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# Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery

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## Abstract

**Objective:** To compare the efficacy of a single dose of 100 µg intramuscular carbetocin to a single dose of intramuscular syntometrine (0.5 mg ergometrine and 5IU oxytocin), in preventing post-partum hemorrhage (PPH) in high risk patients following vaginal delivery.

**Methods:** 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 µg 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.

**Results:** 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 ( $244 \pm 114$  mL vs  $343 \pm 143$  mL, 95% CI 52–146 mL). There was also a significantly reduced drop in hemoglobin in the carbetocin group compared to the syntometrine group ( $0.3 \pm 0.2$  g/dL vs  $0.4 \pm 0.2$  g/dL, 95% CI 0.1–0.2 g/dL).

**Conclusion:** Intramuscular carbetocin may be more effective than intramuscular syntometrine in reducing post-partum blood loss and the drop in hemoglobin level.

**Key words:** blood loss, carbetocin, oxytocic agent, post-partum hemorrhage, syntometrine.

## Introduction

Post-partum hemorrhage (PPH) is the leading cause of maternal death worldwide. In developing countries, it is responsible for the deaths of about 125 000 women each year.<sup>1–2</sup> In Malaysia, post-partum hemorrhage continues to be among the top three leading causes of maternal deaths.<sup>3</sup> As uterine atony is responsible for 80% of PPH occurrences, numerous strategies have been promoted to preserve uterine tonicity.<sup>4</sup> Prendiville *et al.* found that giving a uterotonic agent reduced

the risk of hemorrhage by approximately 40%.<sup>5</sup> Indeed, uterotonic agents were employed in all strategies of active management of the third stage of labour.<sup>6</sup> Which uterotonic agent is ideal for prophylactic use is still being debated.<sup>7</sup>

Syntometrine is a mixture of ergometrine 0.5 mg with oxytocin 5IU which is given by intramuscular injection following the delivery of the anterior shoulder of the baby. It has the combination of rapid onset of action of oxytocin and the sustaining effect of ergometrine and is the agent of choice in the third stage of

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labor at the National University of Malaysia Hospital (HUKM). Khan *et al.* found that although syntometrine resulted in a significant small reduction in PPH compared with oxytocin, it was consistently associated with an increased incidence of side effects.<sup>8</sup>

Carbetocin, a new drug for the prevention of uterine atony, is a synthetic analogue of oxytocin with a half-life of up to 4 to 10 times longer than that of oxytocin.<sup>7</sup> In comparison with oxytocin, it is used as a single-dose injection instead of an infusion and can be given intravenously or intramuscularly. The bioavailability is 80% after intramuscular injection, and the optimal dose used in the third stage of labor is 100 µg.<sup>9</sup> Boucher *et al.* found that the mean blood loss after carbetocin administration was 29 mL less than after oxytocin administration and the percentage of patients with blood loss of 200 mL or less was greater with carbetocin (79% vs 53%,  $P=0.04$ ).<sup>10</sup> Patients receiving carbetocin also require less intervention as compared to oxytocin thus reducing the incidence of PPH.<sup>7,10,11,12</sup> Leung *et al.* found that carbetocin is less likely to induce hypertension and has a low incidence of adverse effects.<sup>13</sup>

There have been no local studies comparing carbetocin to syntometrine in women at risk of PPH following vaginal delivery. Our study is to compare the efficacy and safety of a single 100 µg intramuscular dose of carbetocin to a single intramuscular dose of syntometrine in the prevention of PPH in patients at risk of PPH following vaginal delivery. 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. The incidence of PPH or other adverse event was also compared.

