Carbetocin versus Oxytocin in the Prevention of Postpartum Hemorrhage Following Vaginal Delivery in High Risk Patients

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Abstract

Background: Postpartum hemorrhage is a life threatening situation and one of the important causes of maternal mortality and morbidity, worldwide. **Aim of the work:** To compare the efficacy of carbetocin and oxytocin in preventing postpartum hemorrhage following vaginal delivery in high risk groups. **Patients and methods:** 120 women with gestational age between 37-40 weeks at high risk for primary atonic postpartum hemorrhage and delivered vaginally were randomly divided into two groups. First group: included 60 women, they received carbetocin, 100 mcg IM. Second group: included 60 women, they received Oxytocin 5 IU IM. Both groups received their drug after fetal and before placental delivery.

a statistically significant difference between the two study groups regarding mean blood loss (276.93 ± 120.87 versus 346.42 ± 176.61), occurrence of PPH (3.3% versus 13.3%), hemoglobin and hematocrit difference between before and 24 h after delivery (0.55 ± 0.51 versus 0.998 ± 0.69, p= 0.002) (3.38 ±2.92 versus 4.65±4.18, p= 0.002) respectively and measured hemoglobin and hematocrit 24 h after delivery (being higher in carbetocin group). The effect of carbetocin as regard to estimated blood loss was more obvious in multiparous women. However, there was no significant difference between the two groups regarding need for other uterotonics, the need for blood transfusion and occurrence of nausea, vomiting, abdominal pain, flushing, tachycardia, hypotension, headache, itching and metallic taste. **Conclusions:** Carbetocin is a better alternative to oxytocin in prevention of PPH after vaginal delivery with similar side effects.

Keywords: Carbetocin, oxytocin, postpartum hemorrhage.

Introduction

Postpartum hemorrhage (PPH) is a life threatening situation and one of the important causes of maternal mortality and morbidity, worldwide [1].Postpartum haemorrhage (PPH) has been defined as a bleed of 500 ml or more in vaginal deliveries and in excess of 1000 ml in abdominal deliveries and is usually based on subjective observations [2]. Uterine atony is the most common cause of PPH which contributes to 80% of cases of PPH [3].

Risk factors for PPH include prolonged labor ≥12 h, severe anemia, preeclampsia, antepartum hemorrhage, intrapartum blood loss, history of PPH or retained placenta, body mass index (BMI) ≥35, polyhydramnios, multiple gestation , difficult instrumental delivery, grand multipara, chorioamnionitis and fibroids [4].

Active management of the third stage of labor, particularly Prophylactic administration of uterotonic agents could significantly reduce the rate of postpartum hemorrhage from 18% to 5% compared with that of expectant management [5].

Oxytocin is the most commonly used uterotonic agent because it is at least as effective as ergot alkaloids or prostaglandins and has fewer side effects [6 & 7]. Although oxytocin is rapidly effective and well tolerated, it has short half-life 4-10 min that means it must be administered by continuous intravenous infusion to achieve sustained uterotonic activity.

Carbetocin is a long- acting synthetic analogue of oxytocin with a half-life of 40 minutes, 4 to 10 times longer than that of oxytocin [8]. The onset of action occurs within 2 min, and the duration of action is 1 and 2 h after intravenous and intramuscular injection, respectively [9 &10].

The purpose of this study was to compare the efficacy of carbetocin and oxytocin in preventing postpartum haemorrhage following vaginal delivery in high risk groups.

Subjects and methods

This comparative study was conducted at the emergency unit of the Department of Obstetrics and Gynecology, Benha Teaching Hospital, through the period started from November 2016 to December 2018. The study was applied on 120 candidates randomly into two groups; achieve the inclusion and exclusion criteria. The study protocol was approved by the Local Ethics

Committee and written informed consent was taken from each patient before beginning the study.

Candidates at 37-40 weeks of gestational age with risk factors for developing primary atonic postpartum hemorrhage and delivered vaginally, this risk factors include: history of previous postpartum hemorrhage, multiple gestation, fetal macrosomia, polyhydramnios, chorioamnionitis, induction or augmentation of labor with oxytocin for >12 hours, prolonged labor, grand multipara, body mass index > 35. Putting into consideration the following exclusion criteria: placenta previa, preeclampsia, cardiac, renal or liver diseases, coagulopathy, women with cervical or vaginal tears, known hypersensitivity to oxytocin or carbetocin, refusal to participate in the study.

