Comparative Study between Carbetocin and Syntocinon in Prevention of Postpartum Hemorrhage

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Abstract

Objective: Carbetocin is more effective than syntocinon in prevention of postpartum hemorrhage.

Design: Observational cohort prospective study.

Setting: Zagazig University Hospital, Obstetrics and Gynecology Department from period between January 2012 to November 2012.

Population: 200 patients designed to have elective CS were divided into two groups:

Group A: 100 patients with elective CS take 100mg carbetocine as single dose IV.

Group B: 100 patients with elective CS take 10mg syntocinon as single dose IV.

Methods: The study done between January 2012 to November 2012 at Zagazig University, Obstetrics and Gynaecology Emergency Hospitals.

All patient subjected to history taking, general examination, routine laboratory evaluation, ultrasound evaluation.

Inclusion criteria were; previous one or previous two CS, haemoglobin range 10-12gm/d1, no placenta praevia, single baby, average amniotic fluid.

Exclusion criteria; more than 2 CS, multifetal pregnancy, placenta praevia, polyhydramnios

Main Outcome Measures: Preoperative and postoperative evaluation of hemoglobin measurement were performed. Intraoperative and postoperative evaluation of blood loss, uterine atony, need for another uterotonic agents, and need for blood transfusion were recorded during 1st 24 hours after CS.

Results: The mean age of group A was 29 years, and in group B 30 years old. The subgroup 1 and 2 were equal in both groups; 50 patients in every group with previous one CS and 50 patients in both groups with previous 2 CS. The mean of hemoglobin preoperative were the same 12gm/d1, postoperative mean of haemoglobin were 10.5gm/dl in group A and 10gm/dl in group B. The mean amount of blood loss intraop-eratively were 450m1 in group A and 500m1 in group B. The need for another uterotonic intraoperatively were 10 patients in group A and 12 patients in group B. The need for another uterotonic agent postoperatively was 15 patients in group A and 16 patients in group B, in these patients uterine atony were developed. After statistical analysis of these data there were no significant differences between both groups.

Conclusions: Syntocinon is effective as carbetocine in prevention of postpartum hemorrhage during elective CS. But this need more studies to evaluate the efficacy of carbetocine.

Key Words: Postpartum haemorrhage — Carbetocine — Syntocinon — Caesarian section (CS).

Introduction

THERE are many pharmacological options for the management of postpartum hemorrhage, oxytocin being the first line of treatment. There is as yet no evidence about the safety and efficacy of using carbetocin, an oxytocin agonist, in these patients. The aim was to compare oxytocin with carbetocin for the routine prevention of postpartum hemorrhage in patients with severe preeclampsia. A prospective double-blind randomized controlled trial in 60 women with severe preeclampsia, recruited between July and September 2010. The women were randomized to receive either oxytocin or carbetocin during the third stage of labour. The primary outcome measure was postpartum hemorrhage requiring additional uterotonic, and the secondary outcome measures were the difference in hemoglobin levels between groups, the development of oliguria, and hemodynamic status (mean arterial pressure and heart rate) after administration of the drug. Carbetocin was as effective as oxytocin in the prevention of postpartum hemorrhage in women with severe preeclampsia. Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension in this cohort. Carbetocin is an
appropriate alternative to oxytocin for the prevention of postpartum hemorrhage in women with severe preeclampsia III.

To compare the effectiveness of carbetocin with oxytocin with respect to maintain adequate uterine tone and to reduce the incidence and severity of postpartum haemorrhage. Moreover safety, adverse effects and the need of additional medications were evaluated. Prospective controlled clinical trial. The effect of a single dose of carbetocin (n=55) was compared with oxytocin infusion (n=55) in a women population undergoing to elective caesarean section with regional subarachnoid anaesthesia with at least one risk factor for postpartum haemorrhage. The mean±SD of postoperative pain in the day of surgery in carbetocin group was significantly lower than in oxytocin group and remained significant till the third day after caesarean section. In the day of surgery and the first day after surgery, women of carbetocin group who needed analgesic drugs were significantly lower than women of oxytocin group. The differences of diuresis and of diuretic drugs need were not statistically significant between the two groups. A single carbetocin injection is efficacious and safe on the maintenance of uterine tone and on the limitation of blood losses, in peri- and in postoperative period. In addition, carbetocin was able to reduce pain perception during postoperative days improving quality life of women [21].