## Materials and Methods

This is a prospective randomized controlled study conducted in the Department of Obstetrics and Gynaecology, HUKM, Malaysia. The study was approved by the Research and Ethics Committee of the hospital. A total of 120 pregnant women beyond 36 weeks' gestation with a viable fetus with at least one risk factor for PPH achieving vaginal delivery participated in the study. The PPH risk factors for inclusion used in this study were determined following a review of acknowledged sources.<sup>14–18</sup> The PPH risk factors which were included in this study were a history of blood transfusion or iron sucrose injection pre or post delivery, a history of retained placenta, grandmultiparity (>para 5), twin

pregnancy, fetal macrosomia (fundal height  $\geq 40$  cm or clinical ultrasound estimated fetal weight 3.8–4.0 kg), polyhydramnios (more than one amniotic fluid pocket  $\geq 8.0$  cm or AFI  $\geq 25.0$  cm), induction or augmentation of labor with oxytocin for at least 4 hours or prolonged labor (active phase >12 hours).<sup>19</sup>

Women younger than 18 years old were excluded as were women with history of significant heart disease, hypertension requiring treatment, a history or evidence of liver, renal, vascular disease or endocrine disease (excluding gestational diabetes) or hypersensitivity to oxytocin or carbetocin.

All patients who fulfilled the above criteria were counseled regarding the study and informed consent was obtained on admission to the antenatal ward. On admission to the labor room, they were randomized to receive either carbetocin or syntometrine by computer-generated randomized codes sealed in sequentially numbered envelopes upon reaching 6 cm for multiparous women or full cervical dilatation for primiparous women, in order to reduce the risk of randomizing women who were likely to require caesarean section.

The preparation and administration of the medication was carried out by midwives who were not involved in the management of the patient except for the drug administration. When delivery was imminent, the envelope was opened by the midwife in charge of the patient and the numbered vial of oxytocic agent was kept ready for injection during the third stage of labor. Only patients who had a spontaneous vaginal delivery were included in the trial.

Baseline blood pressure and pulse rate was recorded upon admission to the labor room. Blood samples were drawn to check for hemoglobin levels upon admission to the labor room and repeated on day 1 post delivery.

Labor was managed according to the labor room protocol at HUKM and progress was recorded in a partogram. Pre-induction cervical ripening via mechanical or hormonal agents was permitted. Analgesia during labor was either by regional analgesia or parenteral narcotics. Time of delivery of the baby was recorded. Immediately after delivery of the baby, the selected drug was administered in the upper thigh of the patient intramuscularly.

If uterine tone was not firm or the amount of bleeding was unsatisfactory after the administration of the drug, an additional oxytocic agent was administered. The time interval between initial selected drug administration and the type of additional oxytocic intervention was recorded.

The umbilical cord was clamped immediately after delivery of the baby. Measurement of blood loss by the gravimetric method was started immediately after drug administration, where a new plastic sheet was placed under the patient's thighs following delivery of the baby in order to minimize the error of including amniotic fluid and blood absorbed into drapes. The placenta was delivered via controlled cord traction. All gauzes, tampons and pads which were subsequently used were collected for the first hour following the delivery of the placenta. A digital weighing scale (Soehnle, Venezia) was used. The difference in weight of the material before and after the hour was calculated. A 100 g increase in weight was considered to be equivalent to 100 mL blood.<sup>20,21</sup>

Both assessment of the uterine fundal height after drug administration and the vital signs were monitored at 0, 30 min and 60 min in the labor ward by the main researcher. An increase in systolic and diastolic pressures equal to or greater than 30 and 20 mmHg, respectively, were considered to be significant. The mean levels of blood pressures over the three post injection readings and the mean pulse rate for both groups at each set were calculated.

The number of pads used and the amount of lochia were recorded using a pictogram from the end of delivery till day 1 post delivery. Only standard hospital pads were used by the patients. Pads were changed every 4 hours or earlier to avoid overdrying or flooding.

The patients were monitored for side effects of the selected drug in the first 24 hours post delivery. Patients were questioned for side effects after drug administration, in the recovery room and in the post

natal ward. The patients were also monitored for signs of flushing, sweating, tremor and vomiting. Any other symptoms volunteered or signs observed by the attending doctor or nurse were also recorded.

Any blood transfusion or iron sucrose injection post-partum or incidence of PPH was recorded in the first 24 hours post delivery.

