Oxytocin Infusion after Oxytocin Bolus and Carbetocin Bolus to Reduce Blood Loss During and after Cesarean Section - A Randomized Clinical Trial

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Abstract

Objectives: The aims of the present study were to compare the efficacy of oxytocin bolus alone, oxytocin bolus and infusion, carbetocin bolus alone, and carbetocin bolus followed by oxytocin infusion in reducing blood loss during and after cesarean section and reducing the needs for additional uterotonic agents.

Methods: 200 women scheduled for elective CS under spinal anaesthesia were divided into 4 groups, group I received oxytocin 10 IU bolus followed by placebo In saline for 4 hours, group II received 10 IU oxytocin followed by 40 IU oxytocin in saline for 4 hours, group III received carbetocin 100 µg bolus and placebo in saline for 4 hours, and group IV received carbetocin 100 µg bolus followed by 40 IU oxytocin in saline for 4 hours. The main parameters evaluated were calculated blood loss during CS and 24 hours after in addition to the need for additional uterotonic drugs.

Results: Blood loss was comparable and accepted clinically in the 4 study groups but loss was less during CS in both carbetocin groups. Post-operative blood loss and the needs for additional uterotonic drugs were less in the oxytocin infusion groups. Non of the included women were in need for blood transfusion.

Conclusions: We concluded that carbectocin and oxytocin are comparable drugs for reducing blood loss and maintaining uterine tone during and after CS. Adding oxytocin infusion for 4 hours postoperatively may decrease blood loss and the needs for additional uterotonic agents.

Key Words: Oxytocin – Carbetocin – Bolus – Blood loss – Cesarean section.

Introduction

CESAREAN Section (CS) is the most common operation in women with increasing rate reaching up to 20% to 30% in most developed countries, up to 40% in China and as high as 70% in some Latin American countries [1,2]. Despite significant progress in obstetric care, the problem of bleeding during labor remains unfinished, as the world annual deaths from obstetric haemorrhage reach 125 thousand women [3]. Towards the end of pregnancy the uterus is hyper-perfused by a rate of 500-750ml/min, that will result in average blood loss reaching 1000ml during CS. Many factors would affect blood loss during and after CS e.g. maternal causes (weight, parity, previous CS), fetal causes (multiple gestation, polyhydrominious, malpresentation) and technical causes (operative time, type of incision, placental site and separation technique and type of anesthesia). So, estimation of blood loss during CS is crucially important to decrease morbidity and to avoid the risks of unnecessary blood transfusion [4]. To reduce maternal morbidity and mortality caused by bleeding, it is important to reduce the amount of bleeding during and after CS.

The guidelines of the Royal College of Obstetricians and Gynaecologists (UK) on CS recommended a slow IV bolus dose of 5 IU oxytocin after delivery of the infant [8]. This practice is the same in most Europe and Australia. In UK, a survey of obstetricians and anaesthetists, the use of oxytocin bolus [7] was standard, but dose varied between 5 and 10 IU. Some obstetricians used an additional infusion of oxytocin on a selective or routine basis to high risk cases [8]. In US they recommend the use of oxytocin infusion instead of a bolus dose [9]. The recent Canadian guidelines recommend the use of Carbetocin instead of oxytocin at CS [10]. Carbetocin is as synthetic analog of oxytocin with a half-life 4-10 times longer than that of oxytocin. It is used as a single dose slowly IV or IM injection [11].
The current study is the first four arms prospective clinical study comparing oxytocin bolus, oxytocin bolus and 4 hours infusion, carbetocin bolus and carbetocin bolus and 4 hours oxytocin infusion in reducing blood loss during and after CS.

**Sample size:**

The primary outcome will be the amount of blood loss during and after cesarean section operations for 24 hours. According to previous study of Rashmi et al. [12] and Seikhavat et al. [13] 45 patients had 90% power to detect both sensitivity and specificity higher than 90%. However to allow for multiple comparisons between the four studied groups, and to compensate for possible dropouts, the final sample size in each group will be 50 patients (Total number of patients in the four study groups will be 200).