Material and Methods

This is an observational prospective cohort study done at Zagazig University Hospital, Obstetrics and Gynecology Department, during the period between January 2012 to November 2012. Ethic approval was obtained from Zagazig University ethic committee. All patients designed to have elective CS. All patients were in patient care prepared for operative intervention. Information about the study was available to patient during consenting. The auther (W.S) had discussed the procedures with patients and they accepted and consented.

Funding:
All patients included in the study were at the found of Zagazig University Hospitals.

Study population:
Institutional review board (IRB) approval was taken before the study (January 2012) under number 946 and patients consent after explanation of procedure to them.

200 patients designed to have elective CS were divided into two groups:
Group A: 100 patients with elective CS take 100mg carbitocine as single dose IV.
Group B: 100 patients with elective CS take 10mg syntocinon as single dose IV.

The study done between January 2012 to November 2012 at Zagazig University, Obstetrics and Gynaecology Emergency Hospitals.

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Exclusion criteria: More than 2 CS, multifetal pregnancy, placenta praeavica, polyhydramnios.

In both groups, subgroup 1 with previous one CS and subgroup 2 with previous 2 CS are divided.

Preoperative and postoperative evaluation of hemoglobin measurement were performed. Intraoperative and postoperative evaluation of blood loss, uterine atony, need for another uterotonic agents, and need for blood transfusion were recorded during 1st 24 hours after CS.

Collection of patients data and statistical analysis were done.

Results

The mean age of group A was 29 years, and in group B 30 years old. The subgroup 1 and 2 were equal in both group; 50 patient in every group with previous one CS and 50 patients in both groups with previous 2 CS.

The mean of hemoglobin preoperative were the same 12gm/dl, postoperative mean of haemoglobin were 10.5gm/d1 in group A and 10gm/d1 in group B.

The mean amount of blood loss intraoperatively were 450m1 in group A and 500m1 in group B. The need for another uterotonic intraoperatively were 10 patients in group A and 12 patients in group B. The need for another uterotonic agent postoperatively was 15 patients in group A and 16 patients in group B, in these patients uterine atony were developed.

After statistical analysis of these data there were no significant differences between both groups.
Table (1): Clinical patients criteria (preoperative data).

<table>
<thead>
<tr>
<th></th>
<th>Group A Mean / Range/ number percent</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29 / 20-38</td>
<td>30 / 20-40</td>
</tr>
<tr>
<td>Previous one cs</td>
<td>50 / 50%</td>
<td>50 / 50%</td>
</tr>
<tr>
<td>Previous two cs</td>
<td>50 / 50%</td>
<td>50 / 50%</td>
</tr>
<tr>
<td>Haemoglobin gm/dl</td>
<td>12 / 10-14</td>
<td>12 / 10-14</td>
</tr>
</tbody>
</table>

Table (2): Intraoperative evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Group A Mean / Range/ number percent</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of blood loss (ml)</td>
<td>450 / 300-600</td>
<td>500 / 300-700</td>
</tr>
<tr>
<td>Need for another uterotonics</td>
<td>10 / 10%</td>
<td>12 / 12%</td>
</tr>
</tbody>
</table>

Table (3): Postoperative evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Group A Mean / Range/ number percent</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin level (gm /dl)</td>
<td>10.5 / 9-12</td>
<td>10 / 8-12</td>
</tr>
<tr>
<td>Uterine atony</td>
<td>15 / 15%</td>
<td>16 / 16%</td>
</tr>
<tr>
<td>Need for uterotonics</td>
<td>15 / 15%</td>
<td>16 / 16%</td>
</tr>
</tbody>
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Discussion

Main findings:
Prevention of postpartum hemorrhage is a must to avoid morbididty and mortality in obstetrics. The use of carbitocine was similar in result to use of syntocin in prevention of postpartum hemorrhage.