Analysis of data was made using the Statistical Package for the Social Sciences (SPSS) package version 11.5. Comparison of categorical variables was evaluated with Fisher's exact test with  $P < 0.05$  taken as significant. Where appropriate, 95% confidence intervals (CI) were calculated. Continuous variables were evaluated with the Student's *t*-test.

## Results

A total of 120 women with at least one risk factor for post-partum hemorrhage completed the study. They were randomized to receive either a single intramuscular dose of carbetocin 100 µg or a single ampoule of intramuscular syntometrine (0.5 mg ergometrine and 5IU oxytocin).

Each group was comparable for maternal age, weight, height, body mass index and hematological values at entry, as well as for parity, gestational age, medical disorders and the use of either cervical ripening or epidural analgesia.

Table 1 summarized the risk factors for post-partum hemorrhage presented by our study population. No significant difference was observed between the carbetocin and syntometrine groups with regards to the frequency of individual risk factors.

**Table 1** Distribution of risk factors for post-partum hemorrhage

| Risk factors  | Carbetocin<br><i>n</i> = 60<br><i>n</i> (%) | Syntometrine<br><i>n</i> = 60<br><i>n</i> (%) | <i>P</i> -value |
|---|---|---|-----------------|
| Grandmultipara  | 8 (13)                                      | 4 (7)   | ns              |
| History of retained placenta                            | 3 (5)                                       | 1 (2)   | ns              |
| History of blood transfusion post-delivery              | 1 (2)                                       | 1 (2)   | ns              |
| History of iron sucrose injection pre- or post-delivery | 1 (2)                                       | 0   | ns              |
| Twin pregnancy  | 4 (7)                                       | 2 (3)   | ns              |
| Polyhydramnios  | 0   | 2 (3)   | ns              |
| Fetal macrosomia  | 1 (2)                                       | 2 (3)   | ns              |
| Induction of labor                                      | 6 (10)                                      | 8 (13)  | ns              |
| Augmentation of labor more than 4 hours                 | 32 (53)                                     | 36 (60)                                       | ns              |
| Prolonged labor 1 <sup>st</sup> stage                   | 4 (7)                                       | 4 (7)   | ns              |
| Prolonged labor 2 <sup>nd</sup> stage                   | 0   | 0   | –               |

ns, not significant.

**Table 2** Vital signs

|   | Carbetocin<br><i>n</i> = 60<br>Mean ± SD | Syntometrine<br><i>n</i> = 60<br>Mean ± SD | <i>P</i> -value |
|---|--|--|-----------------|
| Systolic blood pressure on admission = baseline (mmHg)              | 120 ± 57                                 | 120 ± 58                                   | ns              |
| Increase in systolic blood pressure at 30 min from baseline (mmHg)  | 7 ± 4                                    | 7 ± 5                                      | ns              |
| Increase in systolic blood pressure at 60 min from baseline (mmHg)  | 7 ± 4                                    | 7 ± 4                                      | ns              |
| Diastolic blood pressure on admission = baseline (mmHg)             | 73 ± 38                                  | 76 ± 36                                    | ns              |
| Increase in diastolic blood pressure at 30 min from baseline (mmHg) | 1 ± 2                                    | 1 ± 1                                      | ns              |
| Increase in diastolic blood pressure at 60 min from baseline (mmHg) | 1 ± 2                                    | 1 ± 2                                      | ns              |
| Pulse rate on admission = baseline (bpm)                            | 84 ± 5                                   | 86 ± 5                                     | ns              |
| Increase in pulse rate at 30 min from baseline (bpm)                | 2 ± 2                                    | 1 ± 3                                      | ns              |
| Increase in pulse rate at 60 min from baseline (bpm)                | 3 ± 2                                    | 2 ± 3                                      | ns              |

ns, not significant; SD, standard deviation.

Labor characteristics were similar in each group. The duration of first, second and third stages were similar between the groups, with a total duration of labor of  $8 \pm 3$  hours in the carbetocin group and  $8 \pm 3$  hours in the syntometrine group ( $P > 0.05$ ). There was no significant difference in the duration of oxytocin infusion (for induction or augmentation of labor) between the carbetocin and syntometrine groups (carbetocin vs syntometrine;  $5 \pm 2$  hours vs  $4 \pm 2$  hours,  $P > 0.05$ ). Types of perineal tear were similar between the two groups with no cases of cervical tear. There was no significant difference in the different accoucheurs who attended the labor in the two groups.

