Original Article

Carbetocin versus oxytocin and ergometrine for prevention of postpartum hemorrhage following caesarean section

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ABSTRACT

Objective: To compare the effectiveness of carbetocin versus oxytocin and ergometrine when administered after caesarean section for prevention of postpartum hemorrhage (PPH).

Patients and Methods: A prospective randomized observational study in the year 2014 was conducted on 200 women at term undergoing elective cesarean section under regional anesthesia. Women with pre term gestational age, diabetes, hypertension and coronary heart disease were excluded. Women were put into two groups : One group containing 100 women received I.V. carbetocin 100 microgram, while the other group which also contained 100 women received a combination of I.V. oxytocin 5 IU and I.M. Ergometrine 0.2mg after the delivery of the baby. The primary outcome measure: 1-Uterine tone and size were assessed by resting a hand on the fundus of uterus and palpating anterior wall of the uterus one hour after delivery, the presence of boggy uterus with either heavy vaginal bleeding or increasing uterine size is suspicious for uterine atony ; 2- Need of additional oxytocics. Secondary outcome measure: Blood loss and hemoglobin concentration were estimated.

Results: There was a significant difference between both groups as regards uterine atony and need for additional oxytocics after delivery. On the other side, there was no significant association between both study groups as regards vaginal bleeding or HB estimation before and after operation or HB difference.

Conclusion: Carbetocin is more potent long acting oxytocic with less need for other additional uterotonic drugs and less occurrence of uterine atony.

Key Words: Caesarean section**,** carbetocin, ergometrine, oxytocin, postpartum hemorrhage.

Received: 13 November 2017, **Accepted**: 05 December 2017

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ISSN: 2090-7265, February 2018, Vol.8, No.1

INTRODUCTION

Postpartum hemorrhage (PPH) accounts for nearly one quarter of all maternal deaths worldwide[1] and was the second frequent cause of maternal death in the UK during the period the 2000–2002 triennium[2]. In developing countries, PPH is estimated to be responsible for about 28% of maternal deaths[3]. This is because high multiparty, prolonged labor, fibroids and severe anemia (probably caused by close spacing of pregnancies, poor diet or parasitic infections) are common[4].

Caesarean section is a recognized risk factor for PPH5 and the worldwide caesarean delivery rate is increasing[6]. The cesarean section is a bloody operation, about 750 to 1000 ml are lost at most operations and over 1000 ml of blood have lost to bring them into the definition of a postpartum hemorrhage (PPH)[7]. In developing countries, PPH is the main cause of maternal deaths.Uterine atony is the most common cause of immediate heavy PPH[8]. The administration of oxytocics after the delivery of the neonate reduces the likelihood of PPH[9] and 5 IU oxytocin by slow intravenous injection is currently recommended for all caesarean sections[10]. However, the use of additional oxytocic medication is common, to arrest bleeding, or prophylactically if there are risk factors for PPH[11]. Carbetocin is a synthetic analogue of human oxytocin with structural modifications that increase its half life, thereby prolonging its pharmacological effects[12]. Carbetocin has been approved in 23 countries for prevention of uterine atony and excessive bleeding following caesarean delivery in spinal or epidural anesthesia[13].

Oxytocin is a peptide of nine amino acids (Nona peptide). The structure of oxytocin is very similar to that of arginine vasopressin, whose sequence differs from oxytocin by 2 amino acids[14]. The best known mechanism for oxytocin to exert its stimulatory effect on myometrial contractility is by increasing the intracellular concentration of calcium[15]. Owing to its short plasma half-life (mean 3 min), a continuous intravenous infusion is required in order to maintain the uterus in a contracted state. The

 DOI: 10.21608/ebwhj.2018.6218

usual dose is 20 IU in 500 ml of crystalloid solution, with the dosage rate adjusted according to response[16].

Ergometrine is a selective and moderately potent tryptaminergic receptor antagonist in various smooth muscles, being only a partially agonistic or antagonistic at tryptaminergic receptors in the central nervous system. In blood vessels, the alkaloid is only weakly antagonistic of dopaminergic receptors and partially agonistic of α-adrenergic receptors[17].

A study investigated the efficacy of carbetocin vs. oxytocin for prevention of uterine atony in high-risk women undergoing delivery by caesarean section. Significantly, fewer women experienced uterine atony after caesarean delivery with carbetocin (8%) vs. oxytocin (19%). Blood loss>500 ml was only observed in women who received oxytocin[18]. In our study, we investigated the efficacy of carbetocin vs. oxytocin and ergometrine for prevention of PPH in women undergoing caesarean section.

