Original Article

Prevention of postpartum haemorrhage in patients with severe preeclampsia using carbetocin versus misoprostol

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A B S T R A C T

Background: Haemorrhage is a leading cause of maternal death worldwide, accounting for over 30% of maternal deaths in Africa and Asia. Postpartum bleeding was also 1.6 times higher in women with preeclampsia than in normotensive women.

Objective: We aimed to prevent postpartum haemorrhage in patients with severe preeclampsia by using either carbetocin or misoprostol. The primary outcome was postpartum haemorrhage (blood loss of ≥500 ml) while our secondary outcomes included use of other uterotonics, blood transfusion, maternal complications and maternal death.

Methods: This prospective, randomized study was done at Department of Obstetrics and Gynecology, Benha University Hospital, Benha University. 60 pregnant women candidate for vaginal delivery with severe preeclampsia received either carbetocin or misoprostol after delivery of the baby.

Results: Carbetocin was superior to misoprostol with lower duration of third stage of labour (P = 0.036), lower amount of blood loss (P = 0.017) and lower incidence of PPH (P = 0.03). There was no significant difference in the pre-delivery and the post-delivery haemoglobin concentration between the two groups with P = 0.061. The need of additional uterotonics and blood transfusion was higher with misoprostol as compared to carbetocin with P = 0.037 and 0.009, respectively. As regards side effects, misoprostol was associated with shivering and pyrexia in significantly high number of patients as compared to carbetocin while nausea, vomiting and headache were more associated with carbetocin.

Conclusions: Carbetocin was more effective than misoprostol when used in women with severe preeclampsia to prevent postpartum bleeding.

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1. Introduction

Haemorrhage is a leading cause of maternal death worldwide, accounting for over 30% of maternal deaths in Africa and Asia.1 Furthermore, it is a substantial source of maternal morbidity and can have long-term effects on a woman’s health. In very severe cases, hysterectomy may be used to control the bleeding. Maternal haemorrhage can occur in the antepartum, intrapartum or postpartum period. The WHO defines postpartum haemorrhage (PPH) as blood loss of 500 ml or more from the genital tract after delivery, although some studies define PPH as blood loss greater than or equal to 1000 ml as this has greater clinical significance.2 Untreated maternal haemorrhage is associated with adverse health consequences such as renal failure and anaemia and may detrimentally affect a woman’s psychological well-being.3,4

Preeclampsia (PE) is a condition characterized by hypertension and proteinuria in pregnant women, whereas hypertension is defined as blood pressure equal to or exceeding 140/90 mmHg after the 20th week of gestation, and proteinuria is defined as either urinary excretion of more than 300 mg protein in 24 h or presence of 3 mg/dL (≥1+ dipstick test) protein in two random urine samples.5

The World Health Organization (WHO) estimates that PE/E account for at least 16% of maternal deaths in low-resource settings that lack the skilled providers and facilities required for prevention, identification and management of the condition.6

Eskild and Vatten showed that the incidence of severe postpartum bleeding (>1500 ml) was two times higher in women with preeclampsia than in normotensive women (P < 0.005). Postpartum bleeding >500 ml was also 1.6 times higher (P < 0.005) in women with preeclampsia than in normotensive women.7

Misoprostol, an oral prostaglandin E1 analogue that can be administered immediately following delivery, offers an important alternative for PPH prevention in low-resource settings and at home births, where oxytocin is not available or where its use is not feasible. Misoprostol requires no injection supplies or skilled provider for administration. Misoprostol does not need refrigeration and can therefore be stored and provided where there is no electricity. These factors enable programmes for the prevention of PPH using misoprostol to potentially achieve high coverage and use, particularly by women who reside at a distance from a health facility.8,9

Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single-dose injection, either intravenously or intramuscularly. Intravenously administered carbetocin has a half-life of approximately 40 min, around 4–10 times longer than that reported for oxytocin. Following intramuscular injection, carbetocin reaches peak plasma concentrations in less than 30 min and has 80% bioavailability.10,11

The effect of various intravenous and intramuscular doses of carbetocin on the postpartum uterus has been evaluated by tocographic recordings of uterine contractions 24–48 h after vaginal delivery at term in 40 women.12 A single intravenous bolus of 8–30 mg carbetocin or a single intramuscular injection of 10–70 mg carbetocin produced a tetanic uterine contraction within 2 min of drug administration.13 Uterine activity persisted for an average of 120 min following intramuscular injection and an average of 60 min following intravenous injection.12 Thus, these data show that carbetocin onset of action is rapid irrespective of administration route, but the duration of action is longer following intramuscular injection. The optimal carbetocin dose (intravenous or intramuscular) is 100 mg.13 We therefore conducted this randomized trial to compare the efficacy and safety of IV carbetocin with sublingual misoprostol in managing the third stage of labour among women with severe preeclampsia to decrease the incidence of postpartum haemorrhage.

