Carbetocin versus Oxytocin in Decreasing Blood Loss at Caesarean Section

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Abstract

Background: Postpartum hemorrhage (PPH) is excessive blood loss after childbirth, and has been defined as blood loss >500 ml in normal vaginal delivery, or >1000 ml after cesarean section (CS). Postpartum hemorrhage PPH accounts for nearly one quarter of all maternal deaths worldwide.

Purpose: To compare the efficacy and safety of carbetocin with those of oxytocin in reducing intra-operative and postoperative blood loss at caesarean section.

Patients and Methods: This study is a prospective randomized (closed envelop) comparative study conducted in the Obstetrics and Gynecology Department of Benha university hospital and Matria Teaching Hospital. During the period from December 2016 till December 2017. The study included 200 pregnant women undergoing elective cesarean section at term (completed 37 weeks of gestation) with singleton pregnancy divided into 2 groups, group 1 was administered 10 IU oxytocin and group 2 was administered 100µg carbetocin.

Results: Carbetocin was associated with a significantly reduced need for additional uterotonic agents (8% versus 21%, P value=<X0.009) compared with oxytocin in women following C.S. there is significant difference in the amount of estimated blood loss (p value=0.0001) and the incidence of postpartum hemorrhage (p value =0.179), adverse effects, our study show non significant difference between two group.

Conclusion: Carbetocin appears to be more effective than oxytocin for prevention of postpartum hemorrhage in patient undergoing elective cesarean section. According to the results of this study it is found that there is a good overall agreement that Carbetocin might be effective in controlling the amount of blood loss during cesarean section and giving a better chance in prevention of atonic post partum Hemorrhage.

Keywords: Postpartum hemorrhage · Carbetocin · Cesarean section · Oxytocin · Third stage of labor

Introduction

The most frequent cause of PPH is uterine atony, contributing up to 80 % of the PPH cases. Although two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, pre-eclampsia, coagulopathy, multiple gestation and antepartum hemorrhage. Also caesarean section (CS) is a recognized risk factor for PPH and its prevalence is increasing (1).

The impact of PPH on maternal morbidity and mortality makes active management of the third stage of labor to a critical key. To this end, uterotonic agents are administrated immediately after delivery of the baby. The administration of uterotonic medication soon after the delivery of the fetus is an essential part of the active management of third stage of labor that is capable of decreasing the incidence of PPH by 40% (2).
Oxytocin is currently the uterotonic of first choice. It has proven to decrease the incidence of PPH by 40% and has a rapid onset of action (within 1-2 mm) (3). A disadvantage of oxytocin is its short half-life of 4-10 mm, regularly requiring a continuous intravenous infusion or repeated, intramuscular injections. Moreover, large doses or boluses of oxytocin are associated with adverse effects in the form of hypotension, nausea, vomiting, dysrhythmia, ST-t changes, pulmonary edema and severe water intoxication and convulsions (2).

Carbetocin is an eight amino acid long analogue of oxytocin (aonapeptide) and thus has a similar action. Carbetocin primarily agonizes peripherally expressed oxytocin receptors (4). Carbetocin is a long-acting oxytocin analogue indicated for the prevention of uterine atony after child birth. Carbetocin has a rapid onset of action (within 1-2 mm) and a prolonged duration of action (approximately 1 h) because of sustained uterine response with contractions of higher amplitude and frequency. Its safety profile is comparable to that of oxytocin (5).

Endogenous and synthetic oxytocin has a half-life of approximately 3.5 minutes. Carbetocin, in comparison, has a much longer half-life ranging from 85-100 minutes. The bioavailable dose is around 80%. The, elimination half-life following intravenous administration is around 40 minutes, though the elimination mechanism is not entirely known. Studies have shown that elimination is only minimally renal, but may occur at least partially through enzymatic degradation of peptides, primarily on the C-terminal end. Both elimination and volume of distribution are not dose dependent (6).

Carbetocin makes a longer uterine response compared with oxytocin in terms of frequency and amplitude of contractions. Moreover, in comparison with oxytocin or syntometrine, it seems to have fewer gastrointestinal and cardiovascular side effects (8).

Patients & Methods

This study is a prospective randomized (closed envelop) comparative study conducted in the Obstetrics and Gynecology Department of Benha university hospital and Matria Teaching Hospital, during the period from December 2016 till December 2017.

