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Original Research Article

Carbetocin versus oxytocin in placental separation and postpartum hemorrhage in caesarean section: comparative observational study

Khushbu Bashir*, Madieha Sabha

Department of Obstetrics and Gynecology, SKIMS, Soura, Jammu and Kashmir, India

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***Correspondence:**
Dr. Khushbu Bashir,
E-mail: Khushbubashir128@gmail.com

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ABSTRACT

Background: Carbetocin and oxytocin are indicated for the prevention of postpartum haemorrhage (PPH) due to uterine atony. Carbetocin is a newer analogue of oxytocin with longer half life and more heat stable. PPH can be effectively reduced by the prophylactic use of uterotonics. The aims of the present study were to compare effects of oxytocin and carbetocin in separation of placenta, in controlling the blood loss and the additional uterotonic needed in caesarean section (CS) at high risk of primary PPH.
Methods: Women in the carbetocin group (group A) received a bolus of 100 µg IV; women in the control group (group B) received 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (150 mL/ hour). The efficacy of drugs in controlling blood loss was evaluated. Also, the haemodynamic effects and the need for additional uterotonic agents was compared. In addition, we compared the drop in haemoglobin level, the placental separation, the uterine tone.
Results: Both drugs produce hypotension but the effect was greater in oxytocin group. Placental separation was seen early in oxytocin group. Uterine tone was attained earlier in oxytocin group however the tone was maintained persistently in carbetocin group. Additional uterotonic agents were needed in the oxytocin group (46% vs 0%, p=0.05).
Conclusions: A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain sustained and adequate uterine tone and to prevent the PPH. However, there is delayed placental separation and delayed attainment of adequate uterine tone after use of carbetocin.

Keywords: PPH, Uterotonic drugs, Carbetocin, Oxytocin, Lower segment cesarean section

INTRODUCTION

Postpartum haemorrhage (PPH) remains one of the principal causes of maternal deaths in developing nations.[1] The primary PPH is defined as blood loss more than 500 mL after vaginal delivery and more than 1000 mL after CS, that occurs in the first 24 hours after delivery. It has been estimated that over 300,000 women, mostly from developing countries, lose their lives during pregnancy and childbirth every year.[2] PPH accounts for nearly onequarter of maternal deaths worldwide.[3] The most common underlying cause of PPH is uterine atony.[4] However prophylactic use of uterotonics are effective in reducing PPH, and among the uterotonics the drug of choice is oxytocin. Oxytocin is produced in the hypothalamus and is secreted into bloodstream by posterior pituitary gland. Oxytocin stimulates the uterine muscles to contract and also increases production of prostaglandins, which increase the contractions further. It has decreased the incidence of PPH by 40% and has a rapid onset of action and lesser side effects compared to other uterotonics.[5-7] It has a short half-life of 4-10 min due to which it requires a continuous intravenous infusion or repeated intramuscular injections.[8] Nowadays a newer analogue of oxytocin called carbetocin has been introduced. It is a long-acting, with an approximate half-life of 40 minutes and is also indicated for the prevention of uterine atony after child birth by CS. Carbetocin has a rapid onset of action (within 1-2 min) and a prolonged duration of action. Its safety profile is comparable to that of oxytocin.[9] It is also more heat-stable than oxytocin.[10] However both the drugs can be administered intravenously and intramuscularly.

METHODS

This is a comparative, observational study conducted from July 2021 and July 2022 within the obstetrics and gynaecology tertiary care unit of Shere I Kashmir institute of medical sciences. Two hundred women undergoing elective CS were enrolled in the study. They were randomly divided into two groups. Group A consisted of one hundred women who received carbetocin and group B had other hundred women who received oxytocin. Women in the carbetocin group (group A) received a bolus of 100 µg IV at delivery of the anterior shoulder; women in the oxytocin group (group B) received 20 IU of oxytocin in 1000 ml of 0.9% NaCl solution IV (150 mL/ hour) at delivery of the anterior shoulder. A written informed consent was taken from the women planned for CS. Mode of anaesthesia was spinal.

