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Original Article

Carbetocin versus oxytocin in prevention of postpartum hemorrhage in late preterm twin pregnancy following cesarean section: a prospective clinical study

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Abstract

Objective

The objective of this study was to compare effectiveness and safety of carbetocin versus oxytocin infusion in prevention of postpartum hemorrhage (PPH) in women with late preterm twin pregnancy undergoing cesarean section.

Patients and methods

A prospective clinical study was conducted from June 2014 to August 2015 in Shibin El-Kom and Benha Teaching Hospitals in Egypt that enrolled 175 women with late preterm twin pregnancy undergoing cesarean section. Carbetocin group (n = 90) as a single intravenous bolus was compared with oxytocin (n = 85) 10 IU as six infusions as soon as the second twin was delivered, and the outcomes were compared.

Results

The mean blood loss during cesarean section was higher in oxytocin group as compared with carbetocin (685 ± 350 vs. 782.8 ± 370 ml, $P > 0.05$). The incident of primary PPH (>1000 ml) in cesarean delivery was lower in carbetocin group versus oxytocin group (3.33 vs. 11.76%, $P < 0.05$). The difference between hemoglobin levels 24 h after delivery was not significantly lower in carbetocin group ($P > 0.05$). The need for another uterotonic agents in carbetocin was lower than in oxytocin (23.33 vs. 35.29%, $P < 0.05$).

Conclusion

This study found that carbetocin was an acceptable option with reduction of PPH compared with oxytocin in late preterm twin pregnancy undergoing cesarean section, and both had similar safety profile with minor hemodynamic effect.

Keywords: Carbetocin, cesarean section, late preterm twin pregnancy, oxytocin, postpartum hemorrhage

Introduction

Postpartum hemorrhage (PPH) is the important cause of maternal mortality and morbidity, with a worldwide prevalence of ~6%, accounting for nearly one-quarter of all maternal deaths [1]. PPH is reported to have increased in frequency and severity in several industrialized countries [2–5]. Uterine atony is the major cause of PPH, accounting for up to 80% of PPH cases [6]. Therefore, inducing a rapid and effective uterine contraction following delivery is an important issue [7].

Risk factors of uterine atony include history of prior PPH, advanced maternal age, obesity, parity, prolonged or augmented labor, polyhydramnios, severe anemia, chorioamnionitis, preeclampsia, delivery by cesarean section (CS) as well as twin pregnancy, although PPH may also occur in women with no identifiable risk factors [2,8,9].

The incidence of twin gestation accounts for 0.5–2.0% of all pregnancies, with rates varying largely by race/ethnicity and country [10] and is progressively raised as a consequence use

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of ovulation induction and artificial reproductive technologies. There are approximately greater than 70% (350 000 live births) late preterm twin delivery in the USA annually [11]. Menacker and Hamilton [12] reported that the incidence of cesarean deliveries increase in twin pregnancies. Seow *et al.* [7] referred that elective cesarean delivery of twin pregnancy at a gestational age of 37 weeks or greater may increase the risk of blood transfusion.

Active management of third-stage labor helps reduce the rate of severe primary PPH, the need for transfusion, and subsequent uterotonic therapy [13]. Oxytocin is the most widely used and effective uterotonic agent for prevention of PPH [14,15], but it has a rapid onset and short duration of action, which is why, it is better administered intravenously to achieve sustained uterotonic activity [16].

Carbetocin (Pabal), a long-acting synthetic analog of oxytocin with agonist action, can be given in elective CS as a single intravenous bolus over 1 min, instead of a continuous oxytocin infusion, for the prevention of PPH and to decreases the need for additional uterotonic agents [17,18]. Its half-life is 40 min, and uterine contractions occur in less than 2 min after intramuscular or intravenous administration [7]. In addition, oxytocin and carbetocin have similar adverse effect profiles, but its ease of administration [18–20] favors the use of carbetocin over traditional oxytocin regimens in cesarean deliveries [17,18] A recent study by Seaw *et al.* [7] demonstrated that a single 100-mg intravenous bolus of carbetocin is effective and safe as intravenous oxytocin infusion for maintaining adequate uterine tone and preventing postpartum bleeding in infertile women with twin pregnancy undergoing elective cesarean delivery. However, there are currently no data to evaluate the efficacy of carbetocin in women with late preterm twin pregnancy undergoing elective or emergency CS, a risk factor of atonic PPH.

The aim of this study was to compare effectiveness and tolerability of carbetocin versus oxytocin in prevention of PPH in women with late preterm (34–36 weeks) twins pregnancy undergoing CS.

Patients and methods

This prospective clinical study was conducted from June 2014 to August 2015 in the Departments of Obstetrics and Gynecology in Shibin El-Kom and Benha Teaching Hospitals, Egypt. Women with late preterm twin (34–36 weeks of gestation) who underwent CS were included in the analysis. The study was approved by local ethics committee, and informed consents about the study were obtained.

