Comparative Study between Intravenous Bolus Dose of Carbetocin Versus Oxytocin during Cesarean Delivery in Healthy Parturients on Blood Loss: A Randomized Control Trial

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Abstract

Background: Postpartum hemorrhage is a potentially life-threatening complication of both vaginal and cesarean delivery. The most frequent cause of postpartum hemorrhage is uterine atony, therefore, active management of the third stage of labor rather than expectant management is recommended. Oxytocin is the first choice drug for enhancing uterine contraction after delivery. Oxytocin has a short half-life, whereas carbetocin, exerting its effect via the same molecular mechanisms as oxytocin, has a longer half-life, and has been reported to decrease the use of additional oxytocics.

The Aim of Study: Is to compare between the effect of carbetocin versus oxytocin given as intravenous bolus to healthy pregnant women undergoing elective cesarean section as regards hemoglobin concentration after cesarean section.

Patients and Methods: One hundred seventy two patients undergoing elective cesarean section at term were randomized to two groups receiving either 5IU oxytocin or 100 µg carbetocin, complete blood count was done twice, just before and 24 hours after delivery, after delivery of the placenta, the volume of blood loss was assessed.

Results: A significant difference was found between both groups as regards blood loss (434.71 Vs 366.48ml in oxytocin and carbetocin group respectively, \( p=0.013 \)). There was a negative significant correlation between hemoglobin change level and blood loss among oxytocin group (\( r=-0.277, p=0.01 \)), this correlation was non significant among carbetocin group (\( r=-0.179, p=0.096 \)). The hemodynamic data is reassuring with no clinically significant differences between the two interventions.

Conclusion: Carbetocin appears to be as effective as oxytocin for prevention of postpartum hemorrhage.

Key Words: Carbetocin – Oxytocin agonist – Oxytocin – Postpartum hemorrhage.

Introduction

POSTPARTUM Hemorrhage (PPH) is a potentially life-threatening complication of both vaginal and cesarean delivery. PPH complicates 11 % of deliveries worldwide, and is annually responsible for 132 000 maternal deaths [1]. Even with appropriate active management, around 3% of women will experience a PPH following vaginal delivery [2] and a recent study in low risk Australian women suggested it was as high as 12% [3].

Primary PPH is the most common obstetric hemorrhage and is defined by the World Health Organization as the loss of blood estimated to be >500ml from the genital tract within 24 hours of delivery [4]. After this and until 6 weeks’ postpartum, abnormal bleeding from the genital tract is defined as secondary PPH. Hemorrhage is considered severe when blood loss exceeds 1000ml [2].

Regarding Royal College of Obstetrician and Gynecologists (RCOG) risk factors may present antenatally or intrapartum. Antenatal risks include: Suspected or proven placental abruption, known placenta praevia, multiple pregnancy, preclampsia/gestational hypertension, previous PPH, asian ethnicity, obesity (BMI >35) and anaemia (<9g/dl). Intrapartum risks include: Delivery by emergency or elective caesarean section, induction of labour, retained placenta, mediolateral episiotomy, operative vaginal delivery, prolonged labour (> 12 hours), big baby (>4kg), pyrexia in labour, and age >40 years and not multiparous [5].

The major cause of PPH is uterine atony, when the uterus fails to contract fully after delivery of the placenta. There are numerous reasons for the uterus failing to contract effectively; including exhaustion, sepsis, and retained products. Other causes of PPH include perineal trauma, uterine inversion, clotting disorders, pelvic hematomas, and cervical tears. An abnormally implanted pla-
centa (placenta accreta, increta or percreta) can remain in situ and hence prevent the uterus from contracting properly. If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation, and ultimately death [6].