Vital signs were monitored at 0, 30 and 60 min after study drug administration. Changes in mean ( $\pm$  standard deviation) systolic and diastolic blood pressure and heart rate in each group throughout the study period were not statistically significant (Table 2). There were no significant differences in the number of patients with hypertension between the two groups (7 patients [12%] in the carbetocin group vs 9 patients [15%] in the syntometrine group,  $P > 0.05$ ).

Within one minute of delivery, 42% of patients in the carbetocin group and 33% patients in syntometrine group received their respective drugs. Within 2 min, 93% of patients in the carbetocin group and 98% of patients in the syntometrine group had received their respective drugs. Four patients in the carbetocin group and one patient in the syntometrine group received their study drug late which was within 3 min due to inadequate staffing. There were none who received the drugs after 3 min.

Uterine tone increased rapidly after the drug administration, with 95% and 90% of patients in the carbetocin and syntometrine groups, respectively, having a contracted 20 week size uterus at 5 min. No significant

difference was observed between the study groups in the number of women requiring an additional oxytocic agent (3 in the carbetocin group vs 9 in the syntometrine group,  $P > 0.05$ ). The times from study drug administration to additional oxytocic drug administration were similar in the two groups (carbetocin vs oxytocin;  $15 \pm 8$  min vs  $12 \pm 8$  min,  $P > 0.05$ ). Oxytocin infusion 40IU was used as an additional oxytocic in both syntometrine and carbetocin groups.

Symptoms experienced by patients and signs observed by the study team are summarized in Table 3. There was no difference in severity or frequency of symptoms and signs between the two groups (Table 3).

There was significant difference in the mean estimated blood loss between the carbetocin and syntometrine groups with a blood loss of 99 mL higher in the syntometrine group ( $244 \pm 114$  mL vs  $343 \pm 143$  mL, 95% CI 52–145 mL). Post-partum hemorrhage (blood loss greater than 500 mL) was diagnosed in three (5%) women in the carbetocin group compared to six (10%) women in the syntometrine group (Table 4).

There was a significant drop in hemoglobin in the syntometrine group with a mean difference of 0.2 g/dL as compared to the carbetocin group (95% CI 0.1–0.2 g/dL). There was no significant difference in before and after hemoglobin levels between the two groups (mean hemoglobin  $11.3 \pm 1.1$  g/dL in the carbetocin group vs  $11.4 \pm 1.0$  g/dL in the syntometrine group). Ninety-five percent of patients in the carbetocin group had less than a 5% drop in hemoglobin levels as compared to 83% of patients in the syntometrine group with less than a 5% drop in hemoglobin levels. None of the patients in the carbetocin group had more than a 10% drop in hemoglobin levels whereas one patient in the syntometrine group who bled 870 mL

**Table 3** Frequency of symptoms and signs

|                   | Carbetocin<br><i>n</i> (%) | Syntometrine<br><i>n</i> (%) | <i>P</i> value |
|-------------------|----------------------------|------------------------------|----------------|
| Abdominal pain    | 1 (2)                      | 3 (5)                        | ns             |
| Back pain         | 0                          | 1 (2)                        | ns             |
| Headache          | 2 (3)                      | 1 (2)                        | ns             |
| Nausea            | 0                          | 1 (2)                        | ns             |
| Feeling of warmth | 0                          | 0                            | –              |
| Metallic taste    | 0                          | 0                            | –              |
| Other symptoms    | 0                          | 0                            | –              |
| Flushing          | 0                          | 0                            | –              |
| Sweating          | 0                          | 0                            | –              |
| Tremors           | 0                          | 0                            | –              |
| Vomiting          | 0                          | 2 (3)                        | ns             |
| Other signs       | 0                          | 0                            | –              |