2. Patients and methods

We conducted this prospective, randomized study at Department of Obstetrics and Gynecology, Benha University Hospital, since January 2013 till July 2015, after approval of the study protocol by the Local Ethical Committee. A written informed consent was obtained from eligible women before induction or at early stage of labour.

Our inclusion criteria were severe preeclamptic women with single foetus, gestational age more 28 weeks’ and vaginal delivery. Preeclampsia is labelled as severe in the presence of any of the following abnormalities:

1. A persistent systolic blood pressure of >160 mmHg or diastolic pressure of >110 mmHg.
2. Protein excretion of >5 g/24 h.
3. Oliguria (<400 ml/24 h).
4. Platelet count <100,000/mm³.
5. HELLP syndrome.
6. Cerebral or visual disturbances.
7. Persistent severe epigastric pain.
8. Retinal haemorrhages, exudates or papilledema.
9. Intrauterine growth restriction of the foetus.

Our exclusion criteria were HELLP syndrome, eclampsia, abruptioplacentae, polyhydramnios, uterine scar, chorioamnionitis, malpresentation and multiple pregnancies. All patients were in stable condition (no evidence of maternal haemodynamic instability or foetal distress) and their management afterwards followed the standards accepted in our country and established guidelines for the management of hypertensive disorders of pregnancy.

For hypertensive crisis, the first drug used was hydralazine (5 mg IV every 15 min to a maximum total dose of 20 mg); if this was ineffective, nifedipine (Epilat): 10–20 mg orally/30 min (max 50 mg) and then 10–20 mg/4–6 h (max 120 mg/day) or labetalol (20 mg IV every 10 min to a maximum total dose of 300 mg) were used. No patient needed additional treatment for their symptoms or developed antepartum complications that required admission to the intensive care unit. All patients were evaluated hourly and received magnesium sulphate to prevent eclampsia during the pregnancy and for a minimum of 24 h postpartum.

A total of 80 women with severe preeclampsia were screened but only 60 patients were included (Fig. 1). The
patients were randomized and divided into two groups: Group A (30) received a single dose of carbetocin (100 µg in 1 ml ampoule, Pabaf) slow intravenous bolus over 1 min while in Group B (30), misoprostol (600 µg, 3 tablets) was given sublingually after the delivery of the baby.

The third stage of labour was managed as usual by clamping and cutting of umbilical cord, waiting for signs of placental separation and delivering the placenta by controlled cord traction. Duration of the 3rd stage of labour was calculated. The patient was kept in labour room under observation for a period of 1 h, and any complaint such as nausea, vomiting, fever, headache, chills, diarrhoea and shivering was noted. In cases of uterine atony (determined by physical examination and continuous postpartum bleeding) uterus was massaged and additional uterotonics were given and noted (oxytocin and/or prostaglandin, at the discretion of the attending physician). Any requirement for manual removal of the placenta or blood transfusion was also recorded.

The following laboratory assessments (haemoglobin, haematocrit, platelets and renal and liver function tests) were performed in every patient on admission and postpartum. Vital signs (blood pressure, heart rate, respiratory rate) and urine output were measured every hour until at least 24 h after delivery.

2.1. Measurement of blood loss

A clean plastic lined absorbent drape was placed under the woman’s buttocks to collect all the blood lost after delivery of the baby and drainage of the amniotic fluid. The drape was changed as many times as needed. The woman stayed on the drape or was asked to wear a pad over the next 60 min. In the case of severe haemorrhage, we followed the usual guidelines for management of postpartum haemorrhage, and the supplemental treatment was registered. All drapes and pads were weighed on an electronic scale, and the known dry weight of the linen was subtracted. As 1 ml of blood weighs close to 1 g, the balance in grams was assumed to be the total blood loss in ml.