Despite evidence that active management of the third stage of labor reduces the incidence of postpartum haemorrhage, expectant management is still widely practiced, factors accounting for this situation include the desire for a more natural experience of childbirth, the philosophy that active management is unnecessary in low-risk women, and avoidance of the adverse effects of conventional uterotonic agents [7,8]. Oxytocin is a synthetic hormone identical to that produced in the posterior lobe of the pituitary. This medication causes contraction of the uterus with its effect increasing with the gestation as the concentration of myometrial receptors and myometrial gap junctions increase as gestation advances, increasing sensitivity to oxytocin [9].

Oxytocin has numerous physiological effects. Most importantly, it causes contraction, followed by relaxation of the uterus, and at pharmacological doses can cause an increased frequency and incomplete relaxation of uterine musculature. Very few side effects are noted with oxytocin aside from occasional nausea and vomiting. Water intoxication is a theoretical risk rarely encountered. There are no contraindications to the use of this drug for PPH prevention or treatment [10].

In patients in whom uterine atony is perceived to be the cause of PPH, the RCOG recommend a rapid infusion of oxytocin 40IU/500mL crystalloid at 125mL/h, until hemorrhage is controlled [8].

The phenomenon of receptor desensitization may influence the effectiveness of the dose given by the anesthetist at delivery. A recent publication in which a second dose of oxytocin was administered in the same patient, suggested that the cardiovascular response to a second dose was diminished, this could be explained by receptor down-regulation [11]. More definitive laboratory work has shown that there is loss of oxytocin receptors during oxytocin-induced and oxytocin-augmented labor [12].

In view of the fact that repeated doses of oxytocin may become increasingly ineffective, second line uterotonic agents are still required [13]. Second line uterotonic agents include ergot alkaloids [4,14,15] prostaglandins [12,16,17] and syntometrine (a combination of oxytocin and ergometrine). The newly developed synthetic analogue of oxytocin, carbetocin (1-desamino-1-monocarbothioyl[2-O-methyltyrosine]-oxytocin), has a half-life 4-10 times the duration of oxytocin [18]. A tetanic uterine contraction is produced 2 min after an intravenous injection of 8-30g g or intramuscular injection of 10-70g g, which persists for approximately 1 min. Rhythmic uterine contractions persist for 60 and 120 min after intravenous and intramuscular injection respectively [19].

Khan and colleagues [20] suggested that carbetocin may be a more potent oxytocic, but it is unclear whether this will reduce the rate of PPH and in particular major PPH. The reason for this is that only a very large study with many thousands of women would have adequate power to demonstrate a significant difference in this relatively rare outcome. Perhaps, large retrospective studies from countries or institutions where carbetocin is used routinely may provide interesting data, although such studies would be prone to bias.

The side effect profile of carbetocin is similar to that of oxytocin. Preeclampsia remains a contraindication to its use for reasons which are unclear. The issue of receptor desensitization is as yet unstudied, and further work on the efficacy of carbetocin is awaited [21].

The purpose of the present study is to compare between the effect of carbetocin versus oxytocin given to healthy pregnant women undergoing elective cesarean section as regards hemoglobin concentration after cesarean section.

**Patients and Methods**

This is a randomized controlled trial performed on 172 pregnant women undergoing elective cesarean section at term (completed 37 weeks of gestation) with singleton pregnancy, in Ain Shams University, Maternity Hospital, Cairo, Egypt from 2013–2014, where approximately 17000 deliveries take place yearly. Patients were recruited from the outpatient clinic and scheduled for elective cesarean section.

All women participating were informed and consenting for the study and were subjected to the following: Counseling about all the steps of our study, careful history taking regarding age, parity, menstrual history and obstetric history, general examination to exclude medical disorders, abdominal examination and pelvic ultrasound to exclude and obstetric disorder.

Patients with medical disorder as hypertension, diabetes mellitus or on an anticoagulant, and wom-
en with obstetric problems such as severe polyhyramnios, multifetal gestation, placenta previa or placental abruption were excluded from the study as these conditions will increase the risk of postpartum haemorrhage. Also women with history of previous uterine scar other than lower segment cesarean section or who had more than one previous section were excluded from the study.

