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Original Articles

For Postpartum Haemorrhage Prophylaxis between Carbetocin and Oxytocin - A Study in Tertiary Care Hospital

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Abstract

Postpartum haemorrhage is a major cause of maternal deaths and ill health in low- and middle-income countries. Active management of the third stage of labour, which is generally used to reduce blood loss at birth, consists of giving the mother a drug that helps the uterus to contract, early cord clamping and controlled cord traction to deliver the placenta. Different drugs have been tried and generally either intramuscular oxytocin or intramuscular syntometrine is given. Carbetocin is an oxytocin agonist. Oxytocin agonists are a group of drugs that mimic the oxytocin action, oxytocin being the natural hormone that helps to reduce blood loss at birth. The comparison between intramuscular carbetocin and oxytocin showed carbetocin less likely to have heavy bleeding and less likely to require other medications to produce uterine contractions. The study compared carbetocin against oxytocin given in third stage of labour. Therefore, this will be rationale to carry out a study to find out the safety and effectiveness of carbetocin over oxytocin as prophylaxis of post-partum haemorrahge.

Keywords: *Postpartum haemorrhage (PPH); Oxytocin; Carbetocin.*

Introduction:

Postpartum hemorrhage (PPH), defined as bleeding from the genital tract of 1000 mL or more in the first 24 hours following delivery of the baby[1]. Postpartum hemorrhage is an important cause of maternal morbidity and mortality worldwide, accounting for at least 150,000 maternal deaths every year. The World Health Organization (WHO) estimates that 20 million morbidities every year result from postpartum hemorrhage[2]. The decreased prevalence of postpartum hemorrhage in most developed parts of the world probably is due to better management of the third stage of labor. However, this is not true in developing countries. In Africa and Asia, where most maternal deaths occur, PPH accounts for more than 30% of all maternal deaths[3]. The risk of dying from postpartum hemorrhage depends on the amount and rate of blood loss and also on the health status of the mother. Carbetocin is a long-acting synthetic octapeptide analogue of oxytocin with agonist properties. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within two minutes, lasting six minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produced tetanic contractions in less than two minutes, lasting about 11 minutes, and followed by rhythmic contractions for an additional two hours. The prolonged duration of

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activity after intramuscular compared with the intravenous carbetocin was significant (4). In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum, in terms of both amplitude and frequency of contractions. The potential advantage of intramuscular carbetocin over intramuscular oxytocin is its longer duration of action. Its relative lack of gastrointestinal and cardiovascular side effects also proved advantageous compared to syntometrine and other ergot alkaloids. A systematic review of the literature for studies on this subject was conducted and performed a meta-analysis in order to assess the effectiveness and safety of carbetocin in the prevention of PPH[5]. Till now it is recommended that Oxytocin should be used as oxytocic agent either in form of intramuscular injection or intravenous infusion (6). However, it was noticed in medical audit that oxytocic agents were usually used for longer period like 4 hours on an average[7]. With the use of Carbetocin uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100μg. 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. Several data of literature[7,8] suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum haemorrhage. The purpose of this study is to determine the effectiveness and safety of carbetocin versus oxytocin for the prevention of post-partum haemorrahge.

Materials and Methods:

It was a Cross sectional comparative study done in Department of Obstetrics & Gynecology, Chittagong Medical College and Hospital (CMCH), Chattogram, Bangladesh from October 2019 to March 2020. Pregnant women admitted for delivery in CMCH, who were specially at risk of PPH, during the study period were selected as study population. Sample size was determined by power analysis for a two proportion.

Formula for sample size determination for two proportions

$$n = \frac{P_1(1-P_1)+P_2(1-P_2)}{(P_1-P_2)^2}\left(Z_\alpha + Z_\beta\right)^2$$

P_1= Additional oxytocics given in 27.0% (0.27) in oxytocin group

Carbetocin reduced the use of additional oxytocics from 10.1 to 4.7% (7) and hypothesised that carbetocin could halve this figure to 6%, which was a clinically significant finding

P_2 = Additional oxytocics in 6.0% (0.06) carbetocin group

Assuming α =0·05, power=0·80, and equal sample sizes in the two groups.

$$n = \frac{0.27(1-0.27)+0.06(1-0.06)}{(0.27-0.06)^2}\,x\left(1.96+0.85\right)^2$$

n = 45.01

= 45 in each group and the total sample size were 90= (45x2)

Sampling Method: The purposive sampling method was followed in this study.