The rates of haemoglobin and haematocrit were measured at hospitalization and also 24 h after delivery and then were recorded. At this interval, the patients were evaluated in terms of possible complications of administered drugs such as vomiting, diarrhoea, shivering, pyrexia and headache.

All patients had the Foley catheter in situ for 24 h after delivery, and the amount of urine was monitored hourly.

This study had no external funding source. No author had any potential relationships that may pose conflict of interest.

2.2. Outcome measures

Our primary outcome measure was postpartum haemorrhage, defined as a blood loss of ≥500 ml. We analysed the blood loss and change in haemoglobin concentration between admission and discharge while secondary outcomes included use of other uterotonics, blood transfusion, drug reaction (such as headache, vomiting, abdominal pain, pruritus, tacky or bradycardia), severe maternal complications (such as seizures or need for ICU admission) and maternal death.

2.3. Statistical analysis

For a power analysis of 90%, the study needed 30 patients in each group. Results were expressed as mean ± SD, range, numbers and percentages. Intra-group data were statistically analysed using t-test, and inter-group analysis was examined using Chi-square test ($\chi^2$ test). Statistical analysis was conducted using SPSS statistical program (Version 10, 2002). P value < 0.05 was considered statistically significant.
Table 1 – Characteristics of the study population at delivery.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cabotocin Group A (n = 30)</th>
<th>Misoprostol Group B (n = 30)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)*</td>
<td>28.6 ± 6.35</td>
<td>27.5 ± 6.87</td>
<td>T = −0.6</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>79.4 ± 6.98</td>
<td>79.3 ± 7.02</td>
<td>T = −0.1</td>
<td>0.96</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiparous</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>35.4 ± 2.97</td>
<td>34.2 ± 6.99</td>
<td>T = −0.8</td>
<td>0.42</td>
</tr>
<tr>
<td>Initial haemoglobin [Hg], mg/dl*</td>
<td>11.88 ± 1.6</td>
<td>12.14 ± 1.6</td>
<td>T = 0.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Arterial pressure (at delivery)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>157.8 ± 7.4</td>
<td>156.5 ± 8.4</td>
<td>T = −0.7</td>
<td>0.51</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>102.3 ± 7.4</td>
<td>104.2 ± 6.6</td>
<td>T = −0.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Heart rate, bpm (at delivery)*</td>
<td>79.7 ± 7.2</td>
<td>80.5 ± 7.2</td>
<td>T = 0.4</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* Data presented by mean ± standard deviation.
T: t-test; \( \chi^2 \): Chi-square test.
P value <0.05 was considered statistically significant.

3. Results

A total of 80 women with severe preeclampsia were screened but only 60, who fulfilled the required inclusion criteria, were included in the study (Fig. 1). 30 women in Group A received a single dose of carbetocin (100 \( \mu \)g in 1 ml ampoule) and were given slow intravenous bolus over 1 min while in Group B (30 women) misoprostol (600 \( \mu \)g, 3 tablets) was given sublingually after the delivery of the baby. In this study, the baseline characteristics of the two groups were similar, as were the obstetrical intrapartum variables (Table 1). The level of hypertension and the heart rate presented in both groups were similar. There were no significant differences between the two groups before the drug was administered.

The incidence of primary postpartum haemorrhage in the carbetocin Group A was significantly lower (3%) than in the misoprostol Group B (20%) (\( P = 0.04 \)). All cases of primary postpartum haemorrhage occurred either immediately or within 1 h post-delivery while the woman was still in the delivery room (Table 2). There was also a significant difference in the amount of estimated blood loss and was lower in Group A (278 ± 202) than in Group B (403 ± 206) and \( P = 0.02 \) (Table 2).

There were no differences between the carbetocin and misoprostol groups in haemoglobin concentration, estimated blood pressure or in heart rates after delivery (Table 2).

The incidence of blood transfusion, additional oxytocic injection, prolonged third stage (≥30 min) and manual removal of placenta were similar between the two groups (Table 2). There were also no differences between the carbetocin and misoprostol groups in need for ICU admission or maternal death.

