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Original Article

Use of Carbetocin versus Oxytocin for the Prevention of Postpartum Haemorrhage following Caesarean section in Dhaka National Medical College Hospital- An Interventional comparative study

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Abstract:

Background: Postpartum haemorrhage (PPH) is the leading cause of maternal death worldwide. It is a preventable event in abdominal and vaginal deliveries. Preventive measures include prophylactic drug use to aid uterine contraction after delivery, thus avoiding severe blood loss and reducing maternal morbidity and mortality. Carbetocin is a synthetic analogue of oxytocin with a half-life approximately 4-10 times longer than that reported for oxytocin. It combines the safety and tolerability profile of oxytocin with the sustained uterotonic activity of injectable ergot alkaloids.

Objectives: The objective was to compare the effectiveness of carbetocin and oxytocin when administered after uncomplicated cesarean section (CS) for the prevention of postpartum haemorrhage.

Study Design: This is a prospective randomized controlled study comparing the use of carbetocin and oxytocin for the prevention of postpartum haemorrhage following caesarean section of patients admitted at Obstetrics & Gynaecology department of Dhaka National Medical Institute Hospital (DNMIH) from January 2014 to December 2014.

Materials and Methods: A total of 240 patients undergoing caesarean section were randomized to carbetocin (N=120) and oxytocin (N=120) for the prevention of postpartum haemorrhage and analyzed by intention to treat. Women in the carbetocin group (Group A) received a IV bolus of 100μg carbetocin and women in the oxytocin (control) group (Group B) received a IV bolus of 10 IU oxytocin. Baseline demographic and obstetric profile, indications for CS, estimated blood loss, hemoglobin, need for uterine massage, additional uterotonics, uterine tone and involution were compared immediate post-operative and 2 hours after.

Results: Baseline profiles were similar between the two groups. Post-operatively, hemoglobin levels in the carbetocin group were statistically significant and were associated with lesser need for additional uterotonic agents, uterine massage and a well contracted uterus immediate post-operative and 2 hours thereafter. The estimated blood loss was significantly lower in the carbetocin group and blood transfusion required more in oxytocin group however, the two groups did not significantly differ in terms of post-operative blood pressure.

Conclusion: Carbetocin as an uterotonic agent is an acceptable alternative for the prevention of postpartum bleeding in cesarean section. A cost-benefit analysis is mandated.

Keywords: Carbetocin, Oxytocin, Postpartum Hemorrhage, Uterine Tone, Uterine Involution, Randomized Trial.

Introduction

Every minute of every day, a woman dies in pregnancy or childbirth. The biggest killer is obstetric hemorrhage and the most frequent cause is uterine atony with an estimated mortality rate of 140,000 per year or 1 maternal death every 4 minutes.[1]

All pregnant women are at risk of complications during the 3rd stage of labour.[2] Maternal risk factors contribute to the development of postpartum hemorrhage.[3] For women undergoing delivery by cesarean section, there is an increased risk of postpartum hemorrhage compared to vaginal delivery.[4] It is therefore reasonable to advise

routine administration of a uterotonic drug immediately after the baby has been delivered by cesarean section.[4]

Prevention of post-partum haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. The primary PPH is defined as blood loss more than 500ml after vaginal delivery and more than 1000ml after caesarean section that occurs in the first 24 hours after delivery. Almost 500,000 women die for this potentially preventable cause each year, and upto an estimated quarter of these deaths uses to occur as a consequence of haemorrhage at time of delivery.[5] The first cause of haemorrhage at the time of delivery is uterine atony; therefore there is general agreement that management of third stage of labour rather than expectant management is recommended.[6,7,8]

Oxytocin is the drug of choice of postpartum hemorrhage. However, it has a shorter half life compared to carbetocin which has been reported to decrease the need for additional uterotonic and reduce bleeding due to uterine atony in cesarean section.[2] Carbetocin has been approved for use immediately following an elective cesarean section when local or spinal anesthesia has been administered.[9]

The practical guidelines on PPH of the Society of Obstetricians and Gynaecologists of Canada (SOGC)[10] suggest that the active management of the third stage of labour reduces the risk of PPH compared with the expectant management and should be offered and recommended to all women. Oxytocin (10 IU), administered intramuscularly, is the preferred medication for the prevention of PPH in low risk vaginal and caesarean deliveries. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL/hour) is an acceptable alternative for the active management. Carbetocin, given 100 µg as an IV bolus over 1 minute, instead of continuous oxytocin infusion, can be administered in elective caesarean section for the prevention of PPH, in the attempt to decrease the need for therapeutic uterotonics.

