Comparative Study between Carbetocin versus Oxytocin in Prevention of Post-Partum Haemorrhage Following Caesarean Section in High-Risk Pregnancies


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Abstract

Aim of Work: To compare the effectiveness of carbetocin and oxytocin when they are administered at caesarean section for the routine prevention of postpartum hemorrhage in patients with high risk factors of PPH.

Background: One of the Millennium Development Goals set by the United Nations in 2000 is to reduce maternal mortality by three-quarters by 2015. If this is to be achieved, maternal deaths related to Postpartum Hemorrhage (PPH) must be significantly reduced [1].

Study Design: This is a comparative prospective, case-controlled, single centre study (1:1 ratio) conducted from July 2015 and October 2016.

Patients and Methods: Two hundred pregnant women between 34 and 42 weeks of gestation with a viable fetus or fetuses and at least one or more risk factor for PPH undergoing elective or emergency caesarean section under regional anaesthesia. Women were randomised to receive either carbetocin (100 cases)-Group A or oxytocin (100 cases) Group B. (Group A) received a bolus of 100µg IV. (Group B) received 20IU of oxytocin in 500ml of 0.9% NaCl solution as infusion (150 mL/hour) by the anaesthetist after the birth of the baby.

Results: The two groups were comparable in the indication of CS ($p=0.954$). The most frequent indication was previous CS in carbetocin group and obstructed labor in the oxytocin group. Failed induction of labor was a common indication in the two groups. The amount of blood loss after delivery of the baby ranged between 300 and 1700ml. Blood loss in carbetocin group was significantly lower than that in oxytocin group. The frequency of blood loss $\geq 1000$ml was higher in oxytocin group. There was significant difference between the two groups with $p$-value 0.005. Additional uterotonic drugs were administered to 43 women of oxytocin group compared to 18 women of carbetocin group ($p<0.001$). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group.

Conclusions: The current study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs. 18% and $p<0.001$). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group.

Key Words: Post partum haemorrhage – Oxytocin – Carbetocin – Caesarean section.

Introduction

PREVENTION of Post-Partum Haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. The primary PPH is defined as blood loss more than 500mL after vaginal delivery and more than 1000mL after caesarean section, that occurs in the first 24 hours after delivery. Almost 500.000 women die for this potentially preventable cause each year, and up to an estimated quarter of these deaths uses to occur as a consequence of haemorrhage at time of delivery [1].

The first cause of haemorrhage at the time of delivery is uterine atony, therefore there is general agreement that active management of the third stage of labour rather than expectant management is recommended. The third stage of labor is defined as the period that follows delivery and finishes with the delivery of placenta [2].

The administration of uterotonic drugs widely prevents the PPH, significantly decreases the incidence of PPH and therefore it is the main point of active management. Oxytocin (10IU), administered intra-muscularly, is the preferred medication for the prevention of PPH in low-risk vaginal and caesarean deliveries. Care providers should administer this medication after delivery of the anterior shoulder. Intravenous infusion of oxytocin (20 to 40IU in 1000mL, 150mL/hour) [3]. Is an acceptable
alternative for the active management. Although the oxytocin is the most widely accepted uterotonic agent, other drugs are available, but which agent is ideal for prophylactic use is far to be clearly stated. A single dose of carbetocin given 100 µg as an IV bolus over 1 minute has been hypothesed to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in caesarean section [4,5].

Patients and Methods

This is a comparative prospective, case-controlled, single centre study (1:1 ratio) conducted from July 2015 and October 2016. At Sheik Zayed Al-Nahyan Hospital and El-Hussain University Hospital.

After obtaining approval from the Local Ethical Committee and patients consent, two hundred patients were divided equally in two groups women were randomised to receive either carbetocin (100 cases) Group A or oxytocin (100 cases) Group B. (Group A) received a bolus of 100 µg IV. (Group B) received 20IU of oxytocin in 500ml of 0.9% NaCl solution as infusion (150mL/hour) by the anaesthetist after the birth of the baby.

Inclusion criteria: Pregnant women between 34 and 42 weeks gestation with viable pregnancy and at least one or more risk factor for PPH undergoing either elective or emergency C.S.