Adverse effects are presented in Table 3. The incidence of abdominal pain (3% in Group A versus 27% in Group B; \( P = 0.01 \)), fever (0% in Group A versus 17% in Group B; \( P = 0.001 \)), metallic taste (0% in Group A versus 20% in Group B; \( P = 0.01 \)) and shivering (0% in Group A versus 40% in Group B; \( P = 0.0001 \)) were significantly lower in the carbetocin group. The incidence of feeling of warmth, headache, nausea, tachycardia and vomiting were similar in both groups.

In our study, we included the symptoms reported by the patients only if they were not present before the application of

Table 2 – Primary and secondary outcomes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cabotocin Group A (n = 30)</th>
<th>Misoprostol Group B (n = 30)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for additional uterotonic, n (%)</td>
<td>5(17%)</td>
<td>8(27%)</td>
<td>Z = −0.94</td>
<td>0.35</td>
</tr>
<tr>
<td>Duration of third stage of labour (min)*</td>
<td>6.9 ± 6.4</td>
<td>9 ± 6.1</td>
<td>T = 1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Manual removal of placenta</td>
<td>0</td>
<td></td>
<td>Z = −1.78</td>
<td>0.07</td>
</tr>
<tr>
<td>PPH (≥500 ml), n (%)</td>
<td>1(3%)</td>
<td>6(20%)</td>
<td>Z = −2.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean blood loss (ml)*</td>
<td>278 ± 202</td>
<td>403 ± 206</td>
<td>T = 2.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Need for blood transfusion, n (%)</td>
<td>3(10%)</td>
<td>4(13%)</td>
<td>Z = −0.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Postpartum Hg level, g/dl*</td>
<td>11.2 ± 2</td>
<td>10.4 ± 1.8</td>
<td>T = −1.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Arterial pressure (1 h after delivery)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>155 ± 11.8</td>
<td>157 ± 8.4</td>
<td>T = −0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic pressure</td>
<td>102 ± 7.4</td>
<td>104 ± 6.6</td>
<td>T = 1</td>
<td>0.3</td>
</tr>
<tr>
<td>Heart rate, bpm (1 h after delivery)*</td>
<td>84.2 ± 15.3</td>
<td>86.9 ± 15.3</td>
<td>T = 0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Need for ICU admission</td>
<td>0</td>
<td>2(7%)</td>
<td>Z = −1.43</td>
<td>0.15</td>
</tr>
<tr>
<td>Maternal death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data presented by mean ± standard deviation.
T: t-test.
P value <0.05 was considered statistically significant.
Table 3 - Adverse effects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Carbetocin group (n = 30)</th>
<th>Misoprostol group (n = 30)</th>
<th>Z test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abdominal pain</td>
<td>1 (3%)</td>
<td>8 (27%)</td>
<td>-2.53</td>
<td>0.01</td>
</tr>
<tr>
<td>2. Feeling of warmth</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3. Fever</td>
<td>0</td>
<td>9 (17%)</td>
<td>-3.25</td>
<td>0.001</td>
</tr>
<tr>
<td>4. Headache</td>
<td>3 (10%)</td>
<td>2 (6%)</td>
<td>0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>5. Metallic taste</td>
<td>0</td>
<td>6 (20%)</td>
<td>-2.58</td>
<td>0.01</td>
</tr>
<tr>
<td>6. Nausea</td>
<td>3 (10%)</td>
<td>4 (13%)</td>
<td>-0.4</td>
<td>0.69</td>
</tr>
<tr>
<td>7. Shivering</td>
<td>0</td>
<td>12 (40%)</td>
<td>-3.87</td>
<td>0.0001</td>
</tr>
<tr>
<td>8. Tachycardia</td>
<td>3 (10%)</td>
<td>2 (7%)</td>
<td>0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>9. Vomiting</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>-0.59</td>
<td>0.56</td>
</tr>
</tbody>
</table>

P value <0.05 was considered statistically significant.

the drug and if they appeared immediately after administration of it. If a symptom persisted for more than 24 h, we concluded that it was unlikely to be caused by the drug used, and the symptom was not considered an adverse effect.