Carbetocin is a long acting synthetic oxytocin analogue, 1-deamino1-monocarbo (2-OMethyltyrosine) oxytocin, firstly described in 1987. It has a half life of 40 minutes (around 4-10 times longer than oxytocin) and uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100 µg.[11]

A single dose of carbetocin has been hypothysed to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section.[12]

Materials and Methods

Study design, setting and duration

This is a prospective randomized (interventional comparative) case controlled study conducted from January 2014 to December 2014 in the Obstetrics & Gynaecology department of Dhaka National Medical Institute Hospital (DNMIH). Two hundred and forty women undergoing caesarean were enrolled. A written consent was asked from the eligible women on admission.

Study Participants

Inclusion criteria

1. At least 18 years old
2. Term pregnancy (>37 weeks) undergoing caesarean section.
3. Women with risk factors for postpartum haemorrhage like repeat caesarean section, prolonged labour, foetal macrosomia,> gravida 3 and with malpresentation were also included in the study

Exclusion criteria

1. Hypersensitivity to oxytocin and carbetocin
2. Gestational age < 37 weeks
3. Women with placenta praevia or abruptio placenta as they were at a higher risk for PPH.
4. Women undergoing caesarean section with general anaesthesia because carbetocin is licensed for use with regional anaesthesia only
5. Significant disease (heart disease, thyroid disease, preeclampsia, diabetes mellitus, pulmonary disease, liver and renal disease)

Data collection

The study population was divided into two groups. Study group A received a single intravenous injection of 100 microgram carbetocin while study group B received 10IU of oxytocin I/V bolus at delivery of the baby.

The primary outcome of this study was the assessment of the uterine tone and involution within 5 minutes and 2 hours of delivery of placenta. Assessment of the uterine tone between the 2 groups was made by palpation of the uterus by the surgeon whether it was 1) flabby-soft atonic uterus, 2) firm- when gentle pressure depressed the uterus slightly or transiently or 3) well contracted uterus-hard, non-depressible uterus. Likewise, assessment of uterine involution was made with respect to umbilical point 1) below the umbilicus, 2) at the level of the umbilicus and 3) above the umbilicus. Also the

blood loss was checked immediately after caesarean section, defining as haemorrhage a blood loss in excess of 1000 ml or more. Blood loss was estimated by the surgeon in the usual way (visual estimation, number of used swabs and amount of aspirated blood). Vital signs particularly blood pressure recorded pre-operatively, after intervention, 2 hours and 24 hours post-operatively.

The later important outcome of this study was the need for additional uterotonics. The additional uterotonics included additional oxytocin dosage to the drip or giving ergometrine maleate IM/IV or 600 microgram Misoprostol per rectally. Blood transfusion was given to the 2 groups depending on the 24-hour post-operative haemoglobin and clinical assessment of the surgeon.

Statistical analysis

Statistical analysis was carried out by using the statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc. Chicago Illinois, USA). Descriptive statistics included mean and standard deviation for continuous variables. Discrete data were summarized as percentages.

Testing for sample homogeneity at baseline was done using chi-square test and independent t-test. Comparison of outcome was done using independent t-test for continuous data and chi-square for categorical data. All P-values <0.05 were considered significant.

Results

A total of 240 patients were included in the study population of which carbetocin (N=120) and oxytocin (N=120) were used for the prevention of PPH. At baseline there was no significant difference between carbetocin and oxytocin in terms of mean age, parity and gestational weeks. Table-I shows the demographic variables of the study patients. Mean age was found 25.22±4.675 years in Group A and 24.02±4.261 years in Group B. At baseline, there was no significant difference between carbetocin and oxytocin in terms of mean age (mean 25 versus 24, P= .34); gravidity (P=.17); parity (P=.43) and gestational weeks (P=.66). Preoperative systolic and diastolic blood pressure did not statistically differ between the two groups, (P= .32 and .90 respectively).

Tp value reached from independent t-test

Cp value reached from chi square test.

