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Original Article

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

Khalid Abd Aziz Mohamad Ibrahim *, *Ahmed Samy Saad*

Lecturer of Obstetrics and Gynecology, Benha Faculty of Medicine and Benha University Hospital, Benha University Egypt, El Qulyobia Governorate, El Sadat Street, Benha City, Egypt

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ABSTRACT

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 pre-eclampsia 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 cabetocin 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 cabetocin while nausea, vomiting and headache were more associated with cabetocin.

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

Trial registration: http://clinicaltrials.gov/NCT02086994.

☆ Our study was done in Benha University Hospital, Benha University, Egypt.

* *Corresponding author at*: University Post Office No. 13518, Banha City, Egypt.
E-mail addresses: dr.khalidkhader77@yahoo.com, dr.khalidkhader77@fmed.bu.edu.eg (K..A.M. Ibrahim), drahmedsaad@live.com (A.S. Saad).

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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 E_1 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/mm^3.
(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.
(10) Pulmonary oedema.

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

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