Exclusion criteria: Women younger than 18 years old, history of significant heart disease, chronic illness or hypersensitivity to oxytocin or carbetocin. Women undergoing caesarean section with general anaesthesia were excluded, because carbetocin is licensed for use with regional anaesthesia only [6].

A- Patient preparation: On admission, the enrolled patients were subjected to proper full history including; personal, maternal and obstetric history, full general examination was done with especial concern to vital signs (blood pressure, plus, temperature). Routine laboratory investigations were requested and repeated as needed including blood group typing and cross matching, chemistry panel, Complete Blood Count (CBC) and coagulation panel. Continuous pulse oximetry, heart rate and blood pressure measurements and a foley catheter should be placed. The patient vital signs are noted in three readings pre, intra and post-operative.

B- The procedure: Carbetocin (Group A) 100 micrograms was diluted in 10ml normal saline and administered slowly (over 30-60 seconds) intravenously, women in the control group (Group B) received 20IU of oxytocin in 500ml of 0.9% NaCl solution as infusion by the anaesthetist after the birth of the baby. Measurement of blood loss was started immediately after drug administration, defining as haemorrhage a blood loss in excess of 1000ml or more [7].

Primary outcome measures:

Need for additional uteronic treatment during the first 24 hours after carbetocin or oxytocin administration, which may be administered by us for perceived inadequate uterine tone with or without hemorrhage in the first 24 hours after delivery.

Secondary outcome measures:

- Need for blood transfusion during the first 24 hours.
- Need for operative interventions other than the initial CS during the first 24 hours.
- Hemoglobin post versus pre CS.
- Amount of intraoperative blood loss.
- Incidence of intraoperative blood loss >500ml.
- Incidence of intraoperative blood loss >1000ml.
- Uterine tone after uterotonic treatment.
- Incidence of adverse effects.
- Association between high risk factors and incidence of PPH and additional uterotonics.

Results

The current study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs. 18% and p<0.001). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group. Since the present study demonstrated a lower rate of additional oxytocic usage after carbetocin compared with oxytocin, carbetocin may be more effective in preventing uterine atony and thereby PPH.

Table (1) shows the demographic and clinical characteristics of the two studied groups. The two groups were comparable regarding baseline characteristics.

Table (2) shows a detailed list of the risk factors detected in the two groups. The two groups were
comparable in the risk factors of PPH ($p=0.938$). The most frequently encountered risk factor was uterine over distension followed by prolonged labor trial. Uterine overdistension was caused by hydramnios, twins or macrosomic fetus. History of PPH in a previous delivery was a common risk factor as well as antepartum hemorrhage in the current pregnancy. There was no significant difference between the two groups in history of previous CS ($p=0.193$).

The amount of blood loss after delivery of the baby ranged between 300 and 1700ml in the whole studied group. Blood loss in carbetocin group was significantly lower than that in oxytocin group ($p=0.005$) as shown in (Table 3). There was a tendency towards significant difference between the two groups regarding the proportion of cases with PPH, i.e. blood loss $\geq 1000ml$ ($p=0.067$). The frequency of blood loss $\geq 1000ml$ was higher in oxytocin group. Considering severe PPH vs. mild plus moderate bleeding ($<1000ml$), there is no significant difference between the two groups ($p=0.093$).

Table (4) shows uterine response to the test drugs during the intraoperative and postoperative periods. In the two periods, more cases of oxytocin group showed uncontracted uterine muscle in response to the test drug ($p<0.001$, and $=0.004$, respectively). Consequently, additional uterotonic drugs were administered to 43 women of oxytocin group. Considering severe PPH vs. mild plus moderate bleeding ($<1000ml$), there is no significant difference between the two groups ($p=0.093$).

Table (5) shows pre-, intra-and postoperative levels of systolic and diastolic blood pressure. In all readings, oxytocin group showed significantly higher values of blood pressure statistically. However, all values in the two groups were within the clinically accepted ranges Figs. (2,3).