Inclusion Criteria

Women with risk factors for PPH like multiple pregnancy, induction of labour, prolonged labour, precipitate labour, two or more previous caesarean section, presence of uterine fibroids, previous myomectomy, past history of PPH, fetal macrosomia and fetal malformations associated with polyhydramnios or undergoing elective or emergency caesarean section under regional anaesthesia.

Exclusion criteria:

1. Women having chance of PPH other than atonic cause like heart disease, severe PE, eclampsia, placenta previa, gestational age less than 37 weeks etc.
2. Women/attendants who were not interested to give consent to participate in the study.
3. Women having history of bronchial asthma or hypersensitive reaction or epilepsy.
4. PPH due to cervical tear and vaginal lacerations.
5. Women with history of hypersensitivity to carbetocin.

Outcome Variables

Outcome variables were estimated blood loss, vital signs during and after the operation, uterine tone, use of additional oxytotics, primary PPH, incidence of blood transfusion, adverse effect, difference in antepartum and postpartum haemoglobin and cost.

Procedures of Preparing and Organizing Materials

Data was collected by interview, physical & lab examination using a structured questionnaire containing all the variables of interest. Data processing work was of registration of schedules, editing, coding and computerization, preparation of dummy tables, analysis and matching data. The technical matter of editing, coding and computerization was looked by self.

Equipment to be used

A semi-structured case record form was prepared after pretesting which was containing patient profile & details about use of carbetocin or oxytocin in active management of third stage of labour.

Procedures of Collecting Data

Demographic, pregnancy and postnatal data were recorded by the researchers on the study proformas. Women in the carbetocin group (group I) received a bolus of 100 ìg IV carbetocin and in the control group (group II) received 10 IU of oxytocin IM bolus after delivery (vaginal delivery or caesarean section) of the baby. The primary outcome of this study was the evaluation of uterine tone (standardized as Very good, Good, Sufficient, Atony), uterine height (with respect to the umbilical point, UP) was monitored within 5 min, 2 hours of delivery of placenta. Also, the blood loss was checked immediately after delivery, defining as haemorrhage as blood loss in excess of 1000 ml or more (9). Blood loss was estimated by the surgeon in the usual way (visual estimation, by measuring soiled sanitary towel-30 ml, saturated sanitary towel-100 ml, saturated small swab 10X10 cm- 60 ml, in continence pad- 250 ml, saturated large swab 45X45 cm- 350 ml, 100 cm diameter floor spill- 1500 ml, PPH on bed only - 1000 ml, PPH spilling to floor - 2000 ml, full kidney dish- 500 as very good, Good, Sufficient, Atony). The later important outcome of this study was the need for additional uterotonic agents and the evaluation of the drop in haemoglobin level by comparing the haemoglobin concentration on admission with the measure at 24 hours after delivery.

Procedure of Data Analysis

Statistical analysis was carried out by using the Statistical Package for Social Sciences version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated by frequencies and percentages. The quantitative observations were indicated by frequencies and percentages. The results were presented in tables, figures, diagrams. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Student t-test was used for continuous variables. P values <0.05 was considered as statistically significant.

Ethical Implications

Ethical clearance was taken from the ethical committee of Chittagong medical college hospital for approval. Verbal consent was taken from the patients before enrolling them. The respondents were told that they were at liberty to participate and to decline to answer any question during the study. The respondents were given assurance that the findings of the interview or investigation or examination was not used/ disclosed to any unauthorized person or authority other than the research purpose.

Results:

Table I shows characteristics of the study population. The difference was not statistically significant (p>0.05).

Table II shows majority (84.4%) patients was gestational age 38-40 weeks in group I and 88.9% in group II. The mean gestational age was found 40.1±1.8 weeks in group I and 40.2±1.7 weeks in group II. The mean gestational age was not statistically significant (p>0.05).

Two third (66.7%) patients had normal vaginal delivery in group I and 29 (64.4%) in group II. The difference was not statistically significant (p>0.05).

Table V shows associated risk factors of the study patients. The difference was not statistically significant (p>0.05).

Table V shows 27 (60.0%) patients had labour pain in group I and 16 (35.6%) in group II, which was statistically significant (p<0.05) but other indication was not statistically significant (p>0.05).

