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Research Article

Comparative study between effect of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients undergoing cesarean section

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Abstract *Background:* Carbetocin is a long acting structural analog of human oxytocin and is given as single IV bolus following the delivery; it is effective as an oxytocin infusion for several hours because the latter has a very short duration of action which requires a continuous infusion to achieve sustained uterotonic activity.
Multiple pregnancy is one of the most common causes of postpartum hemorrhage. This study was done to compare the effect of carbetocin and oxytocin on uterine contraction and though the use of other uterotonic drugs postoperative in multiple pregnancy patients undergoing elective C.S.
Patients and methods: Sixty patients were enrolled in this study, and they were classified randomly into two groups: group C = received 100 μg carbetocin, group O = received 20 IU oxytocin. We compared between the two groups as regard hemodynamic parameters (heart rate and mean arterial blood pressure), uterine contraction, amount of blood loss and number of patients who needed to reduce isoflurane concentration.
Results: As regards uterine contraction group O needed methylergometrine postoperative significantly more than group C and as regards blood loss; it was significantly decreased more in group C and though less reduction in blood pressure and less effect on heart rate than group O.
Conclusion: Single dose of carbetocin appears to be more effective than oxytocin for several hours on uterine contraction and though preventing postpartum hemorrhage in multiple pregnancy patients undergoing elective caesarian section.

1. Introduction

Primary postpartum hemorrhage (PPH) is the most common form of major obstetric hemorrhage. Definition of PPH is

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the loss of 500 ml or more of blood from the genital tract within 24 h of the delivery of baby [1].

Minor PPH (blood loss 500–1000 ml) and major PPH (more than 1000 ml). Many patients known to be high risk for developing PPH: twin pregnancy, known placenta previa, placental abruption, obesity with BMI > 35; anemia < 9 g/dl, previous PPH and age > 40 years [2].

Almost 500,000 women die for this preventable cause each year especially hemorrhage that occurred at time of delivery [3].

Other nonfatal complications may occur as Sheehan's syndrome (Pituitary infarction), coagulopathy, and organ damage due to hypotension, shock, and risk of hysterectomy [4].

Uterine atony is the first cause of hemorrhage at time of delivery; therefore, active management is better than expectant management of the third stage of labor [5,6]. Third stage of labor is that period following the delivery of baby till placental delivery (see Fig. 1).

Uterotonic agents as oxytocin (10 IU) intramuscularly usually prevent PPH in low-risk vaginal and caesarian deliveries, or intravenous infusion (20–40 IU in 1000 ml, 150 ml/h) which is another alternative because of its short duration (its half-life is approximately 3.5 min) [7,8].

Misoprostol (600 μg orally) is not effective when compared with oxytocin in prevention of PPH, also carries increased adverse effects which are dose related [9].

A long-acting oxytocin derivative, carbetocin, is licensed in the UK specifically for the indication of prevention of PPH. It is given as an IV bolus 100 μg over one minute.

Carbetocin is a synthetic oxytocin analog 1-deamino-1-monocarbo (2-O-methyltyrosine) – oxytocin that binds to oxytocin receptors with higher affinity. Oxytocin receptors are G-protein coupled [10] and there mechanism of action involves second messengers and the production of inositol phosphate [11]. Each ampule contains 100 μg (0.1 mg) of carbetocin (manufacture: Ferring Gmbh, Kiel, Germany) (marketing authorization holder: Ferring Gmbh, Kiel, Germany) (date of revision: June 2006). It is as effective as oxytocin infusion with respect to blood loss following delivery [12–14]. Its contractile effects of the uterus are apparent within two min. and can be observed for approximately one hour [15]. It has half-life of 40 min (4–10 times longer than oxytocin). So it is given as single IV bolus following the delivery of baby at elective or emergency cesarean section [16] and if further uterine stimulation is needed, treatment with other uterotonic drugs should be used. Carbetocin has also been shown to stimulate milk letdown due to its action on oxytocin receptors on the myoepithelial cells and there was not a significant amount of it in breast milk [17]. Side effects are nausea, vomiting, chest pain, tachycardia, hypotension and respiratory distress. Contraindications do not use before delivery (it should not be used to induce or augment labor since it could cause cardiac or respiratory distress to mother or infant) [18] hypersensitivity to carbetocin or oxytocin.