### Table (1): Demographic and clinical characteristics of the two studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>29.7±7.9</td>
<td>29.5±6.5</td>
<td>0.891</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.6±13.3</td>
<td>85.2±13.2</td>
<td>0.329</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.9±2.3</td>
<td>37.4±2.3</td>
<td>0.149</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>2934±569</td>
<td>2906±590</td>
<td>0.730</td>
</tr>
<tr>
<td>Gravidity</td>
<td>4 (1-10)</td>
<td>3 (1-11)</td>
<td>0.182</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (0-7)</td>
<td>2 (0-9)</td>
<td>0.283</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (range).

### Table (2): Risk factors for postpartum hemorrhage detected in the two studied groups.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdistended uterus</td>
<td>17 (17.0%)</td>
<td>19 (19.0%)</td>
<td></td>
</tr>
<tr>
<td>Prolonged labor</td>
<td>15 (15.0%)</td>
<td>14 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>Induction of labor</td>
<td>14 (14.0%)</td>
<td>16 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>Previous CS</td>
<td>14 (14.0%)</td>
<td>14 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>History of Postpartum hemorrhage</td>
<td>12 (12.0%)</td>
<td>15 (15.0%)</td>
<td></td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
<td>8 (8.0%)</td>
<td>6 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>Fibroid uterus</td>
<td>5 (5.0%)</td>
<td>5 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Use of anticoagulant</td>
<td>4 (4.0%)</td>
<td>7 (7.0%)</td>
<td></td>
</tr>
<tr>
<td>Two risk factors</td>
<td>11 (11.0%)</td>
<td>4 (4.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as No. (%).

### Table (3): Amount of postpartum blood loss in the two studied groups.

<table>
<thead>
<tr>
<th>Volume of blood loss (mL)</th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500mL</td>
<td>57 (57.0%)</td>
<td>42 (42.0%)</td>
<td>0.005</td>
</tr>
<tr>
<td>500 to &lt;1000mL</td>
<td>34 (34.0%)</td>
<td>41 (41.0%)</td>
<td>0.067</td>
</tr>
<tr>
<td>1000mL</td>
<td>9 (9.0%)</td>
<td>17 (17.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%).

### Table (4): Response of the uterine muscles to test drugs during the intra- and post-operative periods in the two studied groups.

<table>
<thead>
<tr>
<th>Period</th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus contracted</td>
<td>87 (87.0%)</td>
<td>57 (57.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uterus not contracted</td>
<td>13 (13.0%)</td>
<td>43 (43.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as No. (%).

### Table (5): Blood pressure before, during and after surgery in the two studied groups.

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>110±17</td>
<td>115±29</td>
<td>0.005</td>
</tr>
<tr>
<td>Intra-operative</td>
<td>96±9</td>
<td>93±7</td>
<td>0.045</td>
</tr>
<tr>
<td>Post-operative</td>
<td>106±11</td>
<td>109±8</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>73±7</td>
<td>75±7</td>
<td>0.024</td>
</tr>
<tr>
<td>Intra-operative</td>
<td>64±5</td>
<td>62±4</td>
<td>0.038</td>
</tr>
<tr>
<td>Post-operative</td>
<td>69±7</td>
<td>71±6</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
Table (6): Post-operative side effects of test drugs in the two studied groups.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Carbetocin (n=100)</th>
<th>Oxytocin (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>14 (14.0%)</td>
<td>10 (10.0%)</td>
<td>0.384</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (13.0%)</td>
<td>8 (8.0%)</td>
<td>0.249</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (8.0%)</td>
<td>4 (4.0%)</td>
<td>0.234</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (5.0%)</td>
<td>6 (6.0%)</td>
<td>0.756</td>
</tr>
<tr>
<td>Flushing</td>
<td>4 (4.0%)</td>
<td>4 (4.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (2.0%)</td>
<td>4 (4.0%)</td>
<td>0.687</td>
</tr>
</tbody>
</table>

Data are presented as No. (%).

Discussion

Postpartum Hemorrhage (PPH) is one of the most frequent causes of mortality and morbidity in obstetric population worldwide, causing about 25% of maternal deaths each year [8,9] and 66% of deaths due to PPH are still due to “substandard care” [10]. Moreover, PPH is also the cause of 73% of all serious morbidity during pregnancy and is the most frequent obstetrical cause of admission to Intensive Care Units [11].

