CARBETOCIN FOR PREVENTION OF POSTPARTUM HEMORRHAGE AFTER CESAREAN SECTION IN WOMEN WITH SEVERE PREECLAMPSIA IN COMPARISON TO OXYTOCIN

By

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ABSTRACT

Background: Postpartum hemorrhage (PPH) responsible for twenty to twenty five percent of maternal mortality. The major PPH mechanism is uterine atony, as it is active in fifty nine percent of pregnant. The use of uterotonics after birth is implicit in its avoidance.

Objective: To evaluate the effect of carbetocin in prevention of PPH after cesarean section in pregnant with severe preeclampsia (PE) in comparison to oxytocin.

Patients and Methods: This study involved 100 pregnant with severe PE with gestational age between 28 and 40 weeks. The patients were divided into two equal groups: group (A) received 100 microgram carbetocin dissolved in 5 ml saline 0.9% direct I.V over 3 minutes, and group (B) received 40 i.u oxytocin I.V infusion.

Results: In carbetocin cases, 30 pregnant needed misoprostol to gain a good uterine contraction. In oxytocin cases, although a sustained infusion, ten pregnant had another oxytocin dose, and ten pregnant needed misoprostol dose. Also, prevalence of extra uterotonics doses in the carbetocin and oxytocin cases was 60% and 40%, respectively (P = 0.021). Oxytocin cases had significantly higher mean of period from oxytocin to misoprostol than carbetocin cases (p=0.001).

Conclusion: Carbetocin has the same efficacy and safety of oxytocin in PE. Since it’s easy to administer, it needs a relatively small vehicle capability and has a long-lasting uterotonics efficacy.

Keywords: Postpartum Hemorrhage, Carbetocin, Oxytocin, Severe Preeclampsia.

INTRODUCTION

Preeclampsia (PE) is characterized by high blood pressure (≥140/90 mmHg), and proteinuria where urinary excretion occurs > 300 mg of protein in 24 hours, or 3 mg / dL of protein in 2 randomized urine samples after 20 weeks gestation. The prevalence of PPH is greater in PE patients than normal blood pressure pregnant (Fullerton et al., 2013).

Oxytocin has been the first uterotonics drug for PPH, and carbetocin was recently suggested. Carbetocin is a structural analogue of natural oxytocin, and has a long-acting uterotonics medication for the avoidance of PPH in C.S. Compared to existing uterotonics substances; carbetocin starts rapidly and lasts longer than sustained oxytocin infusion with a similar protection feature. Carbetocin is used as a single intravenous dose, a much smoother
and less error-prone treatment than an oxytocin-dependent infusion (Elbohoty et al., 2016).

In this study, we aimed at determining carbetocin efficacy for prevention of PPH after C.S in pregnant with severe PE compared with oxytocin.

PATIENTS AND METHODS

This was a case control study which involved 100 pregnant with severe preeclampsia between 28 and 40 weeks gestation at AL-AZHAR University Hospitals (AL-Hussein and Bab EL-Sha'riya), and Sohag Teaching Hospital during the period from October 2019 to October 2020.

After ethical committee and consents from the patients, all pregnant were divided into two groups:

- **Group A** received 100 microgram carbetocin dissolved in 5 ml saline 0.9% direct I.V over 3 minutes.
- **Group B** received 40 i.u oxytocin I.V infusions.

Inclusion criteria:

- Systolic blood pressure ≥160.
- Diastolic blood pressure ≥110.
- Proteinuria +2 or more qualitative test.
- Clinical edema.
- Symptoms of CNS dysfunction as severe headache.
- Hepatic abnormality as high liver enzymes at least twice the normal, epigastric pain.
- Thrombocytopenia platelet count less than 100000 micro L.
- Progressive renal abnormality as high serum creatinine, oliguria, and anuria.

Exclusion criteria:

- Grand multipara more than five.
- Multiple fibroids.
- Anemia and malnutrition.
- APH as placenta previa.
- Uterine over distention as macrosomic baby.
- DIC.

All patients had been subjected to comprehensive history, general, local examination, ultrasound imaging and laboratory investigations (urine analysis, hemoglobin level, liver enzymes, creatinine and platelets count).

Statistical analysis:

Recorded data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance or Mann-Whitney U test was used when comparing between two means. Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant when P-value ≤0.05.
RESULTS

Our results involved 100 pregnant. Their mean of age in carbetocin cases was 27.14, and in oxytocin cases was 26.99 years. No significant differences regarding age, gravidity, parity, abortion, gestational age, and severity of PE (Table 1).

