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Role of Carbetocin over Oxytocin Followed by Caesarian Section

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Abstract **Original Research Article**

Introduction: Prevention of post-partum hemorrhage (PPH) is a major issue due to its impact on maternal mortality and morbidity. Primary post-partum hemorrhage (PPH) is the leading cause of maternal mortality in low- income countries and the primary cause of nearly one quarter of all maternal deaths globally. ***Aim of the Study:*** The aim of this study was to assess the effect of carbetocin over oxytocin in consequence of PPH. ***Methods:*** This was a cross- sectional study conducted in the Department of Obstetrics and Gynecology at Chattogram Medical College Hospital (CMCH), Chittagong, Bangladesh during the period from March 2018 to February 2019.Study population was the patient (n=100) with the risk of develops primary PPH following cesarean section. Women fulfilling inclusion criteria was included in the study and divided into 2 groups- Experimental group (n=50 cases) received 100µg of IV carbetocin through intravenous route; Control group (n= 50 cases) received 10 IU oxytocin through intravenous route. Data collection was done by the researcher after taking the written consent. Statistical analyses were done by SPSS 23. ***Result:*** In total 100 patients from both the groups completed the study. In our study we found the mean age was 25.20±5.43 years in carbetocin group and 25.90±5.83 years in oxytocin group. Regarding obstetric indications in carbetocin group majority (28.0%) patients had prolonged labour, 13 (26.0%) P/H/O C/S, 9 (18.0%) obstructed labour. In oxytocin group majority (38.0%) patients had P/H/O C/S, 14 (28.0%) had obstructed labour and 8 (16.0%) had prolonged labour. In 2 hours post-operative mean pulse was found 71.6±7.3 beats/min in carbetocin group and 68.9±5.9 beats/min in oxytocin group. ***Conclusion:*** In our study, it can be concluded that Carbetocin is as effective and safe as Oxytocin in the prevention of PPH following caesarean section. Carbetocin is more heat stable than oxytocin which is of crucial importance to resource poor settings like us. So use of Carbetocin is more beneficial than oxytocin in prevention of PPH.

Keywords: PPH, Obstetric, Indication, Uterotonics.

INTRODUCTION

Primary post-partum hemorrhage (PPH) is the major cause of maternal mortality and morbidity. Post - partum hemorrhage is commonly defined as a blood loss of 500 ml or more within 24 hours after birth (WHO, 2012) [1]. In women with lower body mass (e.g. Less than 60 kg), a lower level of blood loss may be clinically significant [2]. Primary post-partum hemorrhage (PPH) is the leading cause of maternal mortality in low-income countries and the primary cause of nearly one quarter of all maternal deaths globally. Most of them could be avoided through the use of prophylactic uterotonic during the third stage of labour and by timely and appropriate management (WHO, 2012) [3]. According to the United Nations Population Fund (UNFPA) 2017 report, "About one woman dies in every two minutes. Most of these deaths are entirely preventable." [4] Patients known to be high risk for developing PPH are prolonged labour, obstructed labour, multipara, placenta previa, placental abruption, multiple gestation, prolonged rupture of membranes, polyhydramnios, intra amniotic infection, fibroids, uterine anomalies, obesity (BMI >35), anemia, < 9 g/dl, previous H/O PPH and age > 40 years (WHO, 2012) [5].With the introduction of the sustainable