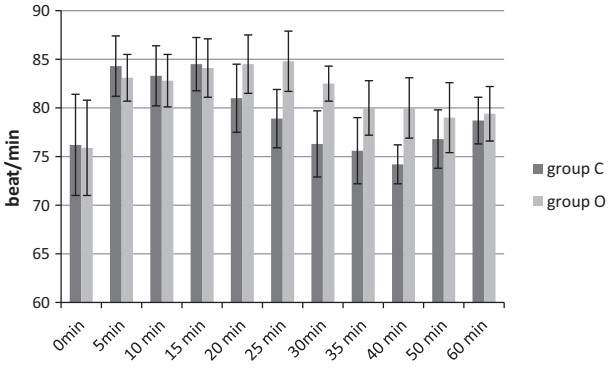

Figure 1 Heart rate values. Group C: Those patients who received carbetocin. Group O: Those patients who received oxytocin.

The aim of the present study was to compare the effect of carbetocin versus oxytocin on the hemodynamics and the effectiveness of uterine contraction and blood loss in twin pregnancy patients undergoing elective C.S. under general anesthesia using isoflurane and though it may contribute carbetocin as substitute to oxytocin for elective C.S. at our institution as well as others.

2. Patients and methods

After getting approval from hospital ethical committee and written informed consent from patients, 60 twin pregnancy patients ASA physical status I, aged 28–36 years, were scheduled for elective cesarean section in Ain Shams University Hospital in the period between November 2012 and June 2013. Exclusion criteria included patients with hypertension, pre-eclampsia, cardiac, respiratory, renal or liver disease, pre-existing bleeding disorder such as hemophilia and women taking therapeutic anticoagulants, hypersensitivity to carbetocin or oxytocin. Patients with preoperative hemoglobin less than 9.5 gm% and those who are pregnant with more than two babies were also excluded from the study.

Pre-operative investigations in the form of ECG, complete blood picture, coagulation profile, liver and kidney functions were performed. A venous cannula 18G size was inserted and basic monitoring (ECG, pulse oximeter, NIBP) was applied. All patients underwent general anesthesia; pre-oxygenation with 100% O_2 for 4 min then induction with intravenous thiopentone sodium 4–7 mg/kg, cisatracurium 0.5 mg/kg to facilitate endotracheal intubation (as all patients underwent elective C.S. and were fasting for at least 8 h) and anesthesia was maintained with oxygen (FiO_2 0.4), isoflurane (MAC 1) and intermittent doses of cisatracurium. Lactated Ringer's solution was infused at a rate of 10–15 ml/kg.

Patients were randomly allocated to lie into two equal groups: group C (no = 30) received 100 μg carbetocin in 10 ml saline, and group O (no = 30) received 20 IU oxytocin in 10 ml of saline solution. Randomization was performed by using computer-generated program. Both drugs were prepared preoperatively and coded so that the working investigator and the obstetrician were blinded of the type of drug injected. The uterotonic drug was injected slowly IV over one minute after delivery of babies.

In all patients, the following parameters were recorded:

- hemodynamic parameters (heart rate and mean arterial blood pressure),
- uterine contraction score; assessed by the obstetrician and scored as very good (4), good (3), sufficient (2), poor (1) or atony (0), and

– amount of blood loss (estimated by counting the number of swabs soaked with blood and also the amount of aspirated blood).