Strengths:
In this study; 200 patients designed to have elective CS were divided into two groups: Group A: 100 patients with elective CS take 100mg carbitocine as single dose IV. Group B: 100 patients with elective CS take 10mg syntocinon as single dose IV.

Preoperative and postoperative evaluation of hemoglobin measurement were performed. Intraoperative and postoperative evaluation of blood loss, uterine atony, need for another uterotonic agents, and need for blood transfuson were recorded during 1st 24 hours after CS.

limitations:
We found that The mean of hemoglobin preoperative were the same 12gm/dl, postoperative mean of haemoglobin were 10.5gm/dl in group A and 10gm/dl in group B. The mean amount of blood loss intraoperatively were 450ml in group A and 500ml in group B. The need for another uterotonic intraoperatively were 10 patients in group A and 12 patient in group B. The need for another uterotonic agent postoperatively was 15 patient in group A and 16 patients in group B, in theses patient uterine atony were developed.

Interpretation:
In this study there were no significant difference between the effect of carbitocine 100mg and syntocinon 10IU in prevention of postpartum hemorrhage in during and after caesarian section (C.S.).

This study has similar aspects regarding the effect of carbitocine on the uterus in comparison to syntocin to that of Moertl MG, et al., 2011 who mention that Effect on maternal heart rate (HR). Statistically indistinguishable haemodynamic effects were seen for carbetocin 1001.ug and 5 IU of oxytocin, with a maximal effect at about 30-40 seconds: HR increased 17.98±2.53 bpm for oxytocin and 14.20±2.45 bpm for carbetocin, with a maximal effect at about 30-40 seconds: HR increased 17.98±2.53 bpm for oxytocin and 14.20±2.45 bpm for carbetocin. Systolic blood pressure (sBP) decreased (-26.80±2.82mmHg for oxytocin versus -22.98±2.75mmHg for carbetocin). Following the maximal effect, women treated with carbetocin recovered slowly to baseline values asymptotically (HR and BP), whereas women treated with oxytocin displayed a slight rebound bradycardia at 200 seconds (-6.8±1.92 bpm). Patients under both treatments showed a similar profile of side effects without any indication of unexpected adverse effects. Both oxytocins have comparable haemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use. Minimal differences in the recovery phase beyond 70 seconds are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin [3].

This study was different in result in comparison to that of Askar, et al. [4], who mention that; To assess and compare the efficacy and safety of a single intramuscular dose of carbetocin to a single intramuscular dose of syntometrine in managing the third stage of labor following vaginal delivery among women with low risk factors for postpartum hemorrhage. Outcome measures compared included postpartum hemorrhage requiring additional uterotonic therapy, incidence of postpartum hemorrhage, amount of intrapartum blood loss as well as adverse effects profile. There was a statistically highly significant difference in the estimated mean blood loss between the carbetocin and syntometrine groups, with a blood loss of 81.5ml higher in the...
syntometrine group. The mean drop of hemoglobin concentration 24h after delivery was 0.8g/dl in carbetocin group and 1.1g/dl in syntometrine group, and the difference was statistically highly significant. Women in the carbetocin group were less likely to experience nausea and vomiting. Single dose of intramuscular carbetocin 10011g may be more effective as compared to a single intramuscular dose of syntometrine in reducing postpartum blood loss with a smaller drop in hemoglobin levels and less adverse effects.

