Carbetocin Versus Oxytocin for Prevention of Postpartum Hemorrhage in Patients With Severe Preeclampsia: A Double-Blind Randomized Controlled Trial

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Abstract

Objective: In patients with severe preeclampsia there is an increased risk of postpartum hemorrhage, but the hemodynamic changes associated with severe preeclampsia make the management of any kind of bleeding particularly troublesome. 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. We aimed to compare oxytocin with carbetocin for the routine prevention of postpartum hemorrhage in patients with severe preeclampsia.

Methods: We performed 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 uterotonics, 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.

Results: 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.

Conclusions: Carbetocin is an appropriate alternative to oxytocin for the prevention of postpartum hemorrhage in women with severe preeclampsia. Considering that it appears not to have a major hemodynamic effect in women with severe preeclampsia and that it uses a lower volume per dose than oxytocin, it should be considered a valid option in the management of the third stage of labour in women with hypertensive disorders of pregnancy.

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Résumé

Objectif : Les patientes qui connaissent une prééclampsie grave sont exposées à un risque accru d'hémorragie postpartum; toutefois, les modifications hémodynamiques associées à la prééclampsie grave rendent la prise en charge de tout type de saignement particulièrement problématique. Il existe de nombreuses options pharmacologiques pour la prise en charge de l'hémorragie postpartum, l'oxytocine constituant l'agent de première intention. Nous ne disposons, à ce jour, d'aucune donnée sur l'innocuité et l'efficacité du recours à la carbétocine (un agoniste de l'oxytocine) chez de telles patientes. Nous avons cherché à comparer l'oxytocine à la carbétocine pour ce qui est de la prévention systématique de l'hémorragie postpartum chez les patientes qui connaissent une prééclampsie grave.

Méthodes : Nous avons mené un essai comparatif randomisé prospectif à double insu auprès de 60 femmes connaissant une prééclampsie grave qui ont été recrutées entre juillet et septembre 2010. Ces femmes ont été affectées, au hasard, à un groupe devant recevoir de l'oxytocine ou à un groupe devant recevoir de la carbétocine au cours du troisième stade du travail. Le principal critère d'évaluation était l'hémorragie postpartum nécessitant l'administration d'utérotoniques additionnels, tandis que les critères d'évaluation secondaires étaient la différence en matière de taux d'hémoglobine constatée d'un groupe à l'autre, l'apparition d'une oligurie et le statut hémodynamique (fréquence cardiaque et tension artérielle moyennes) à la suite de l'administration du médicament.

Résultats : La carbétocine s'est avérée aussi efficace que l'oxytocine pour ce qui est de la prévention de l'hémorragie postpartum chez les femmes qui connaissent une prééclampsie grave. La carbétocine avait un profil d'innocuité semblable à celui de l'oxytocine et elle n'a pas été associée à l'apparition d'une oligurie ou d'une hypertension au sein de cette cohorte.

Conclusions : La carbétocine constitue une solution de rechange appropriée à l'oxytocine pour la prévention de l'hémorragie postpartum chez les femmes qui connaissent une prééclampsie grave. Compte tenu qu'elle ne semble pas exercer un effet hémodynamique important sur les femmes qui connaissent une prééclampsie grave et que son utilisation nécessite un volume par dose moins élevé que l'oxytocine, elle devrait être considérée comme une option valable dans la prise en charge du troisième stade du travail chez les femmes qui présentent des troubles hypertensifs de la grossesse.

INTRODUCTION

Hemorrhage and hypertensive disorders are the greatest contributors to maternal death in developing countries, accounting for more than 30% of direct causes.[1] In developed countries both pathologies, together with embolism, are the main reasons women die during pregnancy. Considering that in 2005 there were 536 000 maternal deaths worldwide (99% in developing countries),[2] any potential for improvement in management of these two disorders should be investigated.