Table-I: Distribution of study population by demographic variable (N=240)

Demographic variables	Group A (N=120)	Group B (N=120)	P value
Age (years)			
≤ 20	26 (21.7%)	33 (27.5%)	.348T
21-30	82 (68.3%)	80 (66.7%)	
>30	12 (10.0%)	07 (05.8%)	
Mean ±SD	**25.22±4.675**	**24.02±4.261**	
Gravidity			
1	45 (37.5%)	61 (50.8%)	
2	28 (23.3%)	26 (21.7%)	
3	31 (25.8%)	25 (20.8%)	.176C
4	14 (11.7%)	06 (05.0%)	
5	01 (00.8%)	02 (01.7%)	
6	01 (00.8%)	-	
Mean±SD	**2.17±1.125**	**1.85±1.026**	
Parity			
1	52 (43.3%)	73 (60.8%)	
2	40 (33.3%)	28 (23.3%)	.433C
3	24 (20.0%)	17 (14.2%)	
4≥	04 (03.3%)	02 (01.7%)	
Mean±SD	**1.83±.863**	**1.57±.796**	
Gestational weeks			
>37-38	70 (58.3%)	72 (60.0%)	
39-40	44 (36.7%)	47 (39.2%)	.663T
41-42	06 (05.0%)	01 (00.8%)	
>42	00 (00.0%)	00 (00.0%)	
Mean±SD	**38.43±1.193**	**38.32±1.168**	
Preoperative SBP (Mean±SD)	**113.71±9.82**	**110.50±11.06**	**.324T**
Preoperative DBP Mean±SD	**74.04±7.198**	**72.21±7.498**	**.903T**

Table-II: Distribution of the study patients by indications of caesarean section.(N=240)

Indications	Group A (n= 120)	Group B (n= 120)	P value
Repeat CS	43 (35.8%)	32 (26.7%)	
CPD	17 (14.2%)	12 (10%)	
Foetal distress	13 (10.8%)	18 (15%)	
IUGR	05 (4.2%)	06 (5%)	
Less FM	09 (7.5%)	10 (8.3%)	
Malpresentation	07 (5.8%)	06 (5%)	**.832C**
Prolonged labour	09 (7.5%)	09 (7.5%)	
Oligohydramnios	06 (5%)	10 (8.3%)	
PROM	05 (4.2%)	08 (6.7%)	
Twin pregnancy	02 (1.7%)	03 (2.5%)	
Big baby	04 (3.3%)	06 (5%)	
Total	**120**	**120**	

The primary indications for caesarean section in this study included repeat CS followed by CPD and foetal distress respectively. Among repeat caesarean section two or more CS was found 12 (27.9%) in the carbetocin group and 8 (25%) in the oxytocin group. The indications of

caesarean section did not statistically differ between the two groups (P=.82)

Table-III: Associated risk factors

Risk factors	Group-A (n= 120)	Group-B (n= 120)	P value
Yes	65 (54.17%)	56 (46.67%)	.365[C]
No	55 (45.83%)	64 (53.33%)	

In this study, it was observed that 54.17% of patients had associated risk factors for PPH in the carbetocin group and 46.67% in the oxytocin group (P=.36) as shown in Table-III.

Table-IV: Distribution of the study patients by need for additional uterotonics and uterine massage

Additional uterotonics	Group-A (n= 120)	Group-B (n= 120)	P value
Yes	10 (8.3%)	62 (51.7%)	0.00[C]
No	110 (91.7%)	58 (48.3%)	
Uterine Massage			
Yes	19 (15.8%)	64 (53.3%)	0.00[C]
No	101 (84.2%)	56 (46.7%)	

A statistically lower proportion of women in the carbetocin group required additional uterotonic agents (mostly 20IU oxytocin in 1000 ml I/V fluid and very rarely Misoprostol and methylergometrine) post-operatively (8.3% versus 62%, P=.00). Therefore, significantly more women required additional uterotonic agents in the oxytocin group. Uterine massage was less required in the same group (15.8% versus 53.3%, P= .00)

Table-V: Observation of the uterine tone in study patients after intervention.

Uterine Tone	Group-A (n= 120)	Group-B (n= 120)	P value
Within 5 minutes			
Flabby	5 (4.2%)	12 (10.0%)	0.00[C]
Firm	14 (11.7%)	53 (44.2%)	
Well contracted	101 (84.2%)	55 (45.8%)	
2H Post-operative			
Flabby	00 (00%)	00 (00%)	0.002[C]
Firm	00 (00%)	9 (7.5%)	
Well contracted	120 (100%)	111 (92.5%)	

Table-VI: Observation of Uterine involution (position of uterine fundus) in relation to Umbilicus.

Involution	Group-A (n= 120)	Group-B (n= 120)	P value
Within 5 minutes			
Below umbilicus	101 (84.2%)	56 (46.7%)	.000[C]
At level of umbilicus	16 (13.3%)	50 (41.6%)	
above umbilicus	3 (2.5%)	14 (11.7%)	
Involution after 2 H			
Below umbilicus	114 (95.0%)	95 (79.2%)	.001[C]
At level of umbilicus	5 (4.2%)	23 (19.2%)	
Above umbilicus	1 (.8%)	2 (1.7%)	

The effects of the two drugs on uterine tone (Table-V) and uterine involution (Table-VI) are presented. A statistically significant higher proportion of uteri in the carbetocin group were well contracted immediately after the intervention was given (84.2% versus 45.8%, P=.000) and 2hours post-operative (100% versus 92.5% , P=.002).