This study was similar in result to that of Tri- opon, et al. [5], who mention that; To compare the efficacy of carbetocin versus oxytocin, during delivery in patients undergoing a caesarian section. A two phase observational study (before/after design) was conducted. Use of carbetocin was considered as a sentinel event. Data for 155 women who received carbetocin during a caesarian section were compared with 155 patients who received oxytocin. The main parameter evaluated was the need for haemostatic surgical techniques (vascular sutures, uterine compression sutures, emergent hysterectomy) during caesarian section. Both populations were comparable, particularly concerning risk factors of postpartum haemorrhage. In the carbetocin group, there was fewer compression sutures during caesarian section (0.6% versus 4.5%, p=0.06), as well as a significant decrease in postoperative intravenous iron administration (6.5% versus 14.5%, p=0.03). Vascular sutures, frequencies of prostaglandin intravenous injections, and blood transfusions during caesarian section were similar in both populations. There wasn't any emergent hysterectomy during the time of this study. Prevention of uterine atony during a caesarian section with carbetocin seems to be as effective as oxytocin. Particularly, decreasing rate of surgical compression sutures with use of carbetocin is not significant, and prospective studies with more patients are necessary to confirm these results.

This study was similar in result to that of Atti- lakos, et al. [6], who mention that; To compare the effectiveness of carbetocin and oxytocin when they are administered after caesarean section for prevention of postpartum haemorrhage (PPH). Double-blind randomised single centre study (1:1 ratio). Teaching hospital in Bristol, UK with 6000 deliveries per annum. Women at term undergoing elective or emergency caesarean section under regional anaesthesia, excluding women with placenta praevia, multiple gestation and placental abruption. Women were randomised to receive either carbetocin 100 microg or oxytocin 5IU intravenously after the delivery of the baby. Perioperative care was otherwise normal and use of additional oxytocics was at the discretion of the operating obstetrician. Analysis was by intention to treat. The proportion of women in each arm of the trial that needed additional pharmacological oxytocic interventions. Significantly more women needed additional oxytocics in the oxytocin group (45.5% versus 33.5%, Relative risk 0.74, 95% CI 0.57-0.95). The majority of women had oxytocin infusions. There were no significant differences in the secondary outcomes, including major PPH, blood transfusions and fall in haemoglobin. Carbetocin is associated with a reduced use of additional oxytocics. It is unclear whether this may reduce rates of PPH and blood transfusions.

This study was similar in result to that of Su, et al. [7], who mention that; Prevention of postpartum haemorrhage is essential in the pursuit of improved health care for women. However, limited literature is available for comparing the use of oxytocin agonist carbetocin with syntometrine in women undergoing vaginal deliveries. We aimed to compare intramuscular carbetocin with intramuscular syntometrine for the routine prevention of postpartum haemorrhage in women who deliver vaginally. Prospective double-blind randomised controlled trial. Tertiary referral centre. Pregnant women with no contraindication for vaginal delivery recruited from January 2005 to April 2008. Participants were randomised to receive either syntometrine or carbetocin during the third stage of labour. Primary outcome measure was postpartum haemorrhage requiring additional uterotonics. Secondary outcome measures were the incidence of postpartum haemorrhage (≥500ml), severe postpartum haemorrhage (≥1000ml) and adverse effects profile. Women in the carbetocin group (13.5%) and in the syntometrine group (16.8%) had postpartum haemorrhage requiring additional uterotonics (p=0.384). 1.6% of women in each group had postpartum haemorrhage (p=1.0) and the estimated blood loss during the third stage of labour was similar between the two groups (p=0.294). Women who had syntometrine were four times more likely to experience nausea (RR=4.2; 95% CI 2.2-7.8) and vomiting (RR=4.3; 95% CI 1.9-9.5) compared with women who had carbetocin. Tremor, sweating, retching and uterine pain were also more likely in the syntometrine group compared with the carbetocin group (p<0.05). Carbetocin has an efficacy similar to syntometrine for prevention of postpartum haemorrhage, but is associated with less adverse effects.