Ethics:

• **Patient information and informed consent:**

  Before being admitted to clinical study, the patient had to consent to participate after the nature, scope and possible consequences of the clinical study have been explained in an understandable form by the researcher himself.

• **Confidentiality:**

  Only the patients' initials were recorded and if the patient's name appears on any other document it was kept in privacy by the investigator.

• **Institutional Review Board (IRB) approval:**

  The clinical research study was conducted in accordance with the current IRB-approved clinical protocol; International Conference on Harmonisation and Good Clinical Practice (ICH GCP) Guidelines and relevant politics, requirements and regulations of Obstetrics and Gynecology Department, Ain Shams University.

Randomization:

Randomization was performed by computer generated randomization system. Women randomized received either 5 iu of oxytocin (SYNTOCINON® NOVARTIS Pharmaceuticals) or 100 µg of carbetocin (PABAL® FERRING Pharmaceuticals LTD) which are the standard clinical doses. According to the random list, the study nurse diluted either oxytocin or carbetocin with 10ml 0.9% NaCl solution into a 20ml syringe. Both drugs were prepared exactly 5 minutes before cesarean delivery, and were then handed to the anesthesiologist. Study medication was double blinded to the clinical staff (obstetricians as well as anesthesiologists) and the technicians performing the measurements.

Study drug administration and clinical management:

Both drugs were administered as an intravenous bolus (delivered in 10 seconds) by the anesthetist after the delivery of the baby and clamping of the cord and before delivery of the placenta. The monitoring and anesthetic techniques were identical for all women. Spinal anesthesia was given for all patients as follows: Local anesthetic lidocaine hydrochloride (XYLOCAINE® Astrazeneca) was injected in preparation for spinal anesthesia by a single-shot technique in a sitting position. The spinal anesthetics used were 10-12mg of bupivacaine (MARCAINE® Astrazeneca) and 20 µg of fentanyl (FENTANYL® Janssen Cilag) were injected intrathecally at L2/3. Fluid, as well as ephedrine infusion or boluses, given as required to achieve hemodynamic stabilization.

Lower segment caesarean section performed through Pfannenstiel incision, following uterine incision, delivery of the baby, and cord clamping, the placenta was delivered by controlled cord traction, and the uterus was repaired intra abdominally (no exteriorisation) in two layers.

Complete blood count was done twice, just before and 24 hours after delivery. Estimation of blood loss began after suction of amniotic fluid and discarding it. After delivery of the placenta, the volume of blood loss was assessed by weight or saturation assessment techniques by subtracting the dry weight of absorbing materials (pads, sponges, etc) from the weight of blood-containing materials and using the conversion 1gm weight = 1ml to quantify the blood volume contained in the materials.

Statistical analysis:

Blood loss:

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Group 1 Mean = 244. SD = 143.
Group 2 Mean = 343. 2-Sided Test.

Hb:

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Group 1 Mean = 0.3. SD = 0.2.
Group 2 Mean = 0.4. 2-Sided Test.

Conclusion:

86 patients required in each group to achieve an alpha error of 5% and a beta error of 10%. Thus, 86 patients in each group was considered sufficient for such data types according to G. Attilakos et al., [22].

Data was collected and tabulated using EXCEL 2007 (Microsoft, Redmond, WA, USA) then data
was analyzed by a computer software SPSS for windows V.21 2007 (Statistical Package for Social Sciences), IBM Corporation, USA.

Difference between the two groups was measured using Student’s $t$-test or Pearson correlation test (for parametric variables) and Wilcoxon rank sum test or ranked spearman correlation test (for non parametric variables).

**Results**

Non significant difference was found in this study between oxytocin group and carbetocin group as regards age (mean of group 1=26.97 years Vs. mean of group 2=26.09 years, $p=0.22$).