Almost three fourth (73.3%) patients had contracted uterine tone within 5 min in group I and 30 (66.7%) in group II. All (100.0%) patients had contracted uterine tone after 2 hours in group I and group II respectively. The difference was not statistically significant (p>0.05).

26.7% patients need for additional utero tonic in group I and 33.3% in group II. The difference was not statistically significant (p>0.05).

12 (26.7%) patients had primary PPH in group I and 19 (42.2%) in group II. Blood transfusion of the study patients, 11.1% patients need blood transfusion in group I and 17.8% in group II, which was not statistically significant (p>0.05).

Table IX shows maternal condition 24 hours after delivery of the study patients. The mean pulse was statistically significant (p<0.05) but other maternal condition 24 hours after delivery were not statistically significant (p>0.05).

Table-I

Distribution of the study patients by demographic variable (n=90)

Characteristics	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Age (years)					
≤20	12	26.7	8	17.8	
21-30	29	64.4	33	73.3	
>30	4	8.9	4	8.9	
Mean±SD	24.5±4.6		24.8±3.6		[a]0.731[ns]
Range (min, max)	19, 40		19, 32		
Married for (years)					
≤5	36	80.0	37	82.2	
6-10	6	13.3	8	17.8	
>10	3	6.7	0	0.0	
Mean±SD	4.1±4.0		4.5±4.2		[a]0.644[ns]
Range (min, max)	1, 18		1, 10		
Area of living					
Rural	12	26.7	17	37.8	
Semi urban	16	35.6	12	26.7	[b]0.480[ns]
Urban	17	37.8	16	35.6	
Educational status					
Illiterate	19	42.2	24	53.3	
Primary	16	35.6	17	37.8	[b]0.203[ns]
SSC	10	22.2	4	8.9	
Economic status					
Low	31	68.9	32	71.1	[b]0.818[ns]
Middle	14	31.1	13	28.9	
Parity					
Primi	23	51.1	29	64.4	
					0.200[ns]
Multi	22	48.9	16	35.6	

ns= not significant; [a] P value reached from unpaired t-test; [b] P value reached from chi square test
Group I= Carbetocin; Group II= Oxytocin

Table-II

Distribution of the study patients by gestational age (n=90)

Gestational age	Group-I (n=45)		Group-II (n=45)		P value
(weeks)	n	%	n	%	
38-42 (Term)	38	84.4	40	88.9	
>42 (Post term)	7	15.6	5	11.1	
Mean±SD	40.1±1.8		40.2±1.7		0.787[ns]
Range (min, max)	38, 44		38, 44		

ns= not significant; P value reached from unpaired t-test

Table-III

Distribution of the study patients by mode of delivery (n=90)

Mode of delivery	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
NVD	30	66.7	29	64.4	
LSCS	10	22.2	11	24.5	0.968[ns]
Ventous	5	11.1	5	11.1	

ns= not significant; P value reached from chi square test

Table-IV

Distribution of the study patients by diagnosis (n=90)

Diagnosis	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Labour pain	27	60.0	16	35.6	0.020[s]
Fetal distress	5	11.1	5	11.1	1.000[ns]
Prolong labour pain	5	11.1	5	11.1	1.000[ns]
Multiple pregnancy	6	13.3	5	11.1	0.748[ns]
Diabetic mellitus	4	8.9	5	11.1	0.500[ns]
CPD	4	8.9	3	6.7	0.500[ns]
Less fetal movement	1	2.2	2	4.4	0.500[ns]
Unfavorable cervix	1	2.2	2	4.4	0.500[ns]
PROM	2	4.4	1	2.2	0.500[ns]
IUD 1	2.2	3	6.7	0.308[ns]	
BOH	1	2.2	2	4.4	0.500[ns]
Breech	3	6.7	2	4.4	0.500[ns]

s=significant, ns= not significant; P value reached from chi square test

Table-V

Distribution of the study patients by associated risk factors (n=90)