Table (1): Maternal baseline characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carbetocin group (n = 50)</th>
<th>Oxytocin group (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.14 ± 4.9</td>
<td>26.99 ± 5.1</td>
<td>0.881</td>
</tr>
<tr>
<td>Gravid</td>
<td>1.8 ± 1.1</td>
<td>1.7 ± 0.9</td>
<td>0.542</td>
</tr>
<tr>
<td>Parity</td>
<td>1.6 ± 0.7</td>
<td>1.4 ± 0.7</td>
<td>0.608</td>
</tr>
<tr>
<td>Abortion</td>
<td>1.5 ± 0.6</td>
<td>1.09 ± 0.5</td>
<td>0.437</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>38.43 ± 2.09</td>
<td>38.85 ± 1.09</td>
<td>0.212</td>
</tr>
<tr>
<td>Severe hypertension, n (%)</td>
<td>37(74)</td>
<td>39(78)</td>
<td>0.640</td>
</tr>
<tr>
<td>Severe proteinuria, n (%)</td>
<td>10(20)</td>
<td>11(22)</td>
<td>0.806</td>
</tr>
<tr>
<td>Oliguria, n (%)</td>
<td>1(2)</td>
<td>1(2)</td>
<td>1.00</td>
</tr>
<tr>
<td>HELLP syndrome, n (%)</td>
<td>10(20)</td>
<td>11(22)</td>
<td>0.806</td>
</tr>
<tr>
<td>Eclampsia/neurologic signs</td>
<td>35(70)</td>
<td>36(72)</td>
<td>0.826</td>
</tr>
</tbody>
</table>

In carbetocin cases, 30 pregnant needed misoprostol to gain a good uterine contraction. In oxytocin cases, although a sustained infusion, ten pregnant had another oxytocin dose, and ten pregnant needed misoprostol dose. Also, prevalence of extra uterotonics doses in the carbetocin and oxytocin cases was 60% and 40%, respectively (P = 0.021). Oxytocin cases had significantly higher mean of period from oxytocin to misoprostol than carbetocin cases (P=0.001). Average period of admission in intensive care unit (ICU) was significantly higher in oxytocin cases (p=0.001) (Table 2).

Table (2): Comparison between cases as regard to extra measures needed

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carbetocin group (n = 50)</th>
<th>Oxytocin group (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for extra uterotonics, n (%)</td>
<td>30(60%)</td>
<td>20(40%)</td>
<td>0.046</td>
</tr>
<tr>
<td>Time interval to extra uterotonics, minutes</td>
<td>11±21.2</td>
<td>80±10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Need for compression balloon, n (%)</td>
<td>15(30%)</td>
<td>1(2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay in intensive care unit, days</td>
<td>8±2.3</td>
<td>12.2±4.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The mean hemoglobin drop, blood loss, and massage times significantly raised in oxytocin cases in comparison to carbetocin cases (P< 0.05), while the blood pressure and respiratory rate were comparable between the two groups (P > 0.05) (Table 3).
**Table (3):** Comparison between cases as regard to hemodynamic changes

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carbetocin group (n = 50)</th>
<th>Oxytocin group (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin drop change (mg/dl)</td>
<td>1.0±0.9</td>
<td>2.1±1.1</td>
<td>0.011</td>
</tr>
<tr>
<td>Bleeding volume (mg/dl)</td>
<td>421.19±110</td>
<td>560.32±162</td>
<td>0.008</td>
</tr>
<tr>
<td>Massage times (Seconds)</td>
<td>3.26±0.7</td>
<td>4.7±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Pulse rate (No.)</td>
<td>87.23±6.4</td>
<td>90.22±5.6</td>
<td>0.015</td>
</tr>
<tr>
<td>Respiratory rate (No./min)</td>
<td>17.91±1.9</td>
<td>17.22±1.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Systolic Blood pressure (mmHg)</td>
<td>109.11±8.2</td>
<td>108.83±8.3</td>
<td>0.866</td>
</tr>
</tbody>
</table>

Regarding side effect, headache (12% versus 4%), dizziness (8% versus 2%), and tremor (10% versus 2%) occurred more frequent in oxytocin cases (P < 0.05); but nausea and vomiting were comparable in all cases (P > 0.05). No cases of urinary retention were founded in all cases. Twenty percent in carbetocin cases and none of in oxytocin cases had pruritus (P < 0.001) (Table 4).

**Table (4):** Comparison between cases as regard to side effects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carbetocin group (n = 50)</th>
<th>Oxytocin group (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting, n (%)</td>
<td>3(6%)</td>
<td>4(8%)</td>
<td>0.352</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>2(4%)</td>
<td>6(12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>6(12%)</td>
<td>8(16%)</td>
<td>0.265</td>
</tr>
<tr>
<td>Tremor, n (%)</td>
<td>1(2%)</td>
<td>5 (10%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>1(2%)</td>
<td>4(8%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Pruritus, n (%)</td>
<td>10(20%)</td>
<td>0(0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Postpartum hemorrhage (PPH) is the primary reason of women death and morbidity. It accounts for about 1 quarter of all mother's deaths, and has incidence of about sex percent. PPH in many developed countries is estimated to have grown in prevalence and magnitude (Mehrabadi et al., 2013).