For some years, pharmacological options for the prevention of postpartum hemorrhage have been explored. Among them is the oxytocin agonist, carbetocin. Carbetocin is a long-acting synthetic oxytocin analogue (1-deamino-1-monocarba-[2-O-methyltyrosine]-oxytocin), with a half life of 40 minutes.[3] Within two minutes of intravenous administration, it has the capacity to generate tetanic uterine contractions that last for six minutes. These tetanic contractions are followed by more rhythmic ones for approximately one hour.[4]

There have been no studies evaluating the safety of carbetocin in preeclamptic patients. Considering its potential advantages over oxytocin (more rapid and longer duration of effect, lower volumes to administer), it is imperative to evaluate this drug in women with preeclampsia. For this reason we conducted a double-blind randomized controlled trial comparing carbetocin and oxytocin for the prevention of postpartum bleeding in women with severe preeclampsia.

MATERIAL AND METHODS

We conducted a prospective, double-blind, randomized controlled study between July 2010 and September 2010. Women with singleton pregnancies of more than 28 weeks' gestation who were admitted to hospital with severe preeclampsia were eligible for the study. Exclusion criteria were HELLP syndrome, blood dyscrasia, and multiple pregnancy. Once the decision to interrupt the pregnancy was made or if the patient went into labour spontaneously, written informed consent was obtained at an early stage of labour by one of the investigators. All patients were in stable condition (no evidence of maternal hemodynamic instability or fetal distress) before randomization, and their management afterwards followed the standards accepted in our country and established in the national guidelines for the management of hypertensive disorders of pregnancy. For hypertensive crisis the first drug used was hydralazine (5 mg IV every 15 minutes to a maximum total dose of 20 mg) and, if this was ineffective, labetalol (20 mg IV every 10 minutes to a maximum total dose of 300 mg). 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 12 hours postpartum.

The patients were randomized to receive a single dose of either carbetocin (100 μg diluted in 10 mL of Ringer's lactate solution) or oxytocin (20 U diluted in 1000 mL of Ringer's lactate solution) intravenously after the delivery of the placenta (following either vaginal birth or Caesarean section). The randomization protocol required a designated member of the staff to open a sealed, opaque envelope containing a computer generated code randomizing the patient into one of the two groups. This code was used to identify the patient; neither the patient nor the investigators knew which drug was used. The codes were broken only after the study was finished and all the information tabulated and analyzed, in this way avoiding detection bias.

Because the two drugs are administered differently, a double dummy system for administration was used. The randomization assigned the patient to one of the two following protocols:

- **Protocol A (carbetocin + placebo)**

  Carbetocin 100 μg + Ringer's lactate solution 10 mL injected directly into the vein over two minutes.

  Ringer's lactate solution 4 mL in 1000 mL of Ringer's lactate solution, administered intravenously at a rate of 125 mL/hour

- **Protocol B (oxytocin + placebo)**

  Ringer's lactate solution 11 mL injected directly into the vein over two minutes.

  Oxytocin 20 U diluted in 1000 mL of Ringer's lactate solution, administered intravenously at a rate of 125 mL/hour

Cases of uterine atony (determined by physical examination and continuous postpartum bleeding) were considered a therapeutic failure, and additional uterotonics were used (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.

Standard laboratory assessments (hemoglobin, hematocrit, platelets, renal and liver function tests) were performed in every patient on admission and postpartum. Vital signs (blood pressure, heart rate, respiratory rate) and diuresis were measured every hour until at least 12 hours after delivery.

The primary outcome of the study was the development of postpartum hemorrhage that required use of additional

uterotonics. Secondary outcomes were hemoglobin concentration after delivery, oliguria (< 0.5 mL/kg/hour), and hemodynamic status (mean arterial pressure and heart rate). Patients were asked about milk letdown, breastfeeding, and lactational failure.

Statistical analysis was performed using EpiInfo version 3.5.3 (Centers for Disease Control and Prevention, Atlanta GA). Differences in continuous variables were analyzed using the Mann-Whitney *U* test and non-continuous variables were analyzed using the chi-square test. Statistical significance was set at $P < 0.05$. The study was approved by the Saint Thomas Hospital's Institutional Ethics Review Committee.