PATEINTS AND METHODS

This prospective randomized observational study which took place in Beni-Suef University Teaching Hospital in 2014 was conducted on 200 women with a singleton term pregnancy undergoing elective caesarean section. Women with multiple gestation, placenta praevia and placental abruption were excluded because there is a higher risk of hemorrhage with these conditions and it was therefore felt to be inappropriate to recruit these women. Women undergoing caesarean section with general anesthesia were also excluded, because carbetocin is licensed for use with regional anesthesia only. Furthermore, we excluded women undergoing caesarean section at less than 37 weeks of gestation (likely to be emergency caesarean sections; a different smaller group from term pregnancies) and women having emergency caesarean section for fetal or maternal distress where, due to time constraints, it was not possible and/or appropriate to recruit or randomize.

Women included in the study were divided into 2 groups: Group (A): included 100 patients who received carbetocin 100 µg diluted in 10 ml normal saline and administered slowly (over 30-60 seconds) intravenously by anesthetist after birth of the baby. Group (B): included 100 patients who received a combination of intraoperative oxytocin 5 I.U which was diluted in 10 ml normal saline and administered slowly over (30-60 seconds) intravenously by anesthetist and intramuscular ergometrine 0.2 mg. The slow administration has been shown to reduce the potentially harmful hemodynamic effects of oxytocin[19, 20] (and presumably carbetocin). Also, intramuscular injection of ergometrine did the same. All women were subjected to full history taking, general and obstetric examination and investigations in the form of preoperative routine labs and obstetric ultrasound, and postoperative serum hemoglobin %.

In all cases, approved ethical committee and patients' verbal consent were taken, information sheet was completed included age, parity, gestational age at delivery, also BMI and hemoglobin concentration noted before cesarean sections and 24 hours post partum. The differences between pre- and post C.S values were calculated in each group.

Primary outcome included uterine tone was assessed by using a hand resting on the fundus and palpating the anterior wall of the uterus. The presence of a boggy uterus with either heavy vaginal bleeding or increasing uterine height can suspect the diagnosis of uterine atony. Also, the need for additional oxytocic drug in each group population was reported and tabulated as a primary outcome. Secondary outcome included blood loss which was estimated postoperatively by giving each woman of each group standard 2 dressings (standard weight of dressing is 25 gm) during 24 hrs postoperative hospital stay and recording weight of blood soaked dressings and volume of lost blood.

The volume of lost blood was estimated by:

1) Weighing the soaked dressings which were prepared for the study as following:

-Weight of blood in a dressing in grams = weight of dressing after removal – weight before application (about 25gm)

-Volume of lost blood in ml = weight of blood in dressings in gm / 1.06 Where (1.06) is the density of whole blood. It's assumed that weight is due only to blood and not environmental water or debris[21]

2) Changes in hemoglobin concentrations before and 24 hours postoperative were estimated. All the resulting data from the two groups collected tabulated and analyzed statistically.

Statistical analysis:

Data was statistically described in terms of mean ± standard deviation (± SD) or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using 2 tailed independent t tests. For comparing categorical data, Chi square (X^2) test was performed. Exact test was used instead when the expected frequency is less than 5. *P* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows.

RESULTS

That study was conducted on 200 pregnant women at gestational age ≥ 37 weeks undergoing elective caesarean section. Women were divided into two groups. Group A included 100 women received intravenous carbetocin. Their mean age was (29.73±6.27) years, mean parity of (0.77±1.00), mean gravidity of (1.38±1.09), mean gestational age(GA) was (38.61±1.11) and mean BMI of

(25.28±3.41), as well as 100 pregnant women(≥ 37 weeks) (group B) who received a combination of intravenous oxytocin and intramuscular ergometrine. Their mean age, parity, gravidity, GA and BMI was (29.57±6.19), (0.65±0.83), (1.37±1.06), (38.31±1.11) and (25.21±3.28), respectively. There were no significant differences between the study groups concerning the age, gravidity, parity, gestational age and BMI (Table 1)

Table1: Baseline characteristics of the study groups

	Carbetocin group (n=100)	Oxytocin+ Ergometrine group (n=100)	*P value*
Age	29.73±6.27	29.57±6.19	0.85 NS
Gravidity	1.38±1.09	1.37±1.06	0.94 NS
Parity	0.77±1.00	0.65±0.83	0.35 NS
Gestational age	38.61±1.11	38.31±1.11	0.59 NS
BMI	25.28±3.41	25.21±3.28	0.88 NS

Data are presented as mean ±S.D.
N.S: Nonsignificant

It was found that uterine atony occurred more in women in the group who received oxytocin with ergometrine (39%) in comparison to carbetocin group (21%). It was obvious that oxytocin group needed more oxytocics than carbetocin group. There was a significant association between both groups as regards uterine atony and the need for oxytocics in which *P* value was 0.005 and 0.002, respectively (Table II).

Table II: The results of the primary outcomes

	Carbetocin	Oxytocin	Total	P value
Uterine atony No	79%	61%	140 70%	0.005*
Yes	21%	39%	60 30%	
Need of oxytocics No	73%	52%	125 62.5%	
Yes	27%	48%	75 37.5%	0.002*

* Statistically significant.