All patients were subjected to full history taking, general, abdominal and obstetric examination. Ultrasound scan, complete blood picture, liver functions and coagulation profile were also done.

The patients included in this study were divided randomly into two groups:
First group:- sixty women were injected intramuscularly by single dose of carbetocin 100µg immediately after fetal and before placental delivery.

Second group:- sixty women were injected intramuscularly by 5IU oxytocin immediately after fetal and before placental delivery.

All participants were followed-up for 24 h. The uterine tone and amount of bleeding were noted and the need for further uterotonic agents was checked also need for blood transfusion. Blood loss was estimated by weighing the swabs and using pictorial charts. PPH was defined as bleeding ≥500 ml. Blood hemoglobin and hematocrit were assessed 24 h after delivery. We recorded possible complications like nausea, vomiting, abdominal pain, flushing, tachycardia, hypotension, headache, itching and metallic taste.

Data were 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 independent t-test. For comparing categorical data, Chi square (z2) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago,

IL) release 15 for Microsoft Windows (2006).

Results

The 120 patients were classified into two groups: First group included 60 patients who received carbetocin and Second group included 60 patients who received oxytocin.

Baseline characteristics of the groups are summarized in (Table 1). There was no significant difference between the groups in age, parity, body mass index, gestational age, fetal birth weight and episiotomy.

Risk factors for atonic PPH were not significantly different between the groups (Table 2).

The amount of bleeding and occurrence of PPH were significantly lower in the carbetocin group (Table 3). The difference between blood hemoglobin levels before delivery and 24 h after delivery were significantly lower in the carbetocin group (Table 4). On the other hand, there was no significant difference between the two groups regarding need for other uterotonics and the need for blood transfusion (Table 5).

Regarding drugs side effects, there was no significant difference between the two groups regarding occurrence of nausea, vomiting, abdominal pain, flushing, tachycardia, hypotension, headache, itching, metallic taste(Table 6).

Table (1): Demographic and characteristic data of participants

Variable	Drug		Mean (SD) Or n (%)	Min.	Max.	Test	P value
Age (years)	**Carbetocin**		30.68 (8.41)	18	45	$t = 0.065$	0.965 NS
	Oxytocin		30.78 (8.46)	18	46		
Parity	**Carbetocin**	Nulliparous	29 (48.3%)	-	-	$\chi^2 = 0.134$	0.714 NS
		Multiparous	31 (51.7%)	1	7		
	Oxytocin	Nulliparous	27 (45.0%)	-	-		
		Multiparous	33 (55.0%)	1	7		
BMI (kg/m^2)	**Carbetocin**		27.997 (4.79)	20	37	$t = 0.321$	0.933 NS
	Oxytocin		28.280 (4.87)	19	38		
Gestational age (weeks)	**Carbetocin**		38.29 (0.92)	37w	40 w	$t = 0.155$	0.877 NS
	Oxytocin		38.31 (0.93)	37w	40 w		
Birth weight (grams)	**Carbetocin**		2959.83 (887.71)	1700	4800	$t = 0.024$	0.981 NS
	Oxytocin		2963.67 (839.53)	1800	4800		
Episiotomy	**Carbetocin**	Yes	28 (46.7%)	-	-	$\chi^2 = 0.033$	0.855 NS
		No	32 (53.3%)	-	-		
	Oxytocin	Yes	29 (48.3%)	-	-		
		No	31 (51.7%)	-	-		

Based on table (1) findings; there were no significant statistical differences between the Carbetocin and Oxytocin groups for all demographic variables at 0.05 level of significant.