RESULTS

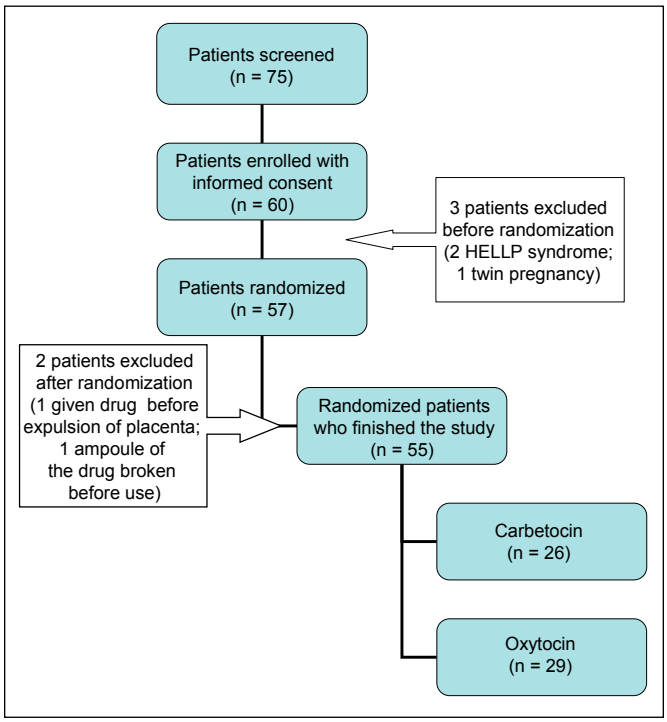
We screened 75 patients, but only 60 fulfilled the required inclusion criteria. These 60 patients were recruited from July to September 2010 (30 were randomized to receive carbetocin and 30 to receive oxytocin). Informed consent was obtained from the 60 patients, but five patients were excluded before the end of the study (two patients developed HELLP syndrome, one had an undiagnosed twin pregnancy, one received the assigned protocol before the extraction of the placenta, and in one patient the ampoule of medication broke before use). The trial profile is shown in the Figure.

The baseline characteristics of the two groups (26 patients in the carbetocin group, 29 in the oxytocin group) were similar (Table 1), as were the obstetrical variables relating to labour and delivery (Table 2). The level of hypertension and the symptoms presented in both groups were similar.

The mean hemodynamic status of the patients (mean arterial pressure and heart rate) one hour before administration of the drug and one and two hours after is shown in Table 3. There were no significant differences between the groups before the drug was administered or at either of the two evaluations afterwards.

The results of analysis of the primary and secondary outcomes are shown in Table 4. There were no differences between the carbetocin and oxytocin groups in the need for additional uterotonics, in hemoglobin concentration after delivery, or in rates of oliguria. Six patients in the carbetocin group developed oliguria, but they all responded to a fluid challenge of 500 mL of Ringer's lactate solution administered IV over 30 minutes. Of the nine patients in the oxytocin group who developed oliguria, seven (77.8%) responded to the initial fluid challenge. One of the remaining patients required a second challenge of the same volume for resolution, and the other required use of diuretics (furosemide 20 mg IV). There was no significant difference between the groups.

Trial profile of participant recruitment and randomization



There were no significant differences between the groups in milk letdown or breastfeeding (Table 5).

Many of the adverse effects observed in both groups, shown in Table 6, can be attributed to the underlying pathology (preeclampsia). We included the symptoms reported by the patients only if they were not present before the application of the protocol and if they appeared immediately after administration of the study drug. If a symptom persisted for more than 24 hours, we concluded that it was unlikely to be caused by the drug used, and the symptom was not considered an adverse effect. Again, there was no significant difference between groups.

DISCUSSION

There are several pharmacological options for the prevention of postpartum hemorrhage. Oxytocin continues to be the first line of treatment. Prostaglandins are also useful (compared with placebo),[5] but they are not as effective as oxytocin,[6] are generally more expensive, and have more side effects. Although use of Syntometrine, a combination of oxytocin and ergometrine, has shown a significant reduction in the risk of postpartum hemorrhage when compared with oxytocin alone,[7] the ergometrine component (d-lysergic acid beta propanolamide, an ergot alkaloid with alpha-adrenergic, dopamine, and serotoninergic properties) is associated with nausea and vomiting,[8] as well as other severe complications such as intracerebral hemorrhage[9] and hypertension.[10]