development agenda which will cover the period 2016-2030, the international community has been set a new target - to reduce the global maternal mortality ratio to less than 70 per 1,00,000 live births, with no country having a maternal mortality rate of more than twice the global average. Post-partum hemorrhage (PPH) is still the leading direct cause of maternal mortality and morbidity globally [6]. In 2016 maternal mortality and health care survey of Bangladesh assess the recent progress in maternal health to create the baseline for health population and nutritional program (HPNSP) and sustainable development goals. They found that between 2001-2010 MMR declined from 322 to 194 per 1,00,000 live birth, this was a remarkable progress. But MMR did not show considerable progress between 2010 and 2016 which was 196 /1,00,000 live birth. Hemorrhage account for 31% percent of MMR. The risk of MMR remains unchanged between 2010 and 2016. (BMMS Survey, 2016) [7]. For prevention of post-partum hemorrhage the prophylactic use of uterotonic agents to enhance natural uterine contraction and retraction following caesarean section and in the third stage of labour following vaginal delivery. Oxytocin is synthesized by specialized cells in the supra optic and paraventricular nucleus of the hypothalamus. Oxytocin acts as a neurotransmitter in the brain. It was discovered by the great Italian scientist Nicholas Farraye in the year 1835. It has a molecular formula of C43H66N12O12S 2. The structure of oxytocin is similar to that of vasopressin but with a few differences. The well-known function of oxytocin is uterine contraction and milk ejection. Oxytocin is the most widely used uterotonic agent but only has a half-life of 4-10 min [8]. Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered 100µg as a single-dose injection, either intravenously or intramuscularly [9, 10]. PPH is defined as blood loss of 500 ml or more and severe PPH as 1000 ml or more in the third stage of labour maternal mortality rates are much lower among developed countries, but hemorrhage remains one of the top causes of maternal deaths over the years [11]. The maternal mortality is highest during the post-partum period. Which contributes about 31% of total MMR This pattern is consistent in 2001, 2010 and 2016. Uterine atony accounts for a significant majority of PPH (BMMS 2016). Prevention of PPH is therefore of significant importance in the pursuit of improved health care for women. This is particularly important in the current context of increasing caesarean delivery rate (Villar 2006), with operative delivery being a recognized risk factor for PPH. Active management of the third stage of labour has been proven to be effective in the prevention of PPH (Begley 2008) [12, 13]. Though there has been an amazing improvement in the management of PPH in recent times, it still contributes to 25% of all maternal deaths worldwide [14]. Cesarean section is a recognized risk factor for PPH and the rate of cesarean delivery has shoot up over the past four decades above 20% in most developed countries [15].

OBJECTIVE OF THE STUDY

The objective of the study was to assess the effect of carbetocin over oxytocin in consequence of PPH.

METHODOLOGY & MATERIALS

This was a cross-sectional study conducted in the Department of Obstetrics and Gynecology at Chattogram Medical College Hospital (CMCH), Chittagong, Bangladesh during the period from March 2018 to February 2019. There were total 100 women in our study. These are the following criteria to be eligible for the enrollment as our study participants: a) Women who had gestational age between 37-40 weeks; b) Women with risk factors for primary post- partum haemorrhage such as: multiple pregnancy, two or more previous caesarean section; c) Women with presence of uterine fibroids & placenta previa; d) Women with previous myomectomy& past history of PPH; e) Women with fetal macrosomia and fetal malformations associated with polyhydramnios; And a) Women with history of hypersensitivity to carbetocin according to the Br National Formulary; b) Women with any previous surgical history; c) Women with presence of hypertension, preeclampsia; d) Women with epilepsy and sensitivity to general anesthesia; e) Women with any history acute illness (e.g., renal or pancreatic diseases, ischemic heart disease etc.) were excluded from our study. Women fulfilling inclusion criteria were included in the study and they were divided into 2 groups- Experimental group (n=50 cases) received 100µg of IV carbetocin through intravenous route and Control group (n= 50 cases) received 10 IU oxytocin through intravenous route. The samples were taken after taking the written informed consent from the patients.

Obstetric Indications

Prolonged labour, obstructed labour, multipara, placenta previa, placental abruption, multiple gestation, prolonged rapture of membrane, intra amniotic infection, polyhydramnios, pregnancy with fibroids, uterine anomalies, previous history of Caesarian section, obesity, anemia, previous history of PPH and age>40 years.

Data Analysis

Data was processed and analyzed by using computer bases software SPSS- 23.0(statistical package for social science). Qualitative variables were analyzed by chi-square test and continuous variables were analyzed by t- test. The statistical terms was included in this study are mean, standard deviation, percentage. Statistical significance was set at $p<0.05$.