**Patients and Methods**

This is a prospective randomised clinical trial conducted from May 2012 to January 2013 at Specialized Obstetric Hospital. After Approval of Local Ethical Committee and a written informed consent, a 200 women undergoing elective cesarean section under subarachnoid block were randomly allocated into 4 groups each 50 women. An online randomization program (http://www.randomizer.org) was used to generate random list and to allocate patients into the four study groups. Random allocation numbers were concealed in opaque closed envelops.

Parturients were examined clinically and by abdominal sonography, complete blood count, renal and hepatic function tests, and coagulation profile was done.

Exclusion criteria were women with coagulopathy, thrombocytopenia, fibroids, placenta praevia, history of previous obstetric haemorrhage more than 1 litre, and women who received anticoagulant and antiplatelets therapy.

All women were anesthetized by the same team using 25G pencil type spinal needle and 12.5mg heavy marcaine and 25 µg fentanyl after preload with 1000ml lactated Ringer’s solution. All cesarean sections were done by the same obstetrician. Intraoperative blood pressure was maintained by IV 6mg ephedrine incremental doses.

With delivery of the foetus, patients were randomly divided into four equal groups, group I (Ob) received 10 IU oxytocin. Slowly IV over 2 minutes and placebo infusion of normal saline, group II (ob+In) received 10 IU oxytocin slowly IV over 2 minutes followed by 40 IU oxytocin on normal saline drip over 4 hours, group III (Cb) received carbetocin 100mg slowly IV over 2 minutes and placebo infusion of normal saline and group IV (Cb+In) received carbetocin 100mg slowly IV over 2 minutes followed by 40 IU oxytocin on normal saline drip over 4 hours. A venous preoperatively blood sample was with drawn for CBC and another sample after 24 hours for CBC also. The number of cases that were in need for added uterotonic drugs were recorded. Also the cases that needed blood transfusion and cases that need to stay in hospital more than 48 hours were recorded.

The calculated estimated blood loss = Estimated blood volume X (preoperative PCV – postoperative PCV) / preoperative PCV. (Where estimated blood volume = Booking weight (kg) X 85ml) [14].

**Results**

This study included 200 term pregnant patients underwent elective CS. Parturients characteristics in the four groups were comparable with no significant differences regarding age, height, weight and parity (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>N (50)</th>
<th>Age (years)</th>
<th>Mean±S.D</th>
<th>Height (cm)</th>
<th>Mean±SD</th>
<th>Weight (kg)</th>
<th>Mean±S.D</th>
<th>Parity</th>
<th>Mean±S.D</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ob</td>
<td>50</td>
<td>28.40</td>
<td>±2.53</td>
<td>158.53</td>
<td>±4.22</td>
<td>68.51</td>
<td>±5.33</td>
<td>1.88</td>
<td>±0.45</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Ob+In</td>
<td>50</td>
<td>27.95</td>
<td>±3.42</td>
<td>159.12</td>
<td>±4.17</td>
<td>69.21</td>
<td>±4.93</td>
<td>2.12</td>
<td>±0.33</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Cb</td>
<td>50</td>
<td>28.88</td>
<td>±2.73</td>
<td>158.91</td>
<td>±3.87</td>
<td>68.30</td>
<td>±5.45</td>
<td>2.01</td>
<td>±0.39</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Cb+In</td>
<td>50</td>
<td>28.19</td>
<td>±3.32</td>
<td>158.17</td>
<td>±4.57</td>
<td>68.39</td>
<td>±5.13</td>
<td>1.97</td>
<td>±0.42</td>
<td>(1-4)</td>
</tr>
</tbody>
</table>