Monitoring vital data during CS showed that there was highly significant difference between oxytocin and carbetocin group as regards systolic blood pressure (110.12 Vs 98.87mmHg in oxytocin and carbetocin group respectively, $p<0.001$) and diastolic blood pressure (71.77 Vs 65.46mmHg in oxytocin and carbetocin group respectively, $p<0.001$). As regards pulse rate non significant difference was found was found between both groups (83.56 Vs 83.78bpm in oxytocin and carbetocin group respectively, $p=0.856$) (Table 1).

A significant difference was found between both groups as regards blood loss (434.71 Vs 366.48ml in oxytocin and carbetocin group respectively, $p=0.013$) (Table 1). There was a negative significant correlation between hemoglobin change level and blood loss among oxytocin group ($r=-0.277, p=0.01$), this correlation was non significant among carbetocin group ($r=-0.179, p=0.096$) Figs. (1,2).

**Discussion**

We found that the delta change of hemoglobin (Hb dC) of the women involved in this study, in oxytocin group range between –0.26 and 0.02gm/dl, with the mean of 0.0489 and SD is ±0.04932. in carbetocin group range between –0.38 and –0.01 gm/dl, with the mean of –0.1148 and SD is ±0.06272, this difference was highly significant, and these results are matching with Atilakos and colleagues [22] who found that carbetocin is more potent than oxytocin and most of the women who were given additional oxytocics received additional oxytocin bolus or infusion. Almost one in three women in the oxytocin arm received an additional oxytocin infusion, which was typically given over 4 hours. The reason for administering additional oxytocics in the oxytocin group (according to the surgeon) was significantly more likely to be PPH treatment.

Contrary to our results, in an earlier study to measure intra-operative blood loss during elective lower segment caesarean section by using alkaline hematin method, which included forty women with...
singleton pregnancies, delivered by elective lower segment caesarean section under general anaesthesia, there was no significant difference in the estimated blood loss or in the postoperative fall in haemoglobin [23]. The method used in estimating blood loss may be imprecise especially for blood loss more than 600ml, instead more accurate means was used in this study beside the larger sample in our study (n=172).

Our results showed that blood loss was significantly higher in the oxytocin group compared to carbetocin group this is because carbetocin causes a tetanic uterine contraction produced 2min after an intravenous injection of 8-30 g or intramuscular injection of 10-70 g, which persists for approximately 1 min. Rhythmic uterine contractions persist for 60 and 120 min after intravenous and intramuscular injection respectively. Su and associates 2012 [24] observed greater blood loss in the oxytocin group compared to the carbetocin group, but the difference was not statistically significant.

Although there is a significant difference in blood pressure between both groups, the hemodynamic data in this study was reassuring with no clinically significant differences between the two interventions. The slow intravenous administration of oxytocics appears to reduce their hemodynamic effects [25]. However, further studies comparing the hemodynamic profiles of carbetocin and oxytocin by invasive monitoring with arterial line will provide more robust data on this subject.

We observed that none of the patients included in both groups had PPH and there is insufficient evidence that 100 g of IV carbetocin is as effective as oxytocin to prevent PPH. So another study is needed to compare the effect of this does of carbetocin (100 g) to oxytocin in the management of PPH.

In spite that, we did not observe any pharmacological interaction with the drugs used in the peri-operative period by the anesthetists or with the drugs used in the postpartum period and also to our knowledge there are no specific studies of the drug interactions carried out with carbetocin.

Developing country as Egypt, the cost of medical service, we found in this study that carbetocin use is not associated with the use of additional oxytocics but to be the drug of choice for the active management of the third stage of labour, this may be offset by the higher cost of carbetocin in comparison to oxytocin. As for our study, the cost of the oxytocin ampoule is 5LE, meanwhile the cost of the carbetocin ampoule is 110LE which may be not applicable in most of the hospitals and among the Egyptian population as Egypt is considered one of the developing countries.

Conclusion:
Carbetocin appears to be effective as oxytocin for prevention of postpartum hemorrhage in patient undergoing elective cesarean section.

References