If uterine contraction score was less than 3 after 5 min, isoflurane concentration was decreased from 1 to 0.5. If still unsatisfactory additional uterotonics were administered as necessary (methylergometrine 100 IU). Patients who lost more than 1200 ml of blood were prepared for blood transfusion to maintain hemodynamic and good tissue perfusion.

We also recorded the number of patients who needed to reduce MAC, those who needed additional uterotonics and also the number of patients who had blood transfusion.

At the end muscle relaxation was reversed with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine.

PASS 11 was used for sample size calculation. Power calculations were based on former studies which revealed that in order to detect a statistically significant difference between the proportions of patients who require additional methergine of 0.4 mg, a sample size of $n = 26$ per group was required. To compensate for dropouts and missing data, the sample size was increased to 30 patients per group. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05.

The statistical analysis was performed using a standard SPSS software package version 17 (Chicago, IL). Data were presented as mean values ± SD, numbers (%) or median (IQR). Student's t-test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the χ^2 test, non-parametric data were compared using Mann–Whitney test, and p values < 0.05 were considered statistically significant.

3. Results

60 twin pregnancy patients undergoing elective C.S. were successfully enrolled in this study, 30 in each group; the variables in demographic data did not show statistically significant differences between the two groups with respect to age, body mass index (BMI), preoperative hemoglobin concentration, parity, hemoglobin, previous C.S., birth weight and duration of anesthesia (Table 1).

Regarding hemodynamic variables, HR showed statistically non-significant differences between the two groups till 20 min after injection of either carbetocin or oxytocin, but after 25 min till 50 min the differences between the two groups were statistically significant: 78.9 ± 31 in group C, while it was 84.8 ± 3 in group O after 25 min and (76.8 ± 3.6) and (79 ± 3) respectively after 50 min; p value was < 0.05 till 60 min and values returned to nonsignificant levels (Table 2).

On the other hand mean arterial blood pressure showed no significant differences between the two groups till 15 min after injection. Changes started to be significant after 20 min 75 ± 2.6 in group C and 70 ± 3.8 in group O; till 50 min values were 75 ± 4.7 in group C and 70 ± 3.7 in group O; p value was < 0.05. Values returned to be nonsignificant after 60 min from injection as shown in Table 3.

There were significant differences between the two groups as regards uterine contraction. Values were expressed as median (range); uterine tone was evaluated 2 min and 2 h after giving either carbetocin or oxytocin. In group C, for those who received carbetocin it was [3] after 2 min and also [3] after 2 h while in group O, for those who received oxytocin it was [2] after 2 min and also after 2 h (p value < 0.001) (Table 4).

Regarding the number of patients who needed to reduce the concentration of inhaled isoflurane from 1 to 0.5, there were

Table 1 Patient characteristics:

	Group (C) ($n = 30$)	Group (O) ($n = 30$)	p-Value
Age (yr)	25.4 ± 4	24.5 ± 3	0.24
BMI (kg/m^2)	25.6 ± 2.7	26 ± 2.8	0.6
Parity	3(2–4)	4(3–5)	0.07
Hemoglobin (gm%)	10 ± 0.9	9.8 ± 0.7	0.068
Previous C.S.	2(1–3)	2(2–2)	0.2
Duration of surgery (min)	33.8 ± 2.7	34 ± 3	0.79
Birth weight (kg)	2.4 ± 0.34	3 ± 0.3	0.2

Group C: Those patients who received carbetocin.
Group O: Those patients who received oxytocin.
Values are expressed as mean ± SD or median (IQR).
$p > 0.05$ was considered statistically nonsignificant.

Table 2 Mean heart rate values in two study groups.