Table 1. Baseline characteristics of the study population

	Carbetocin n = 26 mean (SD)	Oxytocin n = 29 mean (SD)	*P*
Age, years	26.52 (9.12)	26.78 (8.39)	0.91
Gestational age, weeks	37.44 (2.51)	36.93 (2.72)	0.51
Parity	1.80 (2.38)	1.78 (2.14)	0.89
Initial hemoglobin, mg/dL	11.94 (1.31)	12.13 (1.36)	0.53
Associated symptoms of preeclampsia,* n (%)	10 (38.5)	16 (55.2)	0.11
Arterial pressure (upon admittance)			
(a) systolic pressure	161.73 (20.88)	160.10 (18.90)	0.94
(b) diastolic pressure	101.53 (9.24)	104.69 (10.59)	0.30
(c) mean arterial pressure	121.60 (11.48)	122.47 (13.90)	0.57
Coagulation profile difference (patient–control subject)			
(a) prothrombin time	2.09 (1.44)	1.66 (0.77)	0.33
(b) activated partial thromboplastin time	4.13 (2.71)	3.12 (2.55)	0.32

*Associated symptoms include persistent headache, visual symptoms, and epigastric pain.

Table 2. Labour and delivery characteristics of the study population

	Carbetocin n = 26	Oxytocin n = 29	*P*
Duration of 1st stage labour, min, mean (SD)	325 (143.32)	270 (151.58)	0.39
Duration of 2nd stage labour, min, mean (SD)	16.08 (7.83)	14.25 (12.34)	0.26
Duration of 3rd stage labour, min, mean (SD)	7.58 (4.1)	7.81 (4.29)	0.94
Mode of delivery, n (%)			
Vaginal birth	14 (53.8)	16 (55.2)	0.46
Caesarean section	12 (46.2)	13 (44.8)	
Birth weight, mean (SD)	2889.36 (756.82)	2605.82 (630.06)	0.27
Apgar score > 7 (5 min), n (%)	26 (100)	29 (100)	

Table 3. Hemodynamic status before and after administration of the drug

	Carbetocin n = 26 mean (SD)	Oxytocin n = 29 mean (SD)	*P*
Mean arterial pressure, mmHg			
(a) 1 hour before administration	109.50 (9.93)	106.73 (10.37)	0.45
(b) 1 hour after administration	111.75 (7.84)	105.90 (9.17)	0.39
(c) 2 hours after administration	111.17 (4.44)	107.06 (8.65)	0.33
Heart rate, bpm			
(a) 1 hour before administration	73.66 (5.68)	79.57 (15.21)	0.64
(b) 1 hour after administration	81.25 (8.99)	78.50 (19.40)	0.66
(c) 2 hours after administration	84.75 (9.63)	87.83 (17.75)	0.74

Table 4. Primary and secondary outcomes

	Carbetocin n = 26	Oxytocin n = 29	*P*
Need for additional uterotonics, n (%)	0 (0)	1 (3.4)	0.50
Need for blood transfusions, n (%)	0 (0)	3 (10.3)	0.13
Need for instrumental curettage of the uterine cavity, n (%)	2 (8)	4 (13.8)	0.41
Postpartum hemoglobin level, g/dL, mean (SD)	10.8 (1.68)	11.14 (1.76)	0.56
Hemoglobin difference (admission–postpartum), mean (SD)	1.24 (0.87)	1.41 (1.12)	0.81
Oliguria, n (%)	6 (23.1)	9 (31.0)	0.26

Because of this last complication, patients with preeclampsia cannot receive Syntometrine as a prophylactic agent for the prevention of postpartum hemorrhage, the risk of which is increased in this group of patients. Eskild and Vatten[11] 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. It is not clear whether this increased risk is secondary to the presence of angiogenic factors in the maternal circulation[12] or to impaired uterine contractility due to the use of magnesium sulphate.[13] The important point is that the management of any sort of bleeding in preeclamptic patients is further complicated by their altered hemodynamic status. These patients do not have the expected volume expansion of normal pregnancies and will show symptoms following blood loss earlier than normotensive patients. In addition, patients with severe preeclampsia have low serum albumin and total protein levels. The use of intravenous crystalloid solutions can cause fluid accumulation in the extravascular space and trigger cerebral or pulmonary edema.

Oxytocin, the drug of choice in patients with severe preeclampsia, has a short duration of action, and the usual dose requires crystalloid solutions to be administered intravenously for long periods of time to prevent bleeding episodes during and after the third stage of labour. This could lead to the complications described.