Participants were subjected to full history taking, general examination, routine laboratory evaluation, and ultrasound scan. Women with preeclampsia, gestational hypertension, placenta previa, uterine myoma, coagulopathy, and cardiac, renal, and liver diseases were excluded. A total of 175 women were enrolled in this study and divided into two groups. The women in carbetocin group ($n = 90$) received a bolus, slowly over 1 min, intravenous injection of 100-mg (1 ml) dose carbetocin (Pabal Ferring, West Drayton, UK). The women in oxytocin group ($n = 85$) received a continuous intravenous infusion of 10 IU oxytocin (Syntocinon; Novartis, Basel, Switzerland) in 500 ml 0.9% NaCl solution (60 ml/h) in 6 h. All women received their drug immediately after delivery of second twin in both groups and before placental delivery in group A and continued in group B for 24 h afterward to prevent PPH.

Preoperative and postoperative evaluations of blood pressure and hemoglobin level were recorded. Intraoperative and postoperative estimations of blood loss, uterine tone, need for additional uterotonic agents, and need for blood transfusion were recorded during first 24 h after CS. The blood loss was estimated every hour during postpartum period and was assessed in a strict and standardized manner by weighing all dressings, surgical towels, and pad soakage after excluded amniotic fluid volume in each case. PPH was characterized by blood loss more than 1000 ml for CS. Women diagnosed with PPH were treated with repeat oxytocin, misoprostol, or intramuscular ergonovine. Blood transfusion was given according to hemoglobin level and clinical assessment of cases. Women were also evaluated for adverse effects of drugs within 24 h after delivery.

Statistical methods

Data were statistically described in terms of mean ± SD, frequencies (number of cases), and percentages when appropriate. Comparison of numerical variables between the study groups was done using independent *t*-test. *P* values equal to or less than 0.05 were considered statistically significant. All statistical calculations were done using computer program SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, Illinois, USA).

Results

The mean ages of the carbetocin and oxytocin groups were 25.82 ± 4.10 and 26.06 ± 6.49 years, respectively ($P > 0.05$). There were no significant differences between the groups concerning BMI, parity, gestational age of delivery, hemoglobin (g/dl), systolic blood pressure (SBP), and diastolic blood pressure (DBP, mmHg) before CS [Table 1].

The results for the main maternal clinical outcomes are presented in Table 2. The mean amount of blood loss during CS was higher in oxytocin group as compared with carbetocin group (685 ± 350 and 782.8 ± 370 ml, respectively), but the difference was not significant ($P > 0.05$). The incidence of primary PPH (>1000 ml) in cesarean delivery was lower in carbetocin group versus oxytocin group (3.33 and 11.76%, respectively), and the difference was significant ($P < 0.05$). The oxytocin group had a higher incidence of blood transfusion (9.41%) compared with the carbetocin group (2.22%), and the difference was significant ($P < 0.05$). The need for another uterotonic agents

was 23.33% in carbetocin group and 35.29% in oxytocin group, with significant difference between the two groups ($P < 0.05$); in almost all these patients, uterine atony was developed. The difference between blood hemoglobin levels 24 h after delivery was not significantly lower in the carbetocin group ($P > 0.05$). Women in oxytocin group, 2 h after CS, showed a statistically significantly higher SBP and DBP than women in carbetocin group ($P < 0.05$).

Regarding adverse effects of drugs, there was no significant difference between the two groups regarding occurrence of nausea, vomiting, flushing, shivering, dyspnea, palpitations, and itching. The incidence of tachycardia and headache was significantly increased in the carbetocin groups ($P < 0.05$) [Table 3].

Discussion

There is no doubt that the conduct of a twin delivery remains one of the most challenging events in the daily practice of obstetrics [21]. Twin pregnancy is one of the most important risk factors of PPH because of overextension of the uterus [6]. Therefore, the high incidence of blood transfusion and need for additional uterotonic agents noted in twin pregnancy may be owing to PPH [7]. Our results have shown that carbetocin is superior to oxytocin in prevention of PPH in late preterm twin pregnancy following cesarean delivery with at least one risk factor for such complication. This fact can be explained by the known longer half-life of carbetocin when compared with oxytocin causing a more uterine response, in terms of frequency and amplitude of uterine contractions [9,19].

Our study has similar aspects regarding the effect of carbetocin on the uterus in comparison with oxytocin to that of Ortiz *et al.* [22] who found that carbetocin was more effective than oxytocin following CS with at least one risk factor for prevention PPH. We found that women having carbetocin had higher hemoglobin, less blood loss, reduced need for additional uterotonics, and reduced need for blood transfusion when compared with the oxytocin group [22]. This result is similar to other studies that carbetocin is associated with less blood loss compared with syntometrine in the prevention of PPH [17,18,23]. Our finding is in contrast with recent studies that demonstrated there was no difference in the amount of estimated blood loss between carbetocin and oxytocin [20,24,25].