Time (min)	Group C ($n = 30$)	Group O ($n = 30$)	p value
0 (baseline)	76.2 ± 5.16	75.9 ± 4.9	0.83
HR 5 min	84.3 ± 3.1	83.1 ± 2.4	0.07
HR 10 min	83.3 ± 3.09	82.8 ± 2.7	0.058
HR 15 min	84.5 ± 2.74	84.1 ± 3	0.6
HR 20 min	81 ± 3.5	84.5 ± 3	0.08
HR 25 min	78.9 ± 3.1	84.8 ± 3*	< 0.001
HR 30 min	76.3 ± 1.8	82.5 ± 3.4*	0.023
HR 35 min	75.6 ± 2.8	80 ± 3.4*	< 0.001
HR 40 min	74.2 ± 3.1	80 ± 2*	< 0.001
HR 50 min	76.8 ± 3.6	79 ± 3*	0.03
HR 60 min	78.7 ± 2.8	79.4 ± 2.4	0.29

Group C: Those patients who received carbetocin.
Group O: Those patients who received oxytocin.
Values are expressed as mean ± SD.
* $p < 0.05$ was considered statistically significant between the 2 groups.

Table 3 Mean arterial blood pressure.

Time	Group C ($n = 30$)	Group O ($n = 30$)	p value
Baseline MABP	71 ± 6.3	72.1 ± 4.8	0.44
MABP 5 min	69.6 ± 3.6	70 ± 3.4	0.8
MABP 10 min	75.8 ± 2.7	74.3 ± 4	0.08
MABP 15 min	75.2 ± 2.8	71 ± 2.3	0.068
MABP 20 min	75 ± 2.6	70 ± 3.8*	0.003
MABP 25 min	74 ± 2.4	68.7 ± 3*	0.005
MABP 30 min	73.6 ± 2.4	68.8 ± 2.3*	0.004
MABP 35 min	73 ± 2.4	69.4 ± 5*	0.004
MABP 40 min	74 ± 1.8	69.3 ± 4.8*	< 0.001
MABP 50 min	75 ± 4.7	70.5 ± 3.7*	0.03
MABP 60 min	74.4 ± 5	70.6 ± 2.2	0.068

Group C: Those patients who received carbetocin.
Group O: Those patients who received oxytocin.
Data are presented as mean ± SD.
* $p < 0.05$ was considered statistically significant.

Table 4 Uterine contraction score.

Time	Group C ($n = 30$)	Group O ($n = 30$)	p-Value
Uterine tone 2 min	3(2–3)*	2(1–2)	< 0.001
Uterine tone 2 h	3(2–3)*	2(2–3)	< 0.001

Group C: Those who received carbetocin.
Group O: Those who received oxytocin.
Values are expressed as median (range).
* $p < 0.001$ was considered statistically significant.

significant changes between the two groups. In group C only 5 patients (16.7%) needed to reduce isoflurane concentration while in group O it was 15 patients (50%) (p value < 0.001). Also the number of patients who needed methergine was 4 patients (13.3%) in group C while 15 patients (50%) in group O needed one dose and 10 patients (33.3%) needed two doses which means that it is statistically significant as p value was < 0.001. Blood loss in group O patients (721 ± 50 ml) was significantly higher than that in group C patients (437 ± 45 ml) and so the percentage of patients who needed blood transfusion in group O (13.3%) was significantly higher than that in group C (3.33%) (Table 5).

4. Discussion

This study is one of the first studies done to compare carbetocin with licensed dose of oxytocin. Its results demonstrated an increased use of additional oxytocics with oxytocin group. The reason for administering additional oxytocics was significantly more liability to develop postpartum hemorrhage and hence more blood loss.

Concerning oxytocin its cardiovascular effects include hypotension, tachycardia and decrease in cardiac output. This could be sufficient to cause significant compromise in high-risk patients especially if given as rapid IV bolus injection; this effect is markedly reduced if given with slower rate [19]. Some suggest that the preservative, chlorobutanol, is the cause of these hemodynamic changes [20].