Inclusion criteria

Women at age between 20-35 years old with a singleton pregnancy undergoing elective caesarean section after 37 weeks of gestation and confirmed by ultrasound.

Exclusion criteria

- Women with high risk for primary atomic postpartum hemorrhage who undergo CS for multiple gestation, placenta praevia, placental abruption, previous uterine atony, pre-eclampsia, polyhydramios, distension with tumor, clots or accidental hemorrhage, anemia (Hb% < 10 g/dl), prolonged labor were excluded because there is a higher risk of hemorrhage with these conditions and it was therefore felt to be inappropriate to recruit these women.
Women undergoing caesarean section at less than 37 weeks of gestation (likely to be emergency caesarean sections: a different smaller group from term pregnancies) and women having emergency caesarean.

Section for fetal or maternal distress where, due to time constraints, it was not possible and/or appropriate to recruit or randomize.

- Patients have any medical disorders contraindicating the use of carbocin (hepatic or renal disease, serious cardiovascular disorder or epilepsy) or refused to participate in the study.

**Study design**

**Sample size estimation:**

100 participants were included in each group depending on the following equation

$$N = \frac{Z^2 \times PQ}{E^2}$$

$E =$ error, $P =$ proportion affected with disease, $Q = 1 - p$, $Z =$-value (e.g., 1.96 for a 95 percent confidence level).

**The patients will be classified into 2 equal groups as follows:**

- **Group I:** (100 patients) will be given 10 IU oxytocin (Syntocinon, Novartis Pharma AG, Basel, Switzerland) \(^{(9)}\).
- **Group II** (100 patients) will be given 100 ug of carbotocin (Pabal 1ml ampoule 100 ug/ml, Ferring pharmaceuticals, Kiel, Germany) \(^{(9)}\).

The study medication (carbetocin or oxytocin) was diluted in 10 normal saline and administered slowly (over 30-60 seconds) intravenously by the anesthetist after the birth of the baby. The slow administration has been shown to reduce the potentially harmful homodynamic effects of oxytocin (and presumably carbetocin).

**Methods:**

All patients will be subjected to the following:

**A) Preoperative:**

1. Careful Full medical history taking including age, parity and Gestational age as calculated from the first day of the last menstrual period confirmed by ultrasound, indication of C.S., previous postpartum hemorrhage and history of chronic diseases.

2. Thorough clinical examination for determination of baseline clinical data concerning pulse, temperature, blood pressure, body mass index (BMI) and abdominal examination for fundal level detection, prescience of previous abdominal scar and auscultation of fetal heart sound. Vaginal examination was performed for cervical assessment for dilation, effacement, position, head engagement and bulging of membrane.

3. Laboratory investigations including complete blood picture, blood glucose, liver and kidney functions.
4. Abdominal ultrasound to confirm gestational age, inclusion criteria, exclusion criteria and estimation of amniotic fluid index (AFI).

B) Intraoperative:

The study medication (carbetocin or oxytocin) was diluted in 10 ml normal saline and administered slowly (over 30-60 seconds) intravenously by the anesthetist immediately after the birth of the baby. Maternal blood pressure will be measured before C.S., immediately after giving uterotonic drug ad 30 and 60 minutes later.

C) Postoperative:

- Each patient will be asked about some possible side effects of the used uterotonic drug as headache, nausea, heat sensation, abdominal pain, back pain, metallic taste and pruritus. Presence of the following signs (sweating, flushing, tremors and vomiting).

- Two hours after C.S. the following laboratory investigations including hemoglobin concentration, complete blood picture and liver and kidney function tests to assess safety of uterotonic drugs.

Primary outcome

Estimation of blood loss by different methods for each case:

1st method: Calculate amount of blood loss.

1- Estimation of total fluid loss (blood + amniotic fluid) obtained intraoperative:

Total fluid loss= a+(c-b) where a= volume of contents of suction bottle ± fluid loss around table, b= Dry (towels and gowns) and c= Soaked (towels and gowns)

Fluid loss around table is swept by either gowns or dry towels.

Each gram difference in weight between soaked and dry towels equal 1 ml.

2- Estimation of amount of blood loss intraoperative:

Blood loss= (total fluid loss - d) where d= AFV (amniotic fluid volume) AFI (amniotic fluid index) x 30 ml. Note. Weight gowns with sterilization cover then we subtract the cover alone to get net weight of gowns and towels.