Our findings indicated that 60% and 40% of carbetocin and oxytocine, respectively, obtained extra uterotonic administration. The cases had mean intervals of oxytocin injection to misoprostol substantially greater than that of carbetocin. The mean time of the ICU stay in the oxytocin cases was also significantly higher. However, El Behery et al. (2016) revealed that none in carbetocin cases versus 71.5% in oxytocin cases required extra uterotonics. Furthermore, Jin et al. (2016) reported that, in contrast to oxytocin in pregnant after C.S, carbetocin was associated with a significant decreased demand of extra uterotonic medications. Ibrahim et al. (2020) reported that 38% needed extra oxytocin, 8% in carbetocin cases, and 68% in oxytocin cases. This difference was significant. Patients in the oxytocin cases had 9 times the risk of needed other uterotonics as carbetocin cases. One of the four cases in carbetocin group was during CS, and the other 3 patients received the extra oxytocin after delivery during the...
first 3 hours after operation. For the oxytocin cases, 13 patients needed the other oxytocin during the operation and 21 needed after delivery during the first 3 hours after operation. All patients had good uterine contraction thereafter until leaving the hospital.

In the study in our hands, the mean hemoglobin drop, blood loss, and massage times significantly raised in oxytocin cases comparing to carbetocin cases, while the blood pressure and respiratory rate were comparable between the two cases. Ibrahim et al. (2020) reported that the mean change in hemoglobin level 24 hours following CS in the carbetocin cases and in the oxytocin cases, the difference was significant. However, change in platelet count was not significantly different between both groups. Regarding Kansouh and El Naggar (2019), the difference between blood hemoglobin levels 24 hour postdelivery was not significantly lower in the carbetocin cases. Pregnant in oxytocin cases, 2 h after CS, showed a statistically significantly higher SBP and DBP than pregnant in carbetocin cases. However, Reyes and Gonzalez (2011), revealed that there were no differences between the carbetocin and oxytocin cases in hemoglobin concentration after delivery, or in rates of oliguria.

The present study showed that headache, dizziness, and tremor occurred more frequent in oxytocin cases, while nausea and vomiting were comparable in all cases. No cases of urinary retention were founded in all cases. Twenty percent in carbetocin cases and none of in oxytocin cases had pruritus. However, Jin et al. (2016) found that side effect was significantly reduced in the carbetocin cases.

Kansouh and El Naggar (2019), reported that there was no significant difference regarding incidence of nausea, vomiting, flushing, shivering, dyspnea, palpitations, and itching. The prevalence of tachycardia and headache was significantly raised in the carbetocin cases.

Nevertheless, use of meperidine as analgesics after delivery could be responsible for the nausea and vomiting recorded in the postnatal unit. Headache can also be associated with local anesthetic instead of a real uterotonic side effect. Abdominal pain can also be attributed not to the side effects of carbetocin or oxytocin, but to uterine contractions. It is kind of an indicator that the medication is successful in uterine tones and gains the intended goal. The protection and negative effects of carbetocin versus oxytocin after CS were measured in a recent report. The authors revealed that side effects were comparable between both cases, however, pain after delivery in carbetocin cases was significantly lower than in oxytocin cases and still significant from 1st to 3rd day after CS (De Bonis et al., 2012).

Another research showed that a single dose of carbetocin has comparable effect to a two-hour oxytocin infusion, which controls intra-operational blood loss following placental delivery (Larciprete et al., 2013).

**CONCLUSION**

Carbetocin tended to have the same efficacy and safety of oxytocin in PE, since it was easy to administer, needed a
relatively small vehicle capability, and has a long-lasting uterotonic efficacy. So, it may have a better chance in severe PE.

REFERENCES


CARBETOCIN FOR PREVENTION OF POSTPARTUM HEMORRHAGE...

Un carbetocin dans la prévention de l'hémorragie postnéonatale des femmes qui ont accouché de grossesses toxiques sévères, en comparaison avec l'oxytocine. 

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Background: Hemorrhage in obstetrics is a frequent cause of maternal mortality. The uterine muscle is a vital organ for the smooth delivery of the infant. The blood supply of the uterus is crucial for its function. In the case of uterine atony, hemorrhage may occur. The most common cause of uterine atony is uterine inertia. 

Materials and Methods: The study included 100 pregnant women with severe toxemia. The study was divided into two groups: Group A (n=50) received 100 ml of 0.9% saline solution, and Group B (n=50) received 250 mcg of carbetocin. 

Results: The results showed that carbetocin was more effective than oxytocin in preventing uterine atony. 

Conclusion: Carbetocin is an effective drug in the prevention of postpartum hemorrhage.
الميزوبروسستول. كما أن استخدام الجرعات الزائدة من قابضات الرحم كانت 60% بالنسبة لحالات الكاربيتوسين و 40% لحالات الأوكسيتوسين.

الاستنتاج: الكاربيتوسين فعال وأمن مثل الأوكسيتوسين لدى النساء اللواتي يعانون من تسهيم الحمل وذلك لأنه من السهل استخدامه و ذو فعالية لوقت طويل.

الكلمات الدالة: نزيف مابع لولادة، الكاربيتوسين، الأوكسيتوسين.