**Table 4** Blood parameters

|                                 | Carbetocin<br><i>n</i> = 60<br>Mean ± SD | Syntometrine<br><i>n</i> = 60<br>Mean SD | <i>P</i> value   |
|---------------------------------|--|--|------------------|
| Estimated blood loss (mL)       | 244 ± 114                                | 343 ± 143                                | <i>P</i> < 0.001 |
| Range                           | 78–578                                   | 89–870                                   |                  |
| Pre-delivery hemoglobin (g/dL)  | 11.3 ± 1.1                               | 11.4 ± 1.0                               | ns               |
| Post-delivery hemoglobin (g/dL) | 11.0 ± 1.1                               | 11.0 ± 1.0                               | ns               |
| Hemoglobin difference (g/dL)    | 0.3 ± 0.2                                | 0.4 ± 0.2                                | <i>P</i> < 0.001 |
| Blood loss (mL)                 | <i>n</i> (%)                             | <i>n</i> (%)                             |                  |
| <100                            | 4 (7)                                    | 2 (3)                                    | –                |
| 100–199                         | 13 (21)                                  | 5 (8)                                    | –                |
| 200–299                         | 27 (45)                                  | 15 (25)                                  | –                |
| 300–399                         | 10 (17)                                  | 20 (33)                                  | –                |
| 400–499                         | 3 (5)                                    | 12 (20)                                  | –                |
| ≥500 (PPH)                      | 3 (5)                                    | 6 (10)                                   | ns               |
| % of drop in hemoglobin level   |  |  |                  |
| <5%                             | 57 (95)                                  | 50 (83)                                  | –                |
| 5–10%                           | 3 (5)                                    | 9 (15)                                   | –                |
| >10%                            | 0  | 1 (2)                                    | –                |

ns, not significant; SD, standard deviation.

had more than a 10% drop in hemoglobin levels (Table 4). No significant difference was observed with regard to the amount of lochia in the 24 hours post-partum.

In the syntometrine group, a 32-year-old grand-multipara (Gravida 7 Para 6) required 2 units of blood as she had symptoms of anemia following post-partum hemorrhage secondary to uterine atony with post delivery hemoglobin of 7.8 g/dL. Her blood loss was 870 mL with pre-delivery hemoglobin of 9.0 g/dL. No patients in the carbetocin group required blood transfusion. No patient from either group required the high dependency unit (HDU) or the intensive care unit (ICU), the manual removal of the placenta, evacuation of blood clots or hematoma or caesarean hysterectomy.

## Discussion

This was the first local randomized controlled study assessing the effects of carbetocin, a long-acting synthetic oxytocin analogue.

In the absence of preventative measures, previous studies had observed an incidence of post-partum hemorrhage of 5 to 15% for all deliveries in the general population without regard to maternal or fetal risk factors.<sup>6</sup> In this study, we have observed a frequency of post-partum hemorrhage of 7.5%. The incidence of post-partum hemorrhage was seen in both groups with lesser incidence in the carbetocin group as compared to the syntometrine group (5% vs 10%) although this was not statistically significant.

Our study has shown that women at high risk of post-partum hemorrhage who received a single dose of 100 µg intramuscular carbetocin immediately after delivery of their baby, bled 99 mL less (95% CI 52–145 mL) than women who received a single intramuscular dose of syntometrine. A total of 73% of patients in the carbetocin group had blood losses of 300 mL or less whereas 78% of patients in the syntometrine group had blood losses of 300 mL–500 mL. Boucher *et al.*, with the use of a hemoglobin extraction technique, reported that patients treated with oxytocin did bleed approximately 30 mL more than did patients given carbetocin.<sup>13</sup>

There was also a 0.2 g/dL reduced drop of hemoglobin in the carbetocin group than women in the syntometrine group 24 hours after vaginal delivery (95% CI 0.1–0.2 g/dL). Ninety-five percent of patients in the carbetocin groups had less than a 5% drop in hemoglobin level as compared to 83% of patients in the syntometrine group.

