International Journal of Gynecology and Obstetrics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

CLINICAL ARTICLE

Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following an elective cesarean delivery

Ahmed E.H. Elbohoty, Walid E. Mohammed, Mohamed Sweed *, Ahmed M. Bahaa Eldin, Ashraf Nabhan, Karim H.I. Abd-El-Maeboud

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Abbasia, Cairo, Egypt

ARTICLE INFO

Article history:
Received 19 October 2015
Received in revised form 4 January 2016
Accepted 17 May 2016

Keywords:
Atony
Carbetocin
Cesarean delivery
Misoprostol
Oxytocin
Postpartum hemorrhage

ABSTRACT

Objective: To compare the effectiveness and safety of carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following cesarean deliveries. *Methods:* A double-blind randomized controlled trial enrolled patients with a singleton pregnancy scheduled for an elective cesarean delivery at a maternity hospital in Cairo, Egypt, between October 1, 2012 and June 30, 2013. Participants were randomized using a computer-generated sequence to receive treatment with carbetocin, misoprostol, or oxytocin. The primary outcome was the occurrence of uterine atony necessitating additional uterotonics. Per-protocol analyses were performed. Patients, investigators, and data analysts were masked to treatment assignments. *Results:* The present study enrolled 263 patients; data were analyzed from 88 patients treated with carbetocin, 89 treated with misoprostol, and 86 women treated with oxytocin. Further uterotonics were needed for the treatment of 5 (6%) patients who were treated with carbetocin, 20 (22%) patients treated with misoprostol, and 11 (13%) patients treated with oxytocin. In the prevention of uterine atony, carbetocin was comparable with oxytocin (RR 0.41, 95%CI 0.14–1.25) and superior to misoprostol (RR 0.21, 95%CI 0.07–0.58). *Conclusion:* Additional uterotonics were needed less frequently by patients treated with carbetocin. Carbetocin was comparable with oxytocin and superior to misoprostol in the prevention of uterine atony following an elective cesarean delivery.

ClinicalTrials.gov: NCT02053922

1. Introduction

Globally, cesarean delivery is one of the most common major operations that women undergo, and the cesarean delivery rate is increasing worldwide [1]. Postpartum hemorrhage (PPH) following cesarean delivery is a significant problem and a major cause of maternal mortality [2]. WHO defines PPH as blood loss of at least 500 mL within 24 hours of delivery [3].

Patient benefit from reductions in operative blood loss during cesarean delivery through decreased postoperative morbidity and reduced exposure to the risks associated with blood transfusions [4]. The commonest cause of hemorrhage during delivery is uterine atony; consequently, it has generally been agreed that, during delivery, active management of the third stage of labor is preferable to expectant management [5]. Active management of third stage of labor includes controlled cord traction for the expulsion of the placenta during a cesarean delivery and the administration of intramuscular or intravenous oxytocin [3].

Oxytocin is the uterotonic agent that is most widely used and has the greatest availability [6]. Oxytocin has a rapid onset of action, a good safety profile, and has been shown to decrease the incidence of PPH by 40% [7]. Nevertheless, oxytocin has a short half-life (4–10 minutes), necessitating continuous intravenous infusion. Moreover, saturation of myometrial oxytocin receptors could reduce its effectiveness, and excessive dosing can lead to coronary-artery contraction and hypotension; additionally water intoxication can occur owing to its anti-diuretic effects [6].

Alternative treatments have been investigated, including prostaglandins, such as misoprostol, and oxytocin agonists, such as carbetocin [8]. Misoprostol is a prostaglandin E_1 analogue with strong uterotonic properties and has been suggested as an alternative to injectable uterotonic agents for preventing PPH [9]. It is cheap, heat stable, and can be administered through multiple routes; however, it is known to be less effective than oxytocin in preventing PPH [10]. In low-resource settings, patients can be at risk of PPH if oxytocin is stored in suboptimal conditions unless there is a readily available alternative, such as misoprostol [10,11].

