | | | | |
| No | 56 | 93.3 | 50 | 83.3 | **4.63** | **0.03*** |
| Yes | 4 | 6.7 | 10 | 16.7 | | |
| **Elevated Temperature:** | | | | | | |
| No | 55 | 91.7 | 50 | 83.3 | **7.55** | **0.006**** |
| Yes | 5 | 8.3 | 10 | 16.7 | | |

$\chi^2$: Chi square test. NS: Non-significant. *: Significant. **: Highly significant.

## DISCUSSION

There were no statistically significant differences regarding the indication of CS and demographic data between the two groups. All enrolled women had a gestational age more than 28 weeks' gestation, singleton pregnancy. Regarding vital sign, we have noted that during the postpartum period, there was just a decrease of both systolic and diastolic blood pressure among both groups, but no significant differences between both groups regarding the hemodynamic parameters.

**Liu *et al.*** [12] studied 60 women and divided them into two groups (group A) received 100 μg carbetocin and (group B) received 20 IU oxytocin in 500ml Nacl 0.9%, and they observed the hemodynamic status of the patients (mean arterial pressure one hour before administration of the drug and one and two hours after drug administration, no significant differences between the groups. and these results were in agreement with the results obtained by this study.

Also, the present study has shown that postpartum hemoglobin and hematocrit were significantly lower among women received oxytocin compared to women received carbetocin with more blood loss among the oxytocin group. There was a significant decrease in hemoglobin and hematocrit among the oxytocin group compared to pre-operative values.

These results were in disagreement with the results obtained by **Liu *et al.*** [12] who found that there was no significant difference in estimated blood loss and in the drop hemoglobin level**.**

**Reyes and Gonzalez** [13] in their study on hypertensive pregnant women who delivered by either CS or vaginal delivery had also shown no significant difference between both medications regarding post-operative hemoglobin.

Also **Nossair *et al.*** [14] who studied 200 patients divided into two groups (Group A: 100 patients received (100 μg) carbetocin as single dose IV, Group B: 100 patients received (10 Iu) oxytocin as single dose IV. The mean of hemoglobin preoperative were the same 12gm/dl.

Postoperative mean of hemoglobin were 10.5gm/dl in group A and 10gm/dl in group B and so there was no significant difference between both groups regarding hemoglobin change and also these results were in disagreement with the results obtained by this study because in the present study we observed significant decrease hemoglobin level in oxytocin group, may be due to difference in the rate of administration.

In the current study, the difference between both groups regarding the need for additional uterotonic, and blood transfusion, were higher among oxytocin group compared to carbetocin group. The present study has also shown that no one in the carbetocin group required additional uterotonics while 25% of oxytocin group patients did in the form of 2 rectal suppositories of misoprostol to ensure the uterine contraction for long period. This may indicate the efficacy of carbetocin in the prevention of PPH in women with pre-eclampsia when compared to oxytocin.

These results were in disagreement with the results obtained by **Liu *et al.*** [12] who found that there were non-significant differences regarding the need for additional uterotonic, need for blood transfusion between the carbetocin and oxytocin groups. However, the present results were in agreement with the results obtained by **Larciprete *et al.*** [5] who studied 51 women with high risk of PPH and found more women needed additional uterotonic agents in the oxytocin group.

Supporting the current findings **De Bonis and colleagues *et al.*** [15] in their study on 110 women with risk factors of PPH have found that a single carbetocin injection was efficacious and safe on the maintenance of uterine tone and on the limitation of blood loss, in the postoperative period.

Regarding safety, the present study has shown that that there were no significant differences between the two studied groups in frequency of headache but there were statistically significant increase in frequency of nausea, vomiting, abdominal pain and oligo urea in oxytocin group compared to carbetocin group also there were significant increase in frequency of elevated temperature in carbetocin group compared to oxytocin group.

Similar results were obtained by a study carried out by **Askar *et al.*** [16] in which the result showed that the carbetocin group had a fewer r*i*sk of vomiting, headache, and naus*e*a but th*e* differences were not statistically signif*i*cant.

All reported side effects were tolerable and were treated accordingly. Despite this difference regarding incidence of side effects, both drugs were shown to be safe [17]**.**

In conclusion, carbetocin has a superior effect on oxytocin for prevention of PPH in women with pre-eclampsia.

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**Author contribution:** Authors contributed equally in the study.

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