As the uterine atony the most common case of PPH). Active treatment during third stage of labor seems to be the chosen treatment to prevent PPH, which reduces maternal blood loss and the risk of PPH.

The active treatment of the third stage of labor is made up of three interventions:
- Early clamping of the umbilical cord.
- Controlled cord traction.
- Prophylactic oxytocic drug as the anterior shoulder is delivered.

Oxytocin (Syntocinon®) 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 and a good safety profile [12,13]. 5IU oxytocin by slow intravenous injection is currently recommended in the United Kingdom (UK) for all caesarean sections [14]. On the other hand, a significant limitation for its clinical use is represented by its short half-life of 4-10min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections [15,16] and the use of additional oxytocic medication is common to arrest bleeding, or prophylactically if there are risk factors for PPH [17].

Over the past two decades, several other alternatives have been explored. Among the other agents or interventions that have been studied for prevention of PPH, the oxytocin agonist (carbetocin) was suggested as a promising agent for this indication [18]. Carbetocin (Pabal®) is a long-acting oxytocin analogue indicated for the prevention of uterine atony after childbirth by CS under epidural or spinal anaesthesia. Carbetocin has a rapid onset of...
action (within 1-2 min); a prolonged duration of action (approximately 1 h) with a half-life approximately 4-10 times longer than oxytocin [19]. Its standard dosage is a slow single intravenous (over 1 min.) or intramuscular injection of 100 µg. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus.

The primary end point of the current study was the need for additional uterotonic treatment during the first 24 postoperative hours. The carbetocin group was superior to oxytocin group in reducing the use of additional uterotonic drugs (\(p<0.001\)). After adjustment to the type of CS, carbetocin was still more effective in reducing need for additional uterotonics with an odds ratio of 3.7 (95% CI: 1.9-7.1). We found a definitively and significantly reduced additional uterotonics need after CS in the carbetocin-receiving women compared to oxytocin group at high risk for PPH (43% vs. 18% and \(p<0.001\)). [17]; approximately 20% of clinicians reported routine use of oxytocin infusions whereas 80% reported selective use in the presence of risk factors. In our study, most of the women who were given additional oxotocics received additional oxytocin bolus or infusion, which was typically given over 4 hours. The reason for administering additional oxotocics in the oxytocin group was likely to be more liability to develop PPH and hence more blood loss and PPH treatment. This study demonstrates that prophylaxis of uterine atony with carbetocin after CS reduced the need for additional uterotonics by more than 50% with a power of the test of 98%, which is in accordance with the results of Holleboom [20]. Borruto lower rate of additional oxytocin need in women undergoing carbetocin administration during CS and we do reach the same conclusions [21-23].

On this item, Su in the Cochrane of 2007 and in the Cochrane 2012 regarding “Carbetocin for preventing post-partum haemorrhage”, conclude that the use of carbetocin is more effective than oxytocin for preventing PPH in women undergoing CS [24,25]. The amount of bleeding and occurrence of PPH were significantly lower in carbetocin group. They concluded that carbetocin is a better alternative to traditional oxytocin in prevention of PPH in women with at least 2 factors of PPH according to Maged [26].

The secondary outcome of the current study is the evaluation of immediate haemodynamic effects of carbetocin administration. The current study demonstrated that; the haemodynamic data are reassuring with no clinically significant differences between the two interventions and that the two drugs had similar haemodynamic profiles. Although, the slow intravenous administration of oxytocics appears to reduce their haemodynamic effects [27]. The results of the present study demonstrated that carbetocin was more effective at preventing PPH than oxytocin in patients at a high risk of PPH undergoing caesarean delivery. Apparently, fewer cases needed blood transfusion for management of PPH in carbetocin group (\(p=0.091\)). In fact; the frequency of severe PPH was significantly associated with the risk factors in the affected patient (\(p=0.01\)). The presence of more than one risk factor was the most frequent association followed by uterine overdistension. In our study, there was no statistically significant difference between the 2 groups regarding the occurrence of nausea, vomiting, tachycardia, flushing, headache and itching. Overall, the adverse effect profiles appear reassuringly similar between the two medications. It could be argued that some of these are not ‘true’ adverse effects, but rather are the effect of hypotension or surgery.