Carbetocin, a long-acting oxytocin analogue, has been reported to decrease the need for additional uterotonics during cesarean deliveries compared with oxytocin [12]. A 100-μg dose of carbetocin has been recommended for preventing PPH [6]. Carbetocin has been recommended for PPH prevention following elective cesarean deliveries [13]. An

* Corresponding author at: 4 Hosni Osman st., El-Sefarat, Nasr City, Cairo, Egypt. Tel.: +20 100 122 2047; fax: +20 022 434 6058.
E-mail address: drmsweed@med.asu.edu.eg (M. Sweed).

http://dx.doi.org/10.1016/j.ijgo.2016.01.025
0020-7292/

advantage of carbetocin over oxytocin is that, owing to its long half-life, it is administrated as a single intravenous dose, while oxytocin requires repeated administration or continuous infusion over several hours, with variations in doses [2].

The aim of the present study was to evaluate the effectiveness and side effects of carbetocin, misoprostol, and oxytocin in the prevention of PPH in patients undergoing elective cesarean deliveries.

2. Materials and methods

The present prospective randomized double-blind trial was conducted at Ain-Shams University Maternity Hospital, Cairo, Egypt, between October 1, 2012 and June 30, 2013. Patients attending the prenatal clinic at Ain-Shams University Maternity Hospital who were scheduled to undergo an elective cesarean delivery were considered for enrollment. Patients were eligible if they had a singleton pregnancy that had reached full term (duration of pregnancy ≥37 weeks). The exclusion criteria included hypersensitivity to oxytocin, carbetocin, or prostaglandins; contraindication to treatment with prostaglandins (e.g. glaucoma); history of significant heart disease; severe asthma; epilepsy; history or evidence of liver, renal, or vascular disease; history of coagulopathy, thrombocytopenia, or anticoagulant therapy; HELLP syndrome or eclampsia; placental abruption; or contraindication to spinal anesthesia (carbetocin is licensed for use with regional anesthesia only). Approval for the study protocol was obtained from the ethical committee of the department of Obstetrics and Gynecology at Ain-Shams University and written informed consent was obtained from all participants.

Patients fulfilling the recruitment criteria were randomly assigned to treatment with carbetocin, misoprostol, or oxytocin using MedCalc version 13.2.2 (MedCalc Software, Ostend, Belgium). Randomization was performed in a 1:1:1 ratio using a computer-generated sequence. Numbered, sealed envelopes were prepared, with each envelope containing one of the three study drugs and placebos for the other two drugs. Tablet placebos, containing hydrogenated castor oil, hypromellose, microcrystalline cellulose, and sodium starch glycolate were prepared to be identical in size, color, shape, and packing to the tablet study drug. Intravenous placebo ampoules containing normal saline were prepared and were identical in shape and packing to the intravenous study drugs used. All envelopes were prepared by Sigma Pharmaceuticals and were sealed when received by the research team. An envelope was allocated to each patient using the computer-generated sequence. The randomization protocol was concealed from the research team and the primary investigator contacted a central coordinating investigator to identify the envelope to be distributed to each patient. Consequently, patients, investigators, and data analysts were masked to group assignments and unmasking only occurred after data analysis was completed.

Prior to cesarean delivery, the amniotic fluid index (AFI) was estimated using abdominal ultrasonography on the day of delivery or the day before delivery. The uterus was divided into four quadrants; the right and left quadrants were defined by the linea nigra, and the upper and lower quadrants were defined by the umbilicus. The maximum vertical diameter of amniotic fluid in each quadrant was measured in centimeters. The sum of these four quadrants was used to calculate the AFI [14]. The volume of amniotic fluid in mL was estimated by multiplying the AFI by 30 [15]. Hemoglobin concentrations and hematocrit values were obtained for each patient before cesarean delivery.