Table (2): Distribution of risk factors for postpartum hemorrhage among both groups

Variable (Yes)	Drug	n (%)	χ^2 – Test	P value
history of previous postpartum hemorrhage	Carbetocin	6 (10%)	0.323	0.570
	Oxytocin	8 (13.3%)		NS
multiple gestation	Carbetocin	4 (6.7%)	1.009	0.604
	Oxytocin	3 (5%)		NS
fetal macrosomia	Carbetocin	5 (8.3%)	0.120	0.729
	Oxytocin	4 (6.7%)		NS
polyhydramnios	Carbetocin	6 (10%)	1.483	0.477
	Oxytocin	4 (6.7%)		NS
chorioamnionitis	Carbetocin	8 (13.3%)	0.261	0.609
	Oxytocin	10 (16.7%)		NS
induction or augmentation of labor with oxytocin for > 4 hours	Carbetocin	13 (21.7%)	0.051	0.822
	Oxytocin	12 (20%)		NS
prolonged labor	Carbetocin	13 (21.7%)	0.048	0.827
	Oxytocin	14 (23.3%)		NS
grand multipara	Carbetocin	4 (6.7%)	0.152	0.697
	Oxytocin	3 (5%)		NS
body mass index > 35	Carbetocin	4 (6.7%)	1.009	0.604
	Oxytocin	5 (8.3%)		NS
2 risk factors	Carbetocin	3 (5%)	0.000	1
	Oxytocin	3 (5%)		NS

Based on table (2) findings; there were no significant statistical differences between Carbetocin and Oxytocin groups as regards risk factors for postpartum hemorrhage (P > 0.05).

Table (3): Comparing the effects of the two drugs on blood loss.

Variable	Drug	Mean (SD) Or n (%)	Min.	Max.	Test	P value
Estimated blood loss	**Carbetocin**	276.93 (120.87)	80	650	$t = -2.52$	0.013 Sig.
	Oxytocin	346.42 (176.61)	90	880		
Postpartum hemorrhage ≥ 500	**Carbetocin**	2 (3.3%)	-	-	$\chi^2 = 3.927$	0.048 Sig.
	Oxytocin	8 (13.3%)	-	-		

Based on table (3) :there was a statistically significant difference for the estimated blood loss between two drugs (p = 0.013) for Carbetocin group.there was a statistically significant difference for the postpartum hemorrhage between the two drugs (p = 0.048) for Carbetocin group.

Table (4): HB and HCT differences pre and 24h post-delivery in carbetocin and oxytocin groups.

Characteristics	Drug	Mean (SD)	Min.	Max.	P value
HB difference	**Carbetocin**	0.55 (0.51)	0.1	2.80	0.002 Sig.
	Oxytocin	0.998 (0.69)	0.2	2.80	
HCT difference	**Carbetocin**	3.38 (2.92)	1.0	15	0.047 Sig.
	Oxytocin	4.56 (4.18)	1.0	19	

Based on table (4) findings; there were a statistically significant difference between HB and HCT levels before and 24 h after delivery being lower in the carbetocin group.

Table (5): Additional requirements for the patient in carbetocin and oxytocin groups.

Variable	Drug	Or n (%)	χ^2 −Test	P value
Requirement of additional uterotonic medication	**Carbetocin**	8 (13.3%)	0.261	0.609 NS
	Oxytocin	10 (16.7)		
Needs for blood transfusion	**Carbetocin**	1 (1.7%)	0.342	0.559 NS
	Oxytocin	2 (3.3%)		

Based on table (5) findings; there were no significant statistical differences between the two drugs for additional requirements.

Table (6): Comparison between Carbetocin and Oxytocin groups as regard side effects.

Variable (Yes)	Drug	n (%)	Test	P value
Nausea	**Carbetocin**	1 (1.7%)	$\chi^2 = 2.00$	0.368 NS
	Oxytocin	1 (1.7%)		
Vomiting	**Carbetocin**	2 (3.3%)	$\chi^2 = 0.342$	0.559 NS
	Oxytocin	1 (1.7%)		
Abdominal pain	**Carbetocin**	1 (1.7%)	$\chi^2 = 0.342$	0.559 NS
	Oxytocin	2 (3.3%)		
flushing	**Carbetocin**	1 (1.7%)	$\chi^2 = 0.342$	0.559 NS
	Oxytocin	2 (3.3%)		
Tachycardia	**Carbetocin**	2 (3.3%)	$\chi^2 = 0.342$	0.559 NS
	Oxytocin	2 (3.3%)		
Hypotension	**Carbetocin**	1 (1.7%)	$\chi^2 = 0.000$	1.000 NS
	Oxytocin	1 (1.7%)		
Headache	**Carbetocin**	1 (1.7%)	$\chi^2 = 1.034$	0.309 NS
	Oxytocin	3 (5%)		
Itching	**Carbetocin**	3 (5%)	$\chi^2 = 1.034$	0.309 NS
	Oxytocin	1 (1.7%)		
Metallic taste	**Carbetocin**	0 (0 %)	$\chi^2 = 1.008$	0.315 NS
	Oxytocin	1 (1.7%)		

Based on table (6) findings; there were no significant statistical differences between the two drugs for all side effects at 0.05 level of significant.