In our study, SBP and DBP were significantly lower 2 h after CS delivery among women in carbetocin group than women in oxytocin group. These results agree with those of Samimi *et al.* [26] who found that the SBP measurements immediately after delivery were significantly higher in the syntometrine group. Therefore, carbetocin becomes the medication of choice for women with hypertensive disorder or cardiac problems [19], but preeclampsia is still a contraindication to the administration of carbetocin, and further studies will be required to assess the cardiovascular effects of carbetocin before it can be advocated for routine use in preeclamptic patients [27]. However, two studies demonstrated there was a statistically significant lower SBP and DBP immediately after delivery in oxytocin group, and this may be attributed to the difference in sample size between the studies and the use of spinal anesthesia [23,28].

Overall, the adverse effect profiles appear similar in either group in this study, although tachycardia and headache are

Table 1: Demographic data of the patients

	Carbetocin group	Oxytocin group	*P*
Maternal age (years)	25.82±4.10	26.06±6.49	0.08
BMI (kg/m^2)	25.5±6.2	26.2±4.8	0.18
Parity	1.87±0.23	1.23±0.56	0.88
Gestation age of delivery (weeks)	35.67±0.9	35.61±0.7	0.15
Hemoglobin (g/dl)	11.3±1.4	11.1±1.1	0.59
Systolic blood pressure before cesarean section (mmHg)	110.67±5.5	110.54±6.6	0.19
Diasolic blood pressure before cesarean section (mmHg)	75.22±3.7	76.66±4.37	0.18

Data are presented as mean±SD.

Table 2: Outcome data for the two study groups

	Carbetocin (*n*=90)	Oxytocin (*n*=85)	*P*
Weight of first twin (g)	1855±335	1795±325	0.81
Weight of second twin (g)	1980±338	1872±350	0.92
Amount of blood loss during CS (ml)	685±350	782.8±370	0.07
PPH (>1000 ml)	3 (3.33)	10 (11.76)	0.01
Incidence of blood transfusion	2 (2.22)	8 (9.41)	0.05
Uterine atony	25 (27.78)	33 (38.82)	0.05
Need for another uterotonic agents uterotonics	21 (23.33)	3 (35.29)	0.02
Hb 24 h after operation (g/dl)	10.4±1.1	9.9±1.2	0.69
Hb difference (g/ml)	0.9±0.2	1.2±0.2	0.87
Systolic blood pressure 2 h after CS (mmHg)	111.75±5.4	116.56±9.4	0.01
Diastolic blood pressure 2 h after CS (mmHg)	76.67±3.8	81.48±11.54	0.05

Values are represented as mean±SD and *n* (%).CS: Cesarean section; Hb: Hemoglobin; PPH: Postpartum hemorrhage.

Table 3: Drug adverse effects

	Carbetocin (*n*=90)	Oxytocin (*n*=85)	*P*
Nausea	6	4	0.82
Vomiting	7	4	0.43
Tachycardia (pulse>100 beats/min)	18	4	0.01
Flushing	2	1	0.19
Headache	14	7	0.05
Shivering	5	3	0.42
Dyspnea	3	2	0.5
Palpitations	4	3	0.67
Itching	2	0	0.71

Data are presented as *n*.

significantly more common in carbetocin group than oxytocin group. It could be argued that some of these are not true adverse effect but rather are the effect of anesthesia or surgery, and they subside without any treatment.

Our study has several strengths, including detailed information on cases of PPH collected from two teaching hospitals, timing of medication has been reported, and it is the first study, to the best of our knowledge, to compare carbetocin effectiveness and safety with oxytocin after CS in women with at least one risk factor (late preterm twin pregnancy) of developing atonic PPH.

Limitations of our study include difficulty of estimating blood loss during surgery because the blood is mixed with amniotic fluid, which makes the blood loss estimation difficult to accurately measure. Moreover, there is limited statistical power to detect associations between relatively rare conditions (e.g. malpresentation, chorioamnionitis) and PPH. Some inconsistencies between the diagnosis of atonic PPH and estimated blood loss may have been owing to the timing of diagnosis (e.g. made soon after delivery by physician).

In summary, carbetocin is associated with reduction in estimated blood loss, resulting in a significant minimum drop in hemoglobin levels. It also resulted in good uterine tone as early as after delivery of the second twins and prevented the additional administration of uterotonic agents.

Conclusion

Carbetocin reduces the use of additional oxytocin following CS. It is a better alternative to traditional oxytocin in prevention of PPH in late preterm twin pregnancy with at least one risk factor for such complication, and both have similar adverse effects. It may become the medication of choice for women with hypertensive disorders or cardiac problem.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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