3- Estimation of total blood loss: -

Estimation of blood loss intra-operative + blood loss 2 hours post-operative assessed by weighting the soaked pads and subtracting the dry weight pad with each gram (gm) difference in weight: equals one ml.

2nd method: is the mathematical calculation in which the lost blood intraoperatively would be estimated by measuring the hematocrit (Hct) immediately after hospital admission and two hours postoperatively in recovery room. The Actual Blood Loss (ABL) would be calculated from a modification of the Gross formula given below: 

\[
ABL = \frac{Blood\ volume\ (BV) \times \{Hct\ (i) - Hct\ (f)\}}{Hct\ (m)}
\]

\[
BV = Body\ weight\ x\ 70\ ml/Kg.
\]
Hct(i): is the initial pre-operative hematocrit, Hct (f) is the final Hct measured two hours postoperative and Hct (m) is the mean Hct \( \frac{\text{Hct}(i) + \text{Hct}(f)}{2} \). (Gross, 2006).

**Secondary outcomes**

1. The proportion of women in each arm of the trial that needed additional pharmacological oxytocic interventions.
2. The incidence of blood transfusion
3. The adverse effects.
4. Vital signs during and after the operation and uterine tone.

**Methods of randomization:**

Randomization was done by an independent statistician according to a computer generated random numeric table with concealment of treatment allocation for both participant and doctor, by use of sealed opaque sequentially opened envelopes that were given to a third person who assigned patients to each group.

**Ethical Considerations:**

An informed consent will be obtained from each of the participants or one of the responsible relatives before recruitment in the study.

**Results**

**Table (1): Comparative study between the two groups according to hematocrit before and after C.S**

<table>
<thead>
<tr>
<th></th>
<th>Group I (Oxytocin)</th>
<th>Group II (Carbetocin)</th>
<th>St t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT before (Mean±SD)</td>
<td>33.93±1.99</td>
<td>34.1±2.23</td>
<td>0.58</td>
<td>0.56</td>
</tr>
<tr>
<td>HCT after (Mean ±SD)</td>
<td>31.34±2.27</td>
<td>32.52±4.07</td>
<td>2.53</td>
<td>0.012*</td>
</tr>
</tbody>
</table>

The change in postoperative hematocrit (HCT) is significant difference between carbetocin group and oxytocin group with (P value=0.012).

**Table (2): Comparative study between the two groups according to blood loss**

<table>
<thead>
<tr>
<th>Blood loss</th>
<th>Group I (Oxytocin) Mean ±SD</th>
<th>Group II (Carbetocin) Mean ±SD</th>
<th>St t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>486.9±185.3</td>
<td>400.3±168.17</td>
<td>3.46</td>
<td>0.001**</td>
</tr>
<tr>
<td>Intra-op</td>
<td>425.6±176.99</td>
<td>388.8±177.24</td>
<td>1.47</td>
<td>0.14</td>
</tr>
<tr>
<td>Post-op</td>
<td>97.92±51.02</td>
<td>39.3±22.44</td>
<td>-10.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Highly significant difference between oxytocin group and carbetocin group as regarding blood loss. (mean of group 1= 486.9±185.3 vs. mean of group 2=400.3±168.17, p = 0.001). especially post operative (Mean ±SD group 1=97.92±51.02) and (Mean ±SD group 2=39.3±22.44) with p-value = <0.001.

**Discussion**
Postpartum hemorrhage (PPH) is defined as a blood loss >500 ml and serious PPH as a blood loss >1,000 ml. PPH is a serious condition remaining the single main cause of maternal morbidity and mortality. PPH is a potentially life-threatening complication of both vaginal and cesarean delivery, the prevalence of PPH is approximately 6% of all deliveries.

The most frequent cause of PPH is uterine atony, contributing up to 80% of the PPH cases. Although two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, pre-eclampsia, coagulopathy, multiple gestation and antepartum hemorrhage. It is therefore reasonable to advise routine administration of a uterotonic drug immediately after the baby has been delivered by cesarean section. The impact of PPH on maternal morbidity and mortality makes active management of the third stage of labor a critical key. Thus, the administration of a uterotonic medication soon after the delivery of the fetus is an essential that is capable of decreasing the incidence of PPH by 40%.