Statistically significant higher proportions of uteri in the carbetocin group were below the umbilicus immediately after the intervention (84.2% versus 46.7%, P=.000) and 2 hours postoperative (95% versus 79.2%, P=.001).

Table-VII: Distribution of the study patients by estimated blood loss and need for blood transfusion.

	Group-A (n= 120)	Group-B (n= 120)	P value
Estimated Blood loss (ml) Mean (SD)			
< 500 ml	105 (87.5%)	92 (76.7%)	.029[C]
500-1000 ml	15 (12.5%)	28 (23.3%)	
>1000 ml	00 (00%)	00 (00%)	
Blood transfusion			
Yes	20 (16.7%)	28 (23.3%)	.197[C]
No	100 (83.3%)	92 (76.7%)	

The estimated blood loss was significantly lower in the carbetocin group. Blood loss <500 ml was 87.5% in group-A and 76.7 % in group-B respectively (P=.029). In oxytocin group 500-1000 ml of blood loss was found in 23.3% of patients .There was no difference in the incidence of primary postpartum haemorrhage (>1000ml) in both groups as shown in Table-VII. The two groups did not significantly differ in terms of blood transfusion requirements. (P=.197).

Table-VIII: Observation of the study patients after intervention- by haemodynamic status.

Blood Pressure	Group-A (n= 120)	Group-B (n= 120)	P value
Immediate -within 5 min.			
Systolic BP Mean±SD	107.38±5.422	102.46±7.189	.036[T]
Diastolic BP Mean±SD	68.71±7.174	67.83±4.882	.111[T]
2H Post –operative			
Systolic BP Mean±SD	112.58±4.978	108.04±5.473	.906[T]
Diastolic BP Mean±SD	71.45±3.495	71.04±3.362	.386[T]
24H Post-operative			
Systolic BP Mean±SD	114.46±5.531	110.54±5.492	.000[T]
Diastolic BP Mean±SD	72.96±4.514	74.25±4.964	.000[T]

Regarding the haemodynamic effects of carbetocin and oxytocin, both drugs have a hypotensive effect. Systolic and diastolic blood pressure was not significantly different immediate post intervention between the two groups and 2 hours post-operative (Table-VIII).The mean systolic BP after 24 hours of delivery was 114.46±5.531 in carbetocin group and 110.54±5.492 in oxytocin group (P=.001), likewise mean diastolic BP was 72.96±4.514 versus 74.25±4.964 (P=.000) in both groups respectively.

Table-IX: Preoperative and postoperative Haemoglobin levels in patients given carbetocin versus oxytocin.

Hb levels (gm/dl)	Group-A (n= 120)	Group-B (n= 120)	P value
Preoperative Mean±SD	10.85±.805	10.68±.790	.832[C]
24HPost-operative Mean±SD	10.07±.797	9.74±.650	.025[T]
HbDifference Mean±SD	0.773±.296	0.936±.395	.004[T]

In both study group haemoglobin levels before and after 24 hours apart from delivery were similar, confirming no significant difference in the level of blood loss (Table-IX), although we found a tangentially lower Hb decrease at 24 hours from delivery in the carbetocin group (0.773 g/dl vs 0.936g/dl, P=.004).

Discussion

This interventional comparative study was carried out with an aim to compare the haemodynamic effects of carbetocin and oxytocin (effects on blood pressure) and to assess the efficacy of carbetocin over oxytocin in terms of intrapartum blood loss and the additional uterotonic needed to prevent PPH in caesarean section specially in high risk cases.

The primary outcome of the study is the evaluation of immediate haemodynamic effects of carbetocin administration. We know that the haemodynamic effects of an oxytocin bolus consists of systemic vasodilation with hypotension, tachycardia and increase of cardiac output, resulting in dose-dependent hypotension and tachycardia.[13,14,15]

Larciprete et al. obtained that systolic blood pressure was lower in the oxytocin group at the 5th minute after administration, at uterine closure time and at 12 hours post operatively.[16]

The present clinical trial has shown that standard doses of carbetocin prevented significant decreases in haemoglobin post-operatively by having minimal blood loss. Carbetocin also decreased the need for additional uterotonics, uterine massage and the avoidance of blood transfusion. Furthermore, carbetocin was associated with good uterine involution and tone immediate post-delivery when compared to oxytocin.