The use of carbetocin has not yet been approved by the Food and Drug Administration in the United States. It is approved for use in Canada, but it should be used with caution in the patient with severe preeclampsia because of the unknown effects that carbetocin could have on an already delicate hemodynamic state.[14] Blood loss in the preeclamptic patient is sometimes difficult to assess because of several factors (absence of the protective effect of the usual volume expansion of pregnancy, misleading value of blood pressure as an indicator of volume, decreased colloid oncotic pressure). Any measure that could prevent excessive blood loss after delivery in these patients is not only useful but could be considered mandatory. Oxytocin has been the accepted drug for the management and prevention of postpartum hemorrhage.[15] However, the use of oxytocin as part of the active management of the third stage of labour does carry risks. When given as an intravenous bolus, oxytocin causes an increase in heart rate and a decrease in mean arterial blood pressure. The intensity of the change depends on the dose used.[16] Other studies have shown that oxytocin given as an intravenous infusion causes fewer side effects than a bolus,[17] but it is not free of hemodynamic effects.[18] Oxytocin can also cause water retention, being structurally and functionally related to vasopressin (antidiuretic hormone). When oxytocin is used in a high dose (generally > 30 mU/minute IV) it binds to oxytocin and vasopressin receptors in the kidneys, leading to water intoxication (characterized by hyponatremia, confusion, convulsions, and coma). Water intoxication has also been reported with low-dose infusions of oxytocin, although this is rare.[19]

Although the use of isotonic solutions (Ringer's lactate or normal saline) has been advocated by some authors, others recommend volume restriction and even the use of diuretics in the patient with severe preeclampsia because of increased extracellular volume.[20] Moreover, excessive intravenous fluid administration could generate acute pulmonary edema in this population.

Several studies have shown the efficacy and safety of carbetocin in various clinical scenarios. A single intravenous dose of 100 μg of carbetocin has been shown to be as effective as a 16-hour infusion of oxytocin in preventing intraoperative blood loss after Caesarean section.[21] Another study reached a similar conclusion when a single dose of carbetocin was found to have similar efficacy to a two-hour infusion of oxytocin in controlling intraoperative blood loss after placental removal.[22] The use of carbetocin in this study was associated with a smaller number of patients requiring additional uterotonic medications ($P < 0.01$) and uterine massage ($P < 0.01$).

A study conducted by one of us (O.A.R.) compared carbetocin with oxytocin as a prophylactic agent to prevent postpartum hemorrhage in the grand multiparous patient.[23] Carbetocin was found to be as effective as oxytocin. Moreover, it was significantly associated with a reduced need to explore the uterine cavity manually for persistent bleeding.

Two studies compared carbetocin with Syntometrine for management of the third stage of labour and reached similar conclusions.[24,25] A single intramuscular dose of carbetocin is as effective as a single dose of Syntometrine but has fewer side effects. Additionally, Leung et al.[24] showed that carbetocin is not associated with the hypertensive complications generally linked to Syntometrine in women with no history of hypertension.

CONCLUSIONS

The results of this pilot study show that carbetocin is as effective as oxytocin in preventing postpartum bleeding in women with severe preeclampsia, with no alterations in hemodynamic 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.

We plan to conduct a larger study to verify our findings and to gather additional information. However, our

Table 5. Lactation

	Carbetocin n = 26 n (%)	Oxytocin n = 29 n (%)	*P*
Milk letdown postpartum	25 (96.2)	28 (96.6)	0.72
Breastfeeding	22 (84.6)	25 (86.2)	0.58

Table 6. Adverse effects

	Carbetocin n = 26 n (%)	Oxytocin n = 29 n (%)	*P*
Headaches	3 (11.5)	0 (0)	0.09
Palpitations	0 (0.0)	1 (3.4)	0.53
Fever	0 (0.0)	1 (3.4)	0.53
Nausea and vomiting	1 (3.8)	0 (0)	0.47
Others	1 (3.8)	0 (0)	0.47
Hot sensation	1 (3.8)	0 (0)	0.47
Facial flushing	1 (3.8)	0 (0)	0.47
Malaise	1 (3.8)	0 (0)	0.47

preliminary results show that carbetocin can be considered a safe medication for use in patients with a pregnancy-related hypertensive disorder.

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