Associated risk factors	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Induction of labour	12	26.17	13	28.9	0.814[ns]
Augmentation	15	33.3	12	26.7	0.490[ns]
Multigravida	22	48.9	16	35.6	0.200[ns]
Prolong labour	5	11.1	5	11.1	1.000[ns]
Multiple pregnancy	6	13.3	5	11.1	0.748[ns]
DM with polyhydromnion	1	2.2	2	4.4	0.500[ns]
DM with macrosomia	2	4.4	0	0.0	0.247[ns]

ns= not significant; P value reached from chi square test

Table-VI

Distribution of the study patients by observation (n=90)

Observation	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Uterine tone within 5 min					
Contracted	33	73.3	30	66.7	0.490[s]
Flabby	12	26.7	15	33.3	
Uterine tone after 2 hours					
Contracted	45	100.0	45	100.0	-
Flabby	0	0.0	0	0.0	

ns= not significant; P value reached from chi square test

Table-VII

Distribution of the study patients by need for additional utero tonic (n=90)

Need for additional utero tonic	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Yes	12	26.7	15	33.3	0.490[ns]
No	33	73.3	30	66.7	
If yes					
Injection Ergometrine	12	26.7	15	33.3	
Tab misoprostol	11	24.4	12	26.7	
Balloon catheterization	1	2.2	3	6.7	

ns= not significant; P value reached from chi square test

Table-VIII

Distribution of the study patients by maternal blood loss and need for blood transfusion (n=90)

Maternal blood loss	Group-I (n=45)		Group-II (n=45)		P value
	n	%	n	%	
Average	33	73.3	26	57.8	0.120[ns]
Primary PPH	12	26.7	19	42.2	
Need for blood transfusion					
Yes	5	11.1	8	17.8	0.368[ns]
No	40	88.9	37	82.2	

ns= not significant; P value reached from chi square test

Table-IX

Distribution of the study patients by maternal condition 24 hrs after delivery (n=98)

Maternal condition 24 hrs after delivery	Group-I (n=49) Mean±SD		Group-II (n=49) Mean±SD		P value
Pulse (bpm)	89.0±5.7		91.6±5.7		[a]0.048[s]
Range (min, max)	80, 100		80, 100		
Systolic BP (mmHg)	114.2±8.9		116.2±9.8		[a]0.313[ns]
Range (min, max)	100, 130		100, 140		
Diastolic BP (mmHg)	77.3±6.9		78.9±8.0		[a]0.315[ns]
Range (min, max)	60, 80		70, 100		
Fundal height (weeks)	23.4±1.4		22.8±2.1		[a]0.114[ns]
Range (min, max)	20, 28		18, 24		
Anaemia					
Mild	1	2.2	5	11.1	[b]0.101[ns]
Absent	44	97.8	40	88.9	
PV bleeding					
Average	43	95.6	37	82.2	[b]0.044[s]
More than average	2	4.4	8	17.8	

s=significant; ns= not significant; [a] P value reached from unpaired t-test; [b] P value reached from chi square test

Discussion:

This cross-sectional comparative study was carried out with an aim to compare the efficacy of carbetocin over oxytocin in terms of intrapartum blood loss and the additional stat uterotonic needed at high risk of post-partum haemorrhage and also to evaluate the socio-demographic profile and clinical presentation of patients who are at risk of PPH.

In this research work it was observed that sociodemographic profile that is mean age, educational, social status and parity was not statistically significant in two groups (p>0.05). Mean age was found 24.5±4.6 years in group I and 24.8±3.6 years in group II. The mean marital age was found 4.1±4.0 years in group I and 4.5±4.2 years in group II. Reyes et al. (10) found the mean age was 26.52±9.12 years in Carbetocin group and 26.78±8.39 years in Oxytocin group. The difference was not statistically significant (p>0.05) between two groups, which is closely resembled with the present study, 51.1% patients had primi para in group I and 29(64.4%) in group II. The difference was not statistically significant (p>0.05) between two groups. Holleboom et al. (11) had undertaken a study and observed multigravida 28.3% and 23.1% in carbetocin and oxytocin group respectively. The difference was not statistically significant (p>0.05) between two groups. In another study, it was observed multigravida was 46.0% in oxytocin group.