It was found that there was significant association as regards vaginal bleeding between both groups as the mean was (448.50±85.11) in carbetocin as compared with the mean in oxytocin group was (505.05±111.05) at *p value < 0.001*. As regards, HB before operation, the mean in carbetocin group was (11.69±0.88) ; while in oxytocin group, the mean was (11.53±0.85) with no significant association between both groups. The mean of HB 24 hours after operation in carbetocin group was (11.18±0.94) ; while in the other group, the mean was (10.98±0.91) with no significant association. In carbetocin group the mean regarding HB difference was (0.51±0.26) while in oxytocin group the mean was (0.54±0.30) with no significant association. (Table III).

Table III: The results for secondary outcomes

	Carbetocin (n=100)	Oxytocin+ Ergometrine (n = 100)	*P value*
Vaginal Bleeding	448.50±85.11	505.05±111.05	*<0.001**
HB_before operation	11.69±0.88	11.53±0.85	*0.18 NS*
HB_24 hrs after	11.18±0.94	10.98±0.91	*0.14 NS*
HB_ difference	0.51±0.26	0.54±0.30	*0.50 NS*

Data are presented as mean +S.D.
N.S: Non significant
* Statistically significant

DISCUSSION

A cesarean section is an invasive surgical procedure in which a baby is delivered through an abdominal and uterine incision, carries with it many immediate and delayed morbidity and mortality risks[22]. The cesarean section is a bloody operation, about 750 to 1000 ml are lost at most operations and over 1000 ml of blood have lost to bring them into the definition of a postpartum hemorrhage (PPH)[7]. The third stage of labor is potentially the most dangerous part for the mother, and active management may be necessary, i.e. administration of an uterotonic medication before the placenta is delivered[14]. Uterine atony is the commonest cause of primary PPH. Risk factors for uterine atony include uterine over distention (multiple gestation, polyhydramnios, fetal macrosomia), prolonged oxytocin use, abnormal labor, grand multiparity, chorioamnionitis, placenta previa, and use of uterine-relaxing agents (tocolytic therapy, halogenated anesthetics, nitroglycerin)[23].

The routine use of oxytocic drugs in association with the management of the postpartum period reduces

incidence of PPH up to 40% of the total cases of PPH[24]. Several uterotonic agents can be used for prevention and treatment of postpartum hemorrhage including Oxytocin, Ergot alkaloids, Syntometrine and Prostaglandins[25].

Carbetocin is a long-acting oxytocin studied by Dansereau *et al* 1999; they found that the carbetocin group of patients had a decreased incidence of PPH and need for therapeutic oxytocics. The recommended dose of carbetocin is 100 µg given either IM or slowly IV (over 1 minute)[26]. Our study compared between women undergoing cesarean delivery taking carbetocin and those receiving a combination of oxytocin and ergometrine for prevention of PPH.

Our study showed that the results of comparison between two groups as regards the mean values of baseline characteristics were statistically non significant. As regards uterine atony in both groups, there was a significant association. In carbetocin group, only 21% of women suffered uterine atony, while 39% in oxytocin+ergometrine group. The need for additional oxytocic drugs and vaginal bleeding showed also significant association between both groups. However, pre-operative and post-operative HB or HB difference showed no significant association between both groups. Oxytocic drugs were needed in 27% of carbetocin group women, while 48% of oxytocin+ergometrine group needed additional uterotonic drugs. The mean for vaginal bleeding in carbetocin group was (448.50±85.11) while that of oxytocin+ergometrine group was (505.05±111.05).

Some studies were in agreement with our study concerning need for additional uterotonic drugs. Authors compared between carbetocin and oxytocin concerning the need for additional uterotonic drugs. They found significant association between both groups[26, 27, 28]. However, when they tested the need for additional uterotonic agents with carbetocin and oxytocin following vaginal deliveries, they found no statistical significance between both groups. This was in agreement with our thesis despite different mode of delivery. Mode of delivery is an important factor that can influence the treatment outcome. Thus, it is recommended to undertake more studies including patients with different modes of delivery and risk factors for PPH[26, 27, 28].

Concerning pre- and post-operative HB, some authors found that the estimated blood loss in women who underwent cesarean deliveries was more in the oxytocin group. This agreed with our study. There was greater drop in HB in this group. In contrast to our study, in which HB difference between both groups showed no significant association. This difference from our study may be because all above authors used more patients making difference in sample size[29, 30, 31].

As carbetocin appears to have a similar haemodynamic profile to oxytocin (and both appear to have a more 'benign' adverse effect and haemodynamic profile than syntometrine), then carbetocin may become the drug of choice for women who have contraindications to the administration of Syntometrine, such as women with hypertensive disorders of pregnancy and women with cardiac problems[32].

However, we recommend more wide scales of multicentric randomised controlled studies to prove or disprove our study results on carbetocin as along acting synthetic analouge of oxytocin in prophylaxis against atonic postpartum hemorrhage following cesarean sections, mainly for patients with cardiac diseases or hypertension.

CONFLICT OF INTEREST

There are no conflicts of interest.

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