Inclusion criteria was all pregnant women with term gestation with multiple pregnancy, previous CS, uterine fibroids, past h/o PPH, fetal macrosomia, polyhydramnios.

High risk pregnancies with hypertensive disorders of pregnancy, cardiac diseases, renal or the liver diseases, epilepsy, general anaesthesia, hypersensitivity to carbetocin and oxytocin were excluded from the study.

In this study the effects of carbetocin and oxytocin on the blood pressure (BP) after the injection at 1 minute and 5 minutes was noted. The other parameters compared were time taken for placental separation, uterine tone, need for additional uterotonic agents, the drop in haemoglobin level by comparing the haemoglobin concentration on admission with the measure at 24 hours after delivery and the visual estimation of blood loss.

Statistical analysis for a power analysis of 90%, the study needed of 100 patients in each group. Data were expressed as means ± SD or median, as appropriated. Data were tested for normal distribution. Statistical analysis was performed by using Mann-Whitney non parametric test and Fisher's exact test for categorical data. P value of less then 0.05.

RESULTS

It was seen that both the study groups were comparable in baseline characteristics. In both the groups CS was done at term gestation ≥ 38 weeks. Majority of females belonged to rural areas (72%) in carbetocin group and (68%) in oxytocin group. Indication to elective CS were similar for each group, however in the group B the main indication has been polyhydramnios (18% vs 48%, p=0.05) (Table 1). Regarding the haemodynamic effects of carbetocin and oxytocin, both drugs have a hypotensive effect. Both systolic blood and diastolic pressure was lower in the oxytocin group at the 5th minute after administration and at uterine closure time (Table 2). It was seen that there was early separation of placenta in oxytocin group (less than 30 seconds in 74% patients) but in carbetocin group placental separation occurred at more than one minute time (in 77% patients). However, there was no significant difference in the amount of estimated blood loss and in the incidence of primary post-partum haemorrhage (>1000 ml) in both groups as shown in Table 3. Similarly, in both study groups haemoglobin levels before and after 24 hours from delivery were similar. Median haemoglobin value before and after LSCS was 12 gm/dl and 10.8 gm/dl in group A respectively. In group B the median hemoglobin value before and after LSCS was 12.4 gm/dl and 10.4 gm/dl respectively, confirming no significant difference in the level of blood loss (Table 4, p=0.04). It was also seen that uterine tone was gained early in oxytocin group in less than 30 seconds time while it was gained after 60 seconds in carbetocin group. However, the tone was sustained in carbetocin group and no additional utero tonics were given in group A. In the oxytocin group 46% patients needed additional uterotonics (p<0.05).

There weren't any recorded important adverse effects in both study groups, instead nausea and vomiting was observed more in carbetocin group 38% (p<0.05).

Table 1: Characteristics of study population.

Characteristics	Group A, n (%)	Group B, n (%)
Gestational age at delivery (median-range)	38 (38-39)	39 (39-40)
Previous abdominal surgery	42 (42)	32 (32)
Fetal macrosomia	19(19)	11 (11)
History of PPH	11(11)	9 (9)
Twin pregnancy	31(31)	41 (41)
Fetal polyhydramnios	18 (18)	48 (48)

Table 1 shows baseline characteristics are comparable in both groups. However, patients with fetal polyhydramnios were more common in group B, p<0.05.

Table 2: Systolic and diastolic blood pressure during and after CS.

Blood pressure (median value) mmHg	Group A	Group B
At skin incision	119/74 (110-124/65-75)	121/72 (112-120/68-73)
At one minute of injection	115/70 (108-118/60-73)	120/68 (115-119/64-74)
After 5 minute of injection	120/70 (115-124/68-76)	110/60 (109-114/60-68)
At the end of LSCS	124/72 (120-128/68-76)	115/60 (118-125/65-70)
After 24 hours of LSCS	122/80 (115-124/70-81)	120/78 (121-126/72-78)

*Statistically significant p<0.05

Table 2 shows that hypotensive effect was seen in both groups, however effect was profound in oxytocin group.