Majority (84.4%) patients was gestational age 38-40 weeks in group I and 40(88.9%) in group II. The mean gestational age was found 40.1±1.8 weeks in group I and 40.2±1.7 weeks in group II. The mean gestational age was not statistically significant (p>0.05) between two groups. Holleboom et al. (11) found that the mean gestational age was found 38.9±1.0 weeks in Carbetocin group and 38.8±1.0 weeks in group Oxytocin group. The difference was not statistically significant (p>0.05) between two groups, which is consistent with the present study. Similarly, Larciprete et al. (6) and Reyes et al. (10) had observed the identical mean gestational age of their studied patients, thus support the present study. Two third (66.7%) patients had normal vaginal delivery in group I and 29 (64.4%) in group II. The difference was not statistically significant (p>0.05) between two groups. Similarly, Larciprete et al. (6) found two or more C/S was 33.3% in carbetocin group and 23.5% in oxytocin group.

Almost three fourth (73.3%) patients had contracted uterine tone within 5 min in group I and 66.7% in group II. All (100.0%) patients had contracted uterine tone after 2 hours in group I and group II respectively. The difference was not statistically significant (p>0.05). The uterine tone remained well contracted in both the groups even after 24 hours after caesarean section. Physician's subjective experience with carbetocin was

rated as good in 92.0% of the cases[11]. In another study Larciprete et al. (6) observed there was a significant difference in the uterine tone. The uterine contractility was better in the carbetocin group at- 2, 12 and 24 hours after caesarean section, and the difference was statistically significant at 24 hours ($p<0.05$).

Twelve (26.7%) patients need for additional utero tonic in group I and 15 (33.3%) in group II. The difference was not statistically significant ($p>0.05$). In another study Reyes et al. (10) found need for additional uterotonics was 3.4% in oxytocin group, which differ with the current study. 26.7% patients had primary PPH in group I and 42.2% in group II. PPH was higher in group II but not statistically significant ($p>0.05$) between two groups. Holleboom et al. (11) showed the proportion of subjects with blood loss [500 ml (carbetocin 28.8%, oxytocin 26.9%) and [1,000 ml (carbetocin 7.8%, oxytocin 8.4%) was also comparable for both groups. Larciprete et al. (6) reported that 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. In fact, the investigators did not demonstrate any difference in the amount of blood loss after caesarean section and in the drop of haemoglobin level within 2 hours and 24 hours, but we showed in the oxytocin group a significant need (23.5%) of additional uterotonic agents. Previous studies have shown that carbetocin could induce maternal tachycardia and facial flushing[12], but none in our carbetocin subgroup had these adverse events.

This work shows that 11.1% patients need for blood transfusion in group I and 17.8% in group II. Need for blood transfusion was higher in group II, but not statistically significant ($p>0.05$) between two groups, which is similar with Reyes et al.[10] study, where they found 10.3% need for blood transfusions in oxytocin group. Holleboom et al.[11] administrated blood transfusions in 2.2% of the cases in the carbetocin group and 2.7% in the oxytocin group ($p>0.05$). Reyes et al. (10) found that 3 (10.3%) patients needed blood transfusion in Oxytocin group but not needed in Carbetocin group. The difference was not statistically significant ($p>0.05$) between two groups. In another study Attilakos et al. (7) observed that blood transfusion was needed 4 (2.1%) in carbetocin group and 5(2.6%) in oxytocin group. The difference was not statistically significant ($p>0.05$) between two groups, which are comparable with the current study. In this series it was observed that all (100.0%) patients had stable hemodynamic status in group I and group II respectively.

Conclusion:

Primary PPH was more than one fourth in patients treated with carbetocin and 42.2% in patients treated with oxytocin group. All patients had stable haemo dynamic status in both groups. Blood pressure and fundal height were almost similar between two groups. Pulse rate was significantly higher in oxytocin group. PV bleeding was significantly less in carbetocin group. Additional oxytocics and need of blood transfusion were minimum in carbetocin group. Side effect were less in carbetocin group. 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.

Limitations of the Study

1. The study population was selected from one selected hospital, so that the results of the study may not reflect the exact picture of the country.
2. The present study was conducted at a very short period of time with limited fund.
3. The sample size was limited. If the study could be done in a large group of people then the results of the study would be more producible.
4. Potential bias in assessment of blood loss and use of additional oxytocics could not be eliminated.
5. The amount of blood loss was assessed clinically and not by quantitative parameters.

Recommendations

A single intravenous injection of 100 ìgm of carbetocin immediately after birth of the baby in pregnant women undergoing caesarean section under spinal anesthesia can be used effectively and safely. Further studies can be undertaken by including large number of patients.

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