Lower segment cesarean deliveries were performed under spinal anesthesia by a senior registrar who had previously performed at least 300 cesarean delivery procedures. The placenta was removed by cord traction and uterine compression. The uterus was exteriorized and compressed during closure. Closure was achieved using continuous unlocked Vicryl 0 sutures (Ethicon, Somerville, NJ, USA) in two layers. Peritoneum and muscle layers were not closed, and the sheath was closed using the same suture material.

Patients in the carbetocin group treated with a single 1-mL ampoule of carbetocin (100 μg/mL) (Pabal; Draxis/Multipharma, Egypt) added to 10 cm^3 saline that was administered intravenously following the delivery of the neonate [3]. Patients assigned to the misoprostol group received two sublingual misoprostol tablets (each tablet 200 μg) (Misotac; Sigma Pharmaceuticals, Egypt) following the cesarean delivery [4]. Patients who received oxytocin therapy received a single 1-mL ampoule of oxytocin (10 IU/mL) (Syntocinon; Novartis Pharma, Berne, Switzerland) added to 10 cm^3 saline that was administered slowly intravenously following neonatal delivery; additionally, these patients received 20 IU oxytocin added to 500 mL saline administered as an intravenous infusion over 4 hours [3]. Patients in each group also received placebos of the other treatment modalities that were administered according to the same method of the other study drugs.

Additional uterotonics (intravenous oxytocin 10 IU or other ecbolics) were administered if uterine atony was detected through physical examination by the senior registrar and the presence of continuous postpartum bleeding.

Surgical towels were weighed with their wrapping before and after delivery using a highly accurate digital balance. The difference in mass between the dry and soaked towels was calculated. Operative blood loss was calculated using three parameters: (A) the volume of the suction bottle contents (mL), (B) the difference in towel mass (g), and (C) the amniotic fluid volume (mL). Intraoperative blood loss (mL) was calculated as:

$$\textit{Intraoperative blood loss} = (A + B) - C \text{ [15].}$$

Postpartum blood loss during the first 24 hours after delivery was measured by weighing used wound dressings after 24 hours and subtracting the dry weight of the pads. A 100-g increase in mass was considered equivalent to 100 mL of blood or amniotic fluid. The hemoglobin level was tested in the laboratory of the study institution by obtaining a complete blood analysis 24 hours after delivery. Any complications occurring during the postoperative period were recorded.

The primary outcome was the occurrence of uterine atony requiring the use of additional uterotonics. Secondary outcome measures included total blood loss, the difference in hemoglobin level before and 24 hours after delivery, and the development of any adverse events. Details of adverse events were obtained through verbal interviews with patients and through observations made by caregivers and the attending registrar.

A minimum sample size of 241 participants was calculated using PAS 11 (NCSS, Kaysville, Utah, USA) to provide a test significance of 0.05 and a power of 0.8. The target study group size was set at 90 patients in each study arm to account for withdrawals and other patient exclusions.

Data were analyzed on a per-protocol basis using SPSS version 21 (IBM, Armonk, NY, USA) and MedCalc version 12.5 (MedCalc Software, Ostend, Belgium). Comparisons were made between the three groups with an analysis of variance test, Kruskal–Wallis test, or χ^2 test, as appropriate. Relative risks with 95% confidence intervals were calculated to compare the risks of developing uterine atony or developing PPH between the three treatment groups. Results were reported as mean ± SD or number (percentage) and $P < 0.05$ was considered statistically significant.

3. Results

In total, 324 patients were considered for inclusion and were 270 enrolled in the present study (90 in each treatment arm). In the carbetocin treatment arm, two patients were excluded after receiving general anesthesia; one patient was excluded from the misoprostol arm after accidently breaking a drug ampoule and four patients were excluded from the oxytocin treatment arm (two patients received general anesthesia and two accidentally broke drug ampoules) (Fig. 1). No

Please cite this article as: Elbohoty AEH, et al, Randomized controlled trial comparing carbetocin, misoprostol, and oxytocin for the prevention of postpartum hemorrhage following ..., Int J Gynecol Obstet (2016), http://dx.doi.org/10.1016/j.ijgo.2016.01.025