Our results proved that hemodynamic variables; namely the heart rate values showed statistically non-significant differences between the two groups till 20 min after injection of either carbetocin or oxytocin but after 25 min till 50 min, and the differences between both groups were statistically significant. However, the mean arterial blood pressure values showed non-significant differences between the two groups till 15 min after injection. Changes started to be significant after 20 min till 50 min.

A previous study done by Moertl and his co-workers in 2011, showed that patients treated with oxytocin had more pronounced hypotension and hemodynamic rebound than those received carbetocin [7].

Concerning uterine contraction and tonicity, our results revealed a statistically significant better uterine contractility in carbetocin group than oxytocin group both at 2 min and 2 h after injecting the test drug. Also the number of patients who needed to reduce isoflurane concentration from 1% to 0.5% or additional methergine was significantly lower in the carbetocin group.

Larciprete et al. in 2013 [4] showed that uterine contractility was better in carbetocin group at 2, 12 and 24 h after C.S. In agreement with our results, the study done by Borruto et al. [21] 2009, revealed a lower rate of additional uterotonic need in carbetocin group, and this conclusion agrees with many other researches as those done by Su et al. in 2007 [6] and Boucher et al. [14] who concluded that the use of carbetocin is more effective than oxytocin for prevention of postpartum hemorrhage after caesarian section. Dansereau et al., [22] also described a lower additional oxytocics need for treatment of uterine atony in those women who were treated with carbetocin soon after delivery.

In this study, the amount of blood loss and also the need for blood transfusion in oxytocin group patients were found to be higher than those in patients who received carbetocin. On the contrary, in 2013 Larciprette and his coworkers did not demonstrate any difference in the amount of blood loss after CS and in drop of hemoglobin level within 2 h and 24 h between oxytocin and carbetocin groups [4].

As both carbetocin and oxytocin have more benign adverse effect and hemodynamic profile than methylergometrine, carbetocin became the drug of choice for those having contraindications to methylergometrine; such as hypertensive disorders, and cardiac problems. Cardiovascular disease is listed in the cautions with the advice to avoid the use of carbetocin in severe cardiovascular disease as the potent uterotonic effect of carbetocin may shift a considerable blood volume to the systemic circulation with subsequent fluid overload. However carbetocin would be preferable, as it reduces the use of additional oxytocics and also reduces the incidence of PPH as proved by Thomas et al. [23] who confirmed our results.

It is not known whether the carbetocin data from C.S. can be extrapolated to vaginal birth or not. One randomized study [14] of carbetocin versus oxytocin following vaginal birth showed an increased rate of additional uterotonic intervention

Table 5 Number of patients with unsatisfactory uterine tone.

Time	Group C ($n = 30$)	Group O ($n = 30$)	p-Value
Number of patients with reduced isoflurane concentration	5(16.7%)	15(50%)	< 0.001
Number of patients who need methergine	4(13.3%)	15(50%) one dose 10(33.3%) 2 doses	< 0.001
Number of patients who need blood transfusion	1(3.33%)	4(13.3%)	< 0.001
Blood loss (ml)	437 ± 45	721 ± 50	< 0.001

Group C: Those who received carbetocin.
Group O: Those who received oxytocin.
Data are presented as number and percentage of patients or mean (SD).

in the oxytocin group. The additional uterotonic drug indicates a diagnosis of uterine atony which requires intensified monitoring and prolonged observation time in the postoperative recovery area with an increased use of medical staff. The lesser use of additional uterotonics after carbetocin found in this study is an important outcome with possible financial savings. Two studies have compared the cost effectiveness of prophylactic carbetocin and oxytocin after C.S. In low risk patients undergoing elective C.S., carbetocin was not cost saving [24]. In contrast, in those with risk factors for PPH, the mean cost per woman was significantly lower following carbetocin treatment compared with oxytocin one [25].

In conclusion, single dose of carbetocin appears to be more effective than oxytocin with better uterine contraction, less blood loss, less need for inhalational anesthetic reduction, and more hemodynamic stability.

Conflict of interest

None declared.

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