RESULT

Table 1: Distribution of age and pulse & blood pressure of the patient by groups (n=100)

	Carbetocin (n=50)	Oxytocin (n=50)	P value
	mean±SD	mean±SD	
Age	25.20±5.43	25.90±5.83	
Pulse (beats/min)	93.96±12.79	94.20±11.78	0.922
SBP (mmHg)	116.00±15.38	114.40±13.42	0.581
DBP (mmHg)	74.00±8.80	72.60±7.77	0.401

Table 2: Distribution of obstetric parameters and gestational age by groups (n=100)

Obstetric Parameters	Carbetocin (n=50)		Oxytocin (n=50)		P value
	n	%	n	%	
Gravida					
Primi gravida	22	44.0	19	38.0	0.542
Multigravida	28	56.0	31	62.0	
Gestational age (wks)					
<37	5	10.0	6	12.0	
37-40	40	80.0	38	76.0	
>40	05	10.0	06	12.0	
Mean±SD	39.25±1.62		39.31±1.57		0.851

Table 3: Distribution of obstetric indications by groups (n=100)

Obstetric indications	Carbetocin (n=50)		Oxytocin (n=50)		P value
	N	%	N	%	
Prolonged labour	14	28.0	8	16.0	0.147
P/H/O C/S	13	26.0	19	38.0	0.198
Obstructed labour	9	18.0	14	28.0	0.235
Placenta previa	6	12.0	3	6.0	0.243
Multiple gestation	4	8.0	3	6.0	0.500
Intra amniotic infection	2	4.0	0	0.0	0.247
Placental Abruptio	0	0.0	2	4.0	0.247

Table 4: Distribution of post-operative blood loss of the patient by groups (n=100)

Post-operative blood loss (ml)	Carbetocin (n=50)	Oxytocin (n=50)	P value
	mean±SD	mean±SD	
15 minutes	899.0±591.8	943.0±596.2	0.711
30 minutes	41.6±48.8	45.8±58.2	0.766
45 minutes	87.9±63.4	73.7±44.7	0.198
1 hour	92.0±34.1	92.0±27.4	1.000
2 hours	76.0±43.1	65.3±48.09	0.244

Table 5: Distribution of post-operative systolic blood pressure of the patient by groups (n=100)

Post-operative systolic blood pressure (mm of Hg)	Carbetocin (n=50)	Oxytocin (n=50)	P value
	mean±SD	mean±SD	
15 minutes	104.8±7.06	103.2±5.3	0.203
30 minutes	105.8±8.6	105.6±8.6	0.907
45 minutes	110.2±9.4	111.4±8.6	0.507
1 hour	112.8±9.04	113.6±9.4	0.665
2 hours	116.6±7.17	117.8±7.4	0.412

Table 6: Distribution of post-operative diastolic blood pressure of the patient by groups (n=100)

Post-operative diastolic blood pressure (mm of Hg)	Carbetocin (n=50)	Oxytocin (n=50)	P value
	mean±SD	mean±SD	
15 minutes	69.2±5.6	70.8±5.6	0.156
30 minutes	70.0±8.08	70.8±6.6	0.588
45 minutes	71.2±5.6	71.6±4.7	0.699
1 hour	73.2±7.1	73.6±6.6	0.771
2 hours	75.0±5.80	77.0±10.1	0.227

Table 7: Distribution of post-operative pulse of the patient by groups (n=100)

Post-operative pulse (beat/min)	Carbetocin (n=50)	Oxytocin (n=50)	P value
	mean±SD	mean±SD	
15 minutes	83.8±12.01	83.4±7.3	0.841
30 minutes	80.2±9.7	79.7±8.4	0.783
45 minutes	80.7±14.7	77.1±9.3	0.146
1 hour	75.6±11.8	72.4±7.9	0.114
2 hours*	71.6±7.3	68.9±5.9	0.044*

Table 8: Distribution of post-operative uterine tone by groups (n=100)