Discussion

Our results have shown that carbetocin is superior to oxytocin in prevention of PPH after vaginal delivery in women with risk factors for developing atonic PPH. This fact can be explained by the known longer half-life of carbetocin when compared to oxytocin causing a more uterine response, in terms of frequency and amplitude of uterine contractions [11].

100 µg IM carbetocin given to women at high risk for PPH had a higher efficacy than 5 IU IM oxytocin regarding mean blood loss

(276.93 ± 120.87 versus 346.42 ± 176.61) , occurrence of postpartum haemorrhage (3.3% versus 13.3%) ,hemoglobin and hematocrit difference between before and 24 h after delivery (0.55 ± 0.51 versus 0.998 ± 0.69, p= 0.002) (3.38 ±2.92 versus 4.65 ± 4.18, p= 0.002) respectively. This agrees with some studies (12, 16 and 17) while disagrees with others (13, 14 and 15).

There is no significant difference between both groups regarding the need for other uterotonics drugs (13.3% versus 16.7%). These results agree with what was published before (13), but do not agree with other previous studies (12, 14, 15, 16 & 17).

In 1999, a study performed (12) RCT on 694 patients comparing the incidence of PPH in women undergoing elective Caesarean section who received either carbetocin as a 100µg IV bolus or oxytocin as a continuous infusion for 8 hours (25 IU of oxytocin in 1000 mL of Ringer's lactate, 125 mL per hour).. The carbetocin group had decreased need for therapeutic oxytocics (4.7% vs. 10.1%; P < 0.05) [12]. The difference between these results and our scan can be explained by the difference in the studied populations.

A group of researchers did a randomized study on 160 women undergoing vaginal delivery with at least one risk factor for PPH to receive either carbetocin 100 mg IM or oxytocin 10 IU IV oxytocin infusion over 2 h. The need for uterine massage and other uterotonics were significantly lower in the carbetocin group [13]. These results are in agreement with ours. However, they found no significant difference in the amount of bleeding or the hemoglobin difference before and after delivery between the groups. The difference between these results and ours can be explained by the difference in the route and dose of oxytocin used in our study and theirs.

In a double-blind randomized study on 377 women undergoing cesarean sections receiving either carbetocin 100 mg or oxytocin 5 IU intravenously after the delivery of the baby. The carbetocin group needed significantly less uterotonic results (33.5% versus 45.5%, Relative risk 0.74, 95% CI 0.57-0.95). On the other hand, they found no significant difference in the blood loss or difference in hemoglobin before and after the operation between the two groups [14].

A study was performed to compare the hemodynamic effects of oxytocin and carbetocin and to assess the efficacy of these two drugs in terms of blood loss and the

additional uterotonic needed in caesarean section at high risk of primary postpartum hemorrhage. One hundred and two women undergoing cesarean sections receive either 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV or carbetocin 100 mcg IV bolus. More women needed additional uterotonic agents in the oxytocin group (23.5% vs. 0%, $p<0.01$), though there was no significant difference in estimated blood loss and in the dropped hemoglobin level. There was a significant difference in the diuresis, higher in carbetocin group [15].

A double-blinded randomized study was conducted on 200 pregnant women with at least two risk factors for developing atonic PPH, randomized into two groups: Group 1 (100 women) received single 100 mg IM dose of carbetocin and Group 2 received of 5 IU oxytocin IM. Both groups received their drug after fetal and before placental delivery. There was a statistically significant difference between the two study groups regarding amount of bleeding (337.73 ± 118.77 versus 378 ± 143.2), occurrence of PPH (4% versus 16%), need for other uterotonics (23% versus 37%) and hemoglobin difference between before and after delivery (0.55 ± 0.35 versus 0.96 ± 0.62) (all being lower in carbetocin group) and measured hemoglobin 24 h after delivery (being higher in carbetocin group). On the other hand, there was no significant difference between the two groups regarding occurrence of major PPH and the need for blood transfusion. Regarding drugs side effects, there was no significant difference between the two groups regarding occurrence of nausea, vomiting, flushing, dizziness, headache, shivering, metallic taste, dyspnea, and palpitations and itching. The incidence of tachycardia was significantly higher in the carbetocin group [16].