This study was different in result in comparison to that of Nirmala, et al. [8], who mentioned that;
To compare the efficacy of a single dose of 100 microg intramuscular carbetocin to a single dose of intramuscular syntometrine (0.5mg ergometrine and 5IU oxytocin), in preventing post-partum hemorrhage (PPH) in high risk patients following vaginal delivery. A prospective, randomized controlled study was conducted in a tertiary hospital where 120 pregnant women with risk factors for PPH who delivered vaginally were randomized into two groups: The study group where 100 microg intramuscular carbetocin was administered and the control group, who received intramuscular syntometrine. Outcome measures compared included changes in vital signs, amount of intrapartum blood loss, uterine fundal position, addition of another oxytocic agent, side-effects of the drugs, amount of lochia and hemoglobin drop after 24 hours post-partum. Incidence of PPH or other adverse events were also compared. There were no significant differences in terms of requirement for additional oxytocic agents, time interval to well contracted uterus, blood transfusion requirements, adverse effects or complications. There was a significantly lower mean estimated blood loss in the carbetocin group compared to the syntometrine group (244 ±114mL vs 343±143mL, 95% CI 52-146mL). There was also a significantly reduced drop in hemoglobin in the carbetocin group compared to the syntometrine group (0.3±0.2g/dL vs 0.4±0.2g/dL, 95% CI 0.1-0.2g/dL). Intramuscular carbetocin may be more effective than intramuscular syntometrine in reducing post-partum blood loss and the drop in hemoglobin level.

This study was different in result in comparison to that of Leung, et al. 191, who mention that; Syntometrine is an effective uterotonic agent used in preventing primary postpartum haemorrhage but has adverse effects including nausea, vomiting, hypertension and coronary artery spasm. Carbetocin is a newly developed long-acting oxytocin analogue that might be used as an uterotonic agent. We compare the efficacy and safety of intramuscular (IM) carbetocin with IM syntometrine in preventing primary postpartum haemorrhage. Prospective, double-blinded, randomised controlled trial. Delivery suite of a university-based obstetrics unit. Women with singleton pregnancy achieving vaginal delivery after and throughout 34 weeks. Three hundred and twenty-nine eligible women were randomised to receive either a single dose of 100 microgram IM carbetocin or lml IM syntometrine (a mixture of 5IU oxytocin and 0.5mg ergometrine) at the end of second stage of labour. Difference in haemoglobin drop measured 2 days after delivery between the two groups. There was no difference in the drop of haemoglobin concentration within the first 48 hours between the two groups. The incidence of additional oxytocic injections, post-partum haemorrhage (blood loss >or=500ml) and retained placenta were also similar. The use of carbetocin was associated with significant lower incidence of nausea (relative risk [RR] 0.18, 95% confidence interval [CI] 0.04-0.78), vomiting (RR 0.1, 95% CI 0.01-0.74), hypertension 30 minutes (0 versus 8 cases, p<0.01) and 60 minutes (0 versus 6 cases, p<0.05) after delivery but a higher incidence of maternal tachycardia (RR 1.68, 95% CI 1.03-3.57). IM carbetocin is as effective as IM syntometrine in preventing primary postpartum haemorrhage after vaginal delivery. It is less likely to induce hypertension and has a low incidence of adverse effect. It should be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labour.

Conclusion:
Syntocinon is effective as carbitocine in prevention of postpartum haemorrhage during elective CS. But this need more studies to evaluate the efficacy and complications of carbitocine.

Acknowledgment:
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Disclosure of interests:
None.

Contribution to authorship:
W.S. Contributed to the protocol, co-ordinated the study, interviewed the parents, analysed the data and drafted the article. W.S. Contributed also to the revision and final approval of the article.

Details of ethics approval:
The study received approval from the National Research Ethics Committee Zagazig University, Faculty of Medicine. Reference: 29/5/0946. Date of approval: 5 January 2012.

Funding:
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