The four study groups showed that a single dose of 10 IU oxytocin, 10 IU oxytocin followed by 4 hours 40 IU oxytocin infusion, single dose 100 microg carbetocin and single dose 100 microg carbetocin followed by 40 IU oxytocin over 4 hours, all are effective regarding the amount of blood loss intraoperatively during CS which was in group Ob (449±68.96ml), group Ob+In (467.8±67.87ml), group Cb (398.7±60.36ml) and group Cb+In (359±63.13ml). The difference between the oxytocin groups was statistically insignificant while was statistically significant when compared with the third and fourth groups (carbetocin groups). The difference between the third and fourth group was statistically insignificant (Fig. 1).
Regarding blood loss postoperatively, it was clinically accepted in the four study groups. Group Ob+In had the least blood loss volume postoperatively (182 ± 51.72 ml) which was statistically significant when compared with the other three groups. Blood loss in group Ob was (312.46 ± 125.82 ml) and in groupCb was (300.62 ± 85.43 ml) which showed no statistical difference in between. In group Cb+In (264.85 ± 35.25 ml) it was statistically significant different when compared with the second group Ob+In (Fig. 2). In the oxytocin bolus group 10 parturients (20%) needed uterine massage and added uterotonic drugs and also 6 parturients in group carbetocin bolus (12%). Non of the oxytocin bolus and infusion or carbetocin bolus and oxytocin infusion were in need for uterine massage or added uterotonic drugs. No one of parturients included in the study was in need or had blood transfusion. None of the patients stayed in the hospital more than 48 hours.

The results of this study showed that the use of oxytocin bolus (10 IU) and placebo infusion when compared to oxytocin bolus (10 IU) followed by 40 IU oxytocin infusion for 4 hours showed that intraoperative blood loss was comparable but 24 hours postoperative blood loss was significantly lower in infusion group. Also the needs for uterine massage and added uterotonic drugs was higher in the bolus group (20% of patients) which is nil in the infusion group. This may be due short half life of oxytocin adherence to the receptors. Sheehan et al. [14] concluded that an oxytocin infusion in addition to an oxytocin bolus had no effect on overall occurrence of major obstetric haemorrhage compared with oxytocin bolus.

Our results were similar to that concluded by Attilekos et al. [10] who reported less blood loss with the use of carbetocin when compared to oxytocin bolus. Also they reported that the price of carbitocin is small fraction of the total cost of a cesarean section.

Larciprete et al. [16] compared carbetocin bolus against 20 IU oxytocin infusion and concluded that no difference in estimated blood loss and in the drop of hemoglobin level.

Borruto et al. [17] compared carbetocin bolus and oxytoin 20 IU infusion and they found equivalent results regarding maintenance of uterine tonicity and limitation of blood loss during and after CS which is in accordance with our results.

Discussion

Obstetric haemorrhage is a major cause of maternal morbidity and mortality and cesarean section is specially associated with a varying degree of blood loss [15]. In the present study blood loss during and after cesarean section was estimated using the difference in PCV from preoperative level to immediate postoperative and 24 hours postoperatively. The results of this study showed that the use of oxytocin bolus (10 IU) and placebo infusion when compared to oxytocin bolus (10 IU) followed by 40 IU oxytocin infusion for 4 hours showed that intraoperative blood loss was comparable but 24 hours postoperative blood loss was significantly lower in infusion group. Also the needs for uterine massage and added uterotonic drugs was higher in the bolus group (20% of patients) which is nil in the infusion group. This may be due short half life of oxytocin adherence to the receptors. Sheehan et al. [14] concluded that an oxytocin infusion in addition to an oxytocin bolus had no effect on overall occurrence of major obstetric haemorrhage compared with oxytocin bolus.

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Triopon et al. [11] also found that carbetocin is effective as oxytocin during CS.

Bonis et al. [18] in their study when compared carbetocin bolus against oxytocin infusion, they concluded that single carbetocin injection is efficacious and safe on maintenance uterine tone and on limitation of blood loss and carbetocin was able to reduce pain perception post-operatively and placebo infusion but additional infusion of oxytoin did reduce the need for another uterotonic agent, this is in accordance to our results.