In our present study, the levels of HCT were evaluated pre and post-operative in both groups. (the mean±SD of group 1 = 33.93±1.99), and (group 2 = 34.1±2.23) with (P value = 0.56), it is before and (the mean ±SD of group 1 = 31.34±2.27), and (group 2 = 32.52±4.07) with (P value = 0.012) that is after The levels of preoperative Hb and HT showed non significant difference between the two groups while the levels of postoperative Hb and HCT were significantly higher in carbetocin group than oxytocin group concluding that carbetocin showed the best results in controlling the blood loss and maintaining the level of HCT values. Also, the change in pre and postoperative HCT and Hb levels were significantly lower in carbetocin group than oxytocin.

In agreement with these results, post-operatively, hemoglobin and hematocrit levels in the carbetocin group were statistically higher. In contrast, there was no difference in the postoperative drop in hemoglobin and hematocrit, and this could be due to that these values were only recorded if assessed during routine care (i.e., not before labor). Therefore, results may be biased due to measurements in selected patients.

In contrast with our study, Moreover, demonstrated that there were no significant differences in the mean hemoglobin fall after the operation and in the fundal height or uterine tone postnatal.

During the study, the total blood loss was highly significantly lower in carbetocin group (mean = 400.3±168.17ml) when compared to the oxytocin group (mean = 486.9±185.3ml, p = 0.001), and the postoperative blood loss highly significantly lower in carbetocin group (mean = 39.3±22.44) when compared to oxytocin group (mean = 97.92±51.02) and (P value = <0.001). Another recent study found that The estimated blood loss was significantly lower in the carbetocin group (mean = 585mL versus 702.8mL, P = 0.026).

In addition, showed that blood loss was significantly higher in the oxytocin group compared to carbetocin group but not to the degree of PPH and this could be
attributed to that carbetocin causes a tetanic uterine contraction produced 2 min after an intravenous injection of 8-30 mg or intramuscular injection of 10-70 mg, which persists for approximately 1 min. Rhythmic uterine contractions persist for 60 and 120 min after intravenous and intramuscular injection respectively which decrease the uterine atony \(^{19}\) \(^{20}\) considered it a gold-standard against which they compared other methods of determination of blood loss during CS.

According to blood loss of the women involved in this study in oxytocin group range between 250 and 950 ml, this study in oxytocin group range between 250 and 950 ml, with the mean of 434.706 ml and SD is 191.799, in carbetocin group range between 250 and 750 ml, with the mean of 366.477 ml and SD is 165.001 the results showed significant difference between oxytocin group and carbetocin group as regarding blood loss (p = 0.013).

Another study said that the mean blood loss was observed to be greater in the oxytocin group compared to the carbetocin group, but the difference was not statistically significant in their study which included 2653 women, by four trials comparing carbetocin with Oxytocin.\(^{10}\)

In our study the difference between two group according to need to extra tonic drug is statistically highly significantly (p = 0.014), OR 2.3 and CI (1.18-4.49), these results are matching with Attilakos et al. \(^{9}\), that carbetocin is more potent and demonstrated in their study an increased use of additional oxytocics in the oxytocin arm. All the previous studies of carbetocin Boucher et al. \(^{21}\) demonstrated a lower rate of additional oxytocic usage with carbetocin. In accordance with the present study, Holleboom et al. \(^{15}\) demonstrated a lower rate of additional oxytocic usage after carbetocin compared with oxytocin.

Also, another study compared carbetocin with intravenous oxytocin administration for several hours and found that carbetocin resulted in a more rapid and sustained uterine involution, less need for additional uterotonic medication, less need for uterine massage and more often mild blood loss (<200/<500 ml) \(^{21}\).

In agreement with these results, another study confirmed that a single intravenous injection of carbetocin administered during CS significantly reduced the need for additional uterotonic interventions in comparison with classic I.V. oxytocin treatment \(^{22}\). But our result don’t agree with what published by . \(^{21}\).

**Conclusion**

Carbetocin appears to be more effective than oxytocin for prevention of postpartum hemorrhage in patient undergoing elective cesarean section. According to the results of this study it is found that there is a good overall agreement that Carbetocin might be effective in controlling the amount of blood loss during cesarean section and giving a better chance in prevention of atonic post partum Hemorrhage.

**References**