In this current study, it is observed that 16.7 % of patient needed blood transfusion in Group-A and 23.3 % in Group-B. Need for blood transfusion is higher in oxytocin group, but not statistically significant (p>0.05) between the two groups.

Reyes et al. study found 10.3% need for blood transfusion in oxytocin group but not needed in carbetocin group.[17]

In another study, Holleboom et al. administrated blood transfusion in 2.2% of the cases in the carbetocin group and 2.7% in the oxytocin group (p>0.05).[18]

In this study it was observed that ten (8.3%) patients need for additional uterotonic in carbetocin group and 62 (51.7%) in oxytocin group. The difference was statistically significant (P<0.05) between the two groups. The study of Su LL showed that among the women who underwent elective CS, carbetocin resulted in a statistically significant reduction in the need for therapeutic uterotonics compared to oxytocin, but there was no difference in the incidence of postpartum hemorrhage.[19] This review revealed that compared to oxytocin, carbetocin was also associated with a reduced need for uterine massage following both caesarean delivery (RR 0.54; 95% CI 0.37 to 0.79; two trials, 739 women) and vaginal delivery (RR 0.70; 95% CI 0.51to 0.94; one trial 160 women). In our study, after carbetocin administration, the need for uterine massage was 19(15.8%) and with oxytocin it was 64(53.3%).The difference was statistically significant (P<0.05) between the two groups.

The position of the fundus relative to the position of the umbilicus is an indicator of the state of uterine involution. One study showed that the uterine involution in primiparous and premature vaginal deliveries starts from lower values of the symphysis pubis-uterine fundus than in the multiparous and in cases of term delivery. The rates of uterine involution in primiparous increases gradually in the earliest day after delivery (from 0.95 to 1.6 cm per day), while in multiparous this increase starts after the 4th day. When caesarean section is performed and in cases of preterm delivery, the rates of uterine involution are delayed and uneven.[20]

A study by Borruto, et al. reported that the fundus was below the umbilicus in more patients who received carbetocin at 0, 2, 6, and 24 hours on the ward ($P<0.05$). The latter study concluded that a single 100mcg IV injection of carbetocin was as effective as a continuous 2-h infusion of oxytocin in controlling intraoperative blood loss after placental delivery. Mean blood loss after carbetocin administration was 30ml less than after oxytocin administration ($P=0.5$). The percentage of patients with blood loss ≤500ml was greater with carbetocin.[21] We do reach the same conclusion with many other researches.[9,12]

The clinical advantage of carbetocin over oxytocin has been compared. Clinicians prefer to employ carbetocin because of its longer half-life which is approximately 4-10 times longer than that reported for oxytocin. It combines the safety and tolerability profile of oxytocin with the sustained uterotonic activity of injectable ergot alkaloids.

Furthermore, carbetocin can be administered as a single dose injection either intravenously or intramuscularly rather than an infusion over several hours as in case with oxytocin. Another clinical advantage of carbetocin in the prevention of post-partum bleeding is that it has long duration of action compared with intravenous oxytocin alone and a better cardiovascular side effect profile compared with syntometrine.[22,23]

Conclusion

This study was undertaken to determine the safety and effectiveness of carbetocin over oxytocin for the prevention of postpartum haemorrhage. Carbetocin is associated with reduction in estimated blood loss, resulting to a significantly minimum drop in haemoglobin level. It also resulted to good uterine tone and involution as early as post delivery of the neonate and prevented the additional administration of uterotonic agents. A statistically significant higher proportion of uteri in the carbetocin group were well contracted after the delivery of the neonate and 2 hours postoperative. Carbetocin enhanced early postpartum uterine involution. A statistically significant higher proportion of uteri in the carbetocin group were below the umbilicus immediately after the intervention. Therefore, it can be concluded that a single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone, with a similar safety profile and minor antidiuretic effect in the third stage and in the first 24 hours after delivery.

Recommendations

Carbetocin should be considered as a good alternative to the conventional uterotonic agents used in managing the third stage of labour and to prevent post-partum haemorrhage; however its cost prohibits clinicians from prescribing it. Similarly, even if there is a general safety profile for patients with high cardiovascular risk, extreme caution is practiced in its use during hypertension- complicated pregnancies. Further studies on the use of carbetocin in women suspected or diagnosed to have hypertensive disorder or pre-eclampsia is need to see if it could become the drug of choice for this subgroup of pregnant women

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