Table 3: Comparison of blood loss during and after CS.

Blood loss (ml)	Group A (%)	Group B (%)	P value
After delivery of baby			
>1000	9	13	0.04
500-1000	17	19	
<500	74	68	
After 2 hours of LSCS			
>1000	0	0	0.01
500-1000	1	3	
<500	99	97	
After 24 hours of LSCS			
>1000	0	0	
500-1000	0	0	
<500			

Table 3 shows the blood loss was comparable in both the groups.

Table 4: Comparison of median haemoglobin values.

Haemoglobin (median value) (gm/dl)	Group A	Group B
Before LSCS	12	12.4
After 6 hours	11.1	10.9
After 24 hours	10.8	10.4

Table 4 shows haemoglobin values before and after LSCS are comparable p<0.05.

Table 5: Comparison of placental separation and uterine tone.

Mean time (Sec)	Group A (%)	Group B (%)
Taken in placental separation		
<30	0	74
30-60	23	26
>60	77	0
Taken to regain uterine tone		
<30	0	78
30-60	13	22
>60	86	0

Table 5 shows that oxytocin group has early placental separation and early return of uterine adequate tone.

Table 6: Use of additional uterotonics in both groups.

Uterotonics	Group A (%)	Group B (%)
Additional uterotonic used	10	68
Intermittently relaxed uterus	2	58
Sustained uterine contractility	98	42

Table 6 shows that there was increased need for additional uterotonic in group B. Uterine tone was better maintained in group A.

DISCUSSION

The present study compared carbetocin (group A) with oxytocin (group B) in CS s with risk factors for primary post-partum haemorrhage, concerning both the haemodynamic effects of these drugs, and the prevention of PPH. The baseline characteristics of both the groups were comparable and both have a comparable safety profile. Oxytocin and carbetocin both produced hypotension but the effect was more pronounced with oxytocin. There was not any significant difference in the amount of blood loss after CS and in the drop of haemoglobin level within 2 hours and 24 hours of LSCS. we also observed that there was some delay in placental separation (>one minute) and attainment of adequate uterine tone in carbetocin group. However, once the adequate tone was attained in carbetocin group (after one minute of drug administration) it then sustained throughout LSCS. Hence there was no need of additional uterotonics in this group. In contrast there was early separation of placenta (within 30 seconds of drug administration) and early return of adequate uterine tone in oxytocin group. However, this uterine tone was not maintained. Majority of the patients in this group had intermittent uterine atony and to prevent this we used additional uterotonics (in 46% patients). An interesting observation was made that in oxytocin group when carbetocin was used as an additional uterotonic, it produced sustained uterine contractions and maintained uterine tone. Also, no delay in placental separation was seen in the combined use of these drugs (oxytocin infusion for 5 minutes followed by carbetocin administration as an additional drug). Placenta previa, Accreta, pre-eclampsia, eclampsia and general anaesthesia are contraindications to the administration of carbetocin. Regarding the literature about carbetocin, Danzereau et al firstly described a lower additional uterotonic need for treatment of uterine atony in women who took carbetocin soon after delivery.[10-12]

Limitation

There were certain limitations in our study which included the choice of uterotonic on the basis of cost-effectiveness. Also, we could not be establishing which patients benefited most from carbetocin. Similar limitations were seen in other studies conducted on carbetocin. The quality issues of uterotonic agents were yet another limitation in our setup and others similar institutions of developing countries.

CONCLUSION

Carbetocin has prolonged duration of action.It produces sustained uterine response with contractions of higher amplitude and frequency. A single injection of carbetocin is more convenient than an oxytocin bolus injection that

needs to be followed by several hours of oxytocin in infusion. There is no additional use of uterotonics after administration of carbetocin. However, in comparison to oxytocin it causes delayed placental separation and delayed regain of uterine tone. It is used either as primary uterotonic agent or as an additional uterotonic after oxytocin. Although the combined use has an advantage of early placental separation and sustained uterine tone and no intermittent atony. However, the oxytocin drip should be stopped if carbetocin is to be used as an additional uterotonic.

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