In another randomized controlled trial which included 350 singleton pregnant women who delivered were 20 years or older, had a gestational age of at least 34 weeks, had a vaginal delivery, and had at least one risk factor for atonic PPH. 176 women received 100 mcg carbetocin IV immediately after placental delivery, while 174 women received 5 U oxytocin IV. Postpartum blood loss was measured objectively in mL using a postpartum drape with a calibrated bag. The carbetocin group had less postpartum blood loss (146.7 ± 90.4 vs. 195.1 ± 146.2 mL; $p < 0.01$), a lower incidence of atonic PPH (0 vs. 6.3%; $p < 0.01$), less usage of additional uterotonic drugs (9.1 vs. 27.6%; $p < 0.01$), and a lower incidence of postpartum anemia (Hb ≤ 10 g/dL) (9.1 vs. 18.4%; $p < 0.05$)

than the oxytocin group. No significant differences regarding side effects were evident between the groups [17].

The adverse effect profiles appear reassuringly similar between the two medications, the risk of experiencing nausea, vomiting, abdominal pain, flushing, tachycardia, hypotension, headache, itching, metallic taste were similar in women given oxytocin and carbetocin.

There have also been randomized studies of carbetocin versus syntometrine following vaginal birth (18, 19 and 20). All those studies excluded women with significant risk factors for PPH. The syntometrine dose was the approved dose (a mixture of 5 IU oxytocin and 0.5 mg ergometrine) in some studies (18 & 19), and lower than the approved dose in 1 study (that is, ergometrine component 0.2 mg rather than 0.5 mg (20)

However, all studies showed that carbetocin was associated with a significantly lower incidence of adverse effects. One of those studies showed that carbetocin was associated with a lower incidence of hypertension at 30 and 60 minutes but a higher incidence of maternal tachycardia. (18).

A study compared the efficacy and safety of intramuscular (IM) carbetocin with IM syntometrine in preventing primary PPH in a prospective, double-blinded, randomized controlled trial. They found that IM carbetocin was as effective as IM syntometrine in preventing primary PPH after vaginal delivery. It was less likely to induce hypertension and had a low incidence of adverse effect. So, it should be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labor [18].

In a double-blind randomized study was carried out on 370 women with singleton pregnancy achieving vaginal deliveries at or beyond 34 weeks. Women with risk factors for postpartum haemorrhage excluded from the study. Women were randomized to receive either intramuscular syntometrine or intramuscular carbetocin. No significant difference in PPH and addition uterotonics (carbetocin 13.5% vs Syntometrine 16.8%; P=0.38). Carbetocin associated with less adverse effects [19].

In another double blind randomized clinical trial was carried out on 200 pregnant women with a singleton pregnancy. The first group received intramuscular syntometrine (containing 5 units of oxytocin and 0.2 mg ergometrine) and the second group received intramuscular carbetocin after placental delivery. The mean fall in hemoglobin level

in the carbetocin group was significantly lower than the syntometrine group (P < 0.001). Also there were significant differences between the two groups, regarding additional uterotonic drug requirements (P = 0.002). Moreover systolic blood pressure and uterine tone immediately and 30 minutes after drug administration were significantly different (P < 0.001). Incidence rate of tachycardia in the carbetocin group was 13%, in contrast to 5% in the syntometrine group (P = 0.04) [20].

Conclusion:

We concluded that carbetocin is a better alternative to traditional oxytocin in prevention of PPH after vaginal delivery in women with risk factors for atonic PPH with similar side effects and could be routinely used to prevent PPH, which represents the main deaths among parturient women. More trials in low-risk women who undergo vaginal delivery are needed to assess whether carbetocin is superior to conventional uterotonic drugs for the majority of pregnant women.

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