4. Discussion

We conducted this study to compare the efficacy and safety of intravenous carbetocin with sublingual misoprostol in preventing primary postpartum haemorrhage in patients with severe preeclampsia. Carbetocin is a newly developed long-acting oxytocin analogue that has been associated with a low incidence of adverse effects, with a similar tolerability profile to intravenous oxytocin. It has also been associated with a lower incidence of gastrointestinal side effects compared with the combination of oxytocin and ergometrine. Carbetocin appears to have a better cardiovascular side-effect profile than oxytocin or syntometrine. Although misoprostol is an effective uterotonic agent used in preventing primary postpartum haemorrhage, it has adverse effects such as nausea, vomiting, hypertension and coronary artery spasm.

This is the only study, to the best of our knowledge, that compared the efficacy and safety of intravenous carbetocin with sublingual misoprostol in preventing primary postpartum haemorrhage in patients with severe preeclampsia.

The findings from many studies using carbetocin were promising and it was suggested that carbetocin may become the drug of choice for prevention of postpartum haemorrhage after vaginal delivery in high-risk women. More trials in low-risk women who undergo vaginal delivery are needed to assess whether carbetocin is superior to conventional uterotonic drugs for the majority of pregnant women. Available data are encouraging to suggest that carbetocin could become useful for prevention of postpartum haemorrhage even in pre-eclamptic pregnant women. Nevertheless, the careful assessment of the patient’s history and close blood pressure monitoring are mandatory in each patient treated with carbetocin, in particular in those with suspected pre-existing cardiovascular disease.

We demonstrated that significantly lower women in the carbetocin group experienced primary postpartum haemorrhage than that in the misoprostol group (P = 0.04). There was also a significant difference in the amount of estimated blood loss and was lower in carbetocin group than in the misoprostol group (P = 0.02).

We reported that the need for additional uterotonic among the women in our study was (13/60) 22% while the incidence of postpartum haemorrhage in the study was (7/60) 12%. The discrepancy in the incidences of these two outcomes was because we generally did not wait till blood loss exceeded 500 ml before commencing additional uterotonic. In our hospital, additional uterotonic is started when the diagnosis of uterine atony is made.

Our data showed that the incidence of many adverse effects, such as abdominal pain, fever, metallic taste and shivering, was significantly lower for women who received carbetocin than with women who received misoprostol.

In a randomized, double-blind, placebo-controlled study done in Canada 2004, the efficacy of prophylactic carbetocin in prevention of postpartum haemorrhage following vaginal delivery was investigated. The study was conducted in two hospital centres in Canada and enrolled 160 women. Overall, uterotonic intervention was lower in women who received carbetocin with a statistically significant difference (P < 0.025) and this was comparable to our results.

Attilakos et al., in a double-blind, randomized controlled trial included 377 patients to compare carbetocin 100 μg single IV bolus with oxytocin 5 IU single IV bolus after low risk caesarean deliveries. Additional uterotonic were necessary in 33.5% of patients in the carbetocin group patients compared with 45.5% in the oxytocin group (P = 0.023). This is similar to our results but the difference in our study did not reach a significant difference.

The randomized controlled trial done by Nirmala et al. studied 1200 women at high risk for PHH who delivered vaginally to compare carbetocin 100 μg IM with syntometrine IM. The authors found a significant decrease in the mean blood loss as well as a significant smaller decrease in haemoglobin drop in the carbetocin group. This is similar to our results.

The efficacy and safety of carbetocin were shown in several studies. A single intravenous dose of 100 μg of carbetocin has been shown to be as effective as a 16-h infusion of oxytocin in preventing intraoperative blood loss following delivery. Another study reached a similar conclusion when a single dose of carbetocin was found to have similar efficacy to a 2-h infusion of oxytocin in controlling intraoperative blood loss after placental removal. Use of carbetocin in vaginal delivery also revealed a similar safety profile to oxytocin. Although it is
more costly, it has a low incidence of adverse effect. Carbetocin should be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labour.

5. Conclusions

The results of this study showed that carbetocin is more effective than misoprostol when used to prevent postpartum bleeding in women with severe preeclampsia, with no alterations in haemodynamic status and with few side effects. Some of the apparent side effects could be attributed to preeclampsia or to other drugs used in these patients.

5.1. Limitations of the study

There were two major limitations of the study: first was the small sample size and second was the inability to eliminate the use of additional uterotonic and blood transfusion that results in a probability of masking the drop in haemoglobin concentration.

Conflicts of interest

The authors have none to declare.

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