Gungorduk et al. [19] compared the use of oxytocin bolus and placebo infusion with oxytocin bolus and 30 IU oxytocin infusion, data showed reduction in both the use of additional uterotonic agents and major obstetric haemorrhage. However, these results are not generalized because CS were done under general anesthesia which may increase blood loss during surgery due to inhalational agents.

King et al. [20] compared placebo bolus and oxytocin infusion with oxytocin bolus and oxytocin infusion and they found no difference in the need
for additional uterotonic agents after CS. The limitation for this study was that blood loss was estimated visually and was limited to parturients at high risk of uterine atony.

In our study carbetocin reduced blood loss during CS and the use of oxytocin infusion after carbetocin decreased the 24 hours blood loss after CS. This was significantly less blood loss when compared to oxytocin bolus and placebo infusion or oxytocin bolus and oxytocin infusion.

As the post-operative monitoring after CS is varying and depends on clinical judgement, so we are in need for new protocols for use of oxytocin and carbetocin. From our study we advise for use of oxytocin infusion for 4 hours after CS which is effective, safe and unexpensive for reducing post CS blood loss.

Conclusion:

It could be concluded that carbetocin and oxytocin are comparable drugs for reducing blood loss and maintaining uterine tone during and after CS. And adding oxytocin infusion for 4 hours postoperatively may decrease blood loss and the needs for additional uterotonic agents.

P.S. There was conflict of interest in this research.

References


الحقن بالاكسينوسون بعد الحقن بالاكسينوسون والكاريتوسون لتقليل فقدان الدم بعد الولادة القäsارية: دراسة عشوائية اكلينيكية

الهدف:
الهدف من هذه الدراسة هو مقارنة فعالية الحقن بالاكسينوسون وحقن الحقن بالاكسينوسون والكاريتوسون وحقنهما والكاريتوسون متبوعاً بالاكسينوسون في تقليل الدم المفقود أثناء و بعد الولادة القäsارية و تقليل الحاجة إلى أدوية قاَبة لدراهم.

الطريقة:

1. مجموعتان من جرى إجراء الولادة القäsارية الإختيارية بمختبر نصفي، وقد قسمن إلى أربعة مجموعات: المجموعة الأولى: تلقى الأكسينوسون عشرة وحدات دوَّلية بالحقن متبوعا بالبراباسين في محلول الملح لمدة أربعة ساعات.
2. المجموعة الثانية: تلقى عشرة وحدات دوَّلية الأكسينوسون متبوعاً بالبراباسين في محلول الملح لمدة أربعة ساعات.
3. المجموعة الثالثة: تلقى الكاريتوسون 100 ميكرجرام بالحقن والبراباسين في محلول الملح لمدة أربعة ساعات.
4. المجموعة الرابعة: تلقى الكاريتوسون 100 ميكرجرام بالحقن متبوعاً بالبراباسين في محلول الملح لمدة أربعة ساعات.

وجاءت القياسات الأساسية المقدرة محصورة على أساس فقدان الدم أثناء الولادة القäsارية و زمناً أربعة و عشرون ساعة فيما بعد بالإضافة إلى المزيد من قواَب الدم.

النتائج:
فقدان الدم كان م atasقاً ومختلفاً اكلينيكياً في الأربعة مجموعات قد الدراسة ولكن النتائج كان أقل أثناء الولادة القäsارية في مجموعة الكاريتوسون. فقدان الدم بعد العملية والاحتياج إلى المزيد من قواَب الدم كان أقل في مجموعة الأكسينوسون. لم تحتاج أي من السيدات إلى نقل الدم.

المستنتاج:

لم تُنتائج أن الكاريتوسون والأكسينوسون كليهما عقار م قادر لتقليل فقدان الدم واستمرار التقلص الرحمي أثناء وبعد الولادة القäsارية.

وإضافة الأكسينوسون مدة أربعة ساعات بعد العملية من الممكن أن تقلص فقدان الدم والحاجة إلى المزيد من قواَب الدم.