**Conclusion:**

The current study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonics agents in patients at high risk for PPH undergoing CS (43% vs. 18% and \(p<0.001\)). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group.

**References**


5- LARCPRETE G., MONTAGNOLI C., FRIGO M., PANETTA V., TODDE C., ZUPPANI B., CENONZE C., BOMPIANI A., MALANDRENIS I., CIRESE A. and VALENSISE H.: Carbetocin versus oxytocin in caesarean


مقارنة الكاريبيتيسين بالأوكسيتوسين
في منع النزيف الرحمي ما بعد الولادة القيصرية
في الحالات الأكثر عرضة للنزيف الرحمي

إن منع النزيف المهبل بعد الولادة هو قضية رئيسية لما لها من تأثير على معدلات الوفيات وال yat发病率 بين الأمهات. يتم تعريف نزيف ما بعد الولادة الأولي على أنه فقدان من 500 مل بمعدل الولادة المهبلية أكثر من 1000 مل بعد عملية القيصرية في خلال 24 ساعة الأولى بعد الولادة.

إن السبب الأول للنزيف عند الولادة هو الورم غير المقصص. وبالتالي هناك إتفاق عام بتوصية على التعامل النشط للمرحلة الثالثة من الولادة.

عقار الكاريبيتيسن يعطي في المرحلة الثالثة من الولادة القيصرية بجرعة 60 وحدة عااية من عقار الأوكسيتوسين مخفين على 1000 مل بمعدلات 150 مل في الساعة.

وهناك عقاقير أخرى مثل عقار الكاريبيتيسن الذي يستخدم كجرعة واحدة بتركيز 100 ميكروجرام يعطى وردية على شكل جرعة واحدة لمدة دقيقة يفترض أن يعمل لمدة تمايل إعطاء عقار الأوكسيتوسين لمدة 16 ساعة متصلة بالوريد فيما يخص درجة انقباض الورم وتقليقل مخاطر نزيف ما بعد الولادة القيصرية.

الهدف من الرسالة: مقارنة فعالية عقار الكاريبيتبيسون والأوكسيتوسين حين إعطاؤهما كإجراء إخترازي ما بعد الولادة القيصرية لمنع نزيف ما بعد الولادة في الحالات الأكثر عرضة للنزيف.

طريقة الدراسة: الدراسة تتضمن 2000 سيدة حامل ما بين 20 و 42 أسبوع عمل بجناة حبة جينين واحد أو أكثر معها عامل واحد أو أكثر من مخاطر نزيف ما بعد الولادة القيصرية اختياري أو مثارة تحت تأثير مدخن نصفي وقد قسموا إلى مجموعتين كالتالي:

السيدة في المجموعة (أ) تم إعطاؤهم 100 ميكروجرام وردية من عقار الكاريبيتيسن جرعة واحدة والسيدات في المجموعة (ب) تم إعطاؤهم 20 وحدة عااية من عقار الأوكسيتوسين مخفين على 50 مل من محلل الورم بتركيز 0.9 % بمعدل 150 مل في الساعة.

نتائج النهاية: نقطة النهاية الأولية كانت الحاجة إلى عقاقير إضافية بعد كل من عقار الكاريبيتيسن والأوكسيتوسين في كل من المجموعتين لمنع نزيف ما بعد الولادة.

النتائج النهائية التالية تشمل تقدير كمية الدم المفقود داخل العملية وليست مع قياس الوعاء الحيوية ما بعد القيصرية.

وجامط النتائج كالتالي:

- جرعة إضافية من العقاقير القاضية للورم تم إعطاؤها إلى 34 سيدة من مجموعة عقار الأوكسيتوسين إلى 18 سيدة من مجموعة عقار الكاريبيتيسن.

في نتائجنا يضح إحصائيًا أن إنقباض الورم كان أفضل في مجموعة الكاريبيتيسن عن مجموعة الأوكسيتوسين بعد حقن المقار وإختباره داخل العملية القيصرية وليست مع قياس الوعاء الحيوية ما بعد القيصرية.

بعد الولادة.