The amount of difference in blood loss and the drop in hemoglobin levels was trivial; as this study is limited by the small sample size. However, these effects on the prevention of post-partum hemorrhage would be beneficial in clinical practice especially in patients with anemia in pregnancy if high cost and risk of blood transfusion is taken into consideration. A larger study needs to be conducted to determine the clinical efficacy of carbetocin in terms of reduction of post-partum blood loss and drops in hemoglobin levels.

The lack of significant difference in requirement for additional uterotonic medication between the two groups was a contrast to the findings of a large multicentre trial of carbetocin following caesarean birth, in which women who received a single 100 µg intravenous carbetocin dose required significantly less oxytocic intervention than those who required an 8-hour oxytocin infusion.<sup>7</sup> Inclusion criteria for the caesarean birth study did not take into account the women's risk factors for post-partum haemorrhage.<sup>7</sup> A randomized controlled trial by Boucher *et al.*, however, involving 160 women with at least one risk factor for post-partum hemorrhage is in agreement with our study, showing that there was no significant difference in requirement for additional uterotonic medication between women receiving a single 100 µg intramuscular carbetocin and women receiving a continuous 2-hour oxytocin infusion.<sup>10</sup> The discrepancy may be that women at high risk of post-partum hemorrhage after a vaginal delivery have an inherent tendency for excessive post-partum bleeding in spite of the preventative measures taken.

Carbetocin appeared well tolerated in this population, with no safety concerns as judged by the assessment of symptoms, signs, vital signs or other adverse events.

In non-pregnant women, an intravenous dose of carbetocin 4 to 8 times higher than the one used in the current study produced a mild transient decrease in diastolic blood pressure.<sup>22</sup> In this study, it was not seen presumably because a lower dosage was used. Rather, a mild increase in both systolic and diastolic blood pressure was observed which was of no clinical importance. There were no significant cases of hypertension between the two study groups. The lack of significant differences in vital signs between the two treatment groups supported equivalent safety between a single intramuscular carbetocin 100 µg and a single intramuscular syntometrine (0.5 mg ergometrine and 5IU oxytocin).

Some adverse events that occurred in the study patients, namely abdominal pain and headache, were observed previously during clinical pharmacology studies with carbetocin and probably represent the typical side effects of neuroendocrine peptides.<sup>22,23</sup> Other adverse events, however, were more likely to be the result of epidural analgesia or opiates. For example, nausea and vomiting were typical side effects of opiates that were routinely used as analgesia in this study.

A potential complication using oxytocics in the third stage of labor is retained placenta.<sup>24,25</sup> When ergometrine is compared with oxytocin, the risk of retained placenta is significantly increased.<sup>24</sup> Yuen *et al.*<sup>26</sup> reported a higher incidence of retained placenta associated with the use of syntometrine compared with intramuscular oxytocin, but a similar finding was not observed in our study. This might be related to the different methods of delivering placenta. In that trial, the placenta was not delivered until signs of placental separation appeared, in contrast to the early clamping of the umbilical cord and immediate controlled cord traction in our study. Such early intervention allows the placenta to be delivered before the occurrence of uterine spasm, thereby reducing the risk of retained placenta. No patient from either group required HDU or ICU admission, manual removal of the placenta, evacuation of blood clots or hematoma or caesarean hysterectomy.

An intramuscularly injected carbetocin has a bioavailability of about 80% and as it is longer acting,<sup>9,22,23</sup> it is a good option in a clinical setting where an intravenous line is not easily available. However, evaluation

of the benefits of intramuscular carbetocin compared with syntometrine need to be determined in each clinical situation with patient safety, convenience and economic constraints in mind.

We concluded that a single dose of intramuscular carbetocin 100 µg may be more effective as compared to a single intramuscular syntometrine (0.5 mg ergometrine and 5IU oxytocin) in reducing post-partum blood loss with a smaller drop in hemoglobin levels. Carbetocin is combined with the safety of oxytocin with the longer duration of action of ergot preparations and as such has the potential to become the drug of choice in the prevention of post-partum hemorrhage.

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