Uterine tone	Carbetocin (n=50)		Oxytocin (n=50)		P value
	N	%	N	%	
15 minutes					
Contracted	42	84.0	43	86.0	0.779
Not contracted	8	16.0	7	14.0	
30 minutes					
Contracted	49	98.0	50	100	0.500
Not contracted	1	2.0	0	0.0	
45 minutes					
Contracted	50	100	50	100	-
1 hour					
Contracted	50	100	50	100	-
2 hours					
Contracted	50	100	50	100	-

Table 9: Distribution of need for additional uterotonic drugs and need of blood transfusion by study groups (n=100)

	Carbetocin (n=50)		Oxytocin (n=50)		P -value
	n	%	N	%	
Uterotonic drug					
Yes	7	14.0	27	54.0	0.001
No	43	86.0	23	46.0	
Blood transfusion					
Yes	8	16.0	17	34.0	0.038
No	42	84.0	33	66.0	

Table-10: **Distribution of Hb% and HCT of the patient by groups (n=100)**

Hb% and HCT	Carbetocin (n=50)	Oxytocin (n=50)	P value
	Mean±SD	Mean±SD	
Hb%(gm/dl)			
Pre-operative	10.89±1.39	11.19±1.02	0.221
Post-operative	10.77±1.07	10.60±1.16	0.448
HCT (%)			
Pre-operative	34.19±3.80	34.75±2.25	0.416
Post-operative	34.43±2.12	33.97±3.18	0.396

In our study table 1 shows the distribution of age and pulse & blood pressure of the patient by groups. The mean±SD of age was 25.20±5.43 years & 25.90±5.83 years pulse was (93.96±12.79) & (94.20±11.78), SBP was (116.00±15.38) & (114.40±13.42) and DBP was (74.00±8.80) & (72.60±7.77) among carbetocin and oxytocin group respectively. Here, table 2 shows the distribution of obstetric parameters and gestational age by groups. We found multigravida was 28(56.0%) in carbetocin group and 31(62.0%) in oxytocin group. Majority patients had gestational age 37-40 weeks in both groups. The mean gestational age was found 39.25±1.67 weeks in carbetocin group and 39.31±1.57 weeks in oxytocin group. In table 3 we showed the distribution of obstetric indications by groups. We found majority (28.0%) patients had prolonged labour, 13(26.0%) had P/H/O C/S and 9(18.0%) had obstructed labour in carbetocin group. In oxytocin group majority (38.0%) patients had P/H/O C/S, 14(28.0%) had obstructed labour and 8(16.0%) had prolonged labour. Table 4 shows the distribution of post-operative blood loss of the patient between two groups. The mean±SD of post-operativemean blood loss in 15 minutes was

(899.0±591.8) & (943.0±596.2); in 30 minutes was (41.6±48.8) & (45.8±58.2); in 45 minutes was (87.9±63.4) & (73.7±44.7) among carbetocin & oxytocin groups. There was no statistical comparison between carbetocin and oxytocin group in 1 hour. In 2 hours, we found (76.0±43.1) & (65.3±48.09) among carbetocin & oxytocin group respectively. Table 5 shows the distribution of post-operative systolic blood pressure of the patients between Carbetocin and Oxytocin group. We found post-operative systolic blood pressure significantly higher in Oxytocin than Carbetocin after 15,30, 45, 60 &120 minutes. Table 6 shows the distribution of post-operative diastolic blood pressure of the patient. There were no significantly differences of post-operative mean diastolic blood pressure (DBP) among carbetocin and oxytocin group after 15,30,45, 60 & 120 minutes. Table 7 shows the distribution of post-operative pulse of the patients among carbetocin & oxytocin. We found no significant differences of mean pulse after 15,30,45 & 60 minutes. The post-operative mean pulse was found 71.6±7.3 beats/min in carbetocin group and 68.9±5.9 beats/min in oxytocin group at two hours respectively. Table 8 shows the distribution of post- operative uterine tone. After 15 minutes uterine tone was found contracted 42(84.0%) in carbetocin group and 43(86.0%) in oxytocin group. After 30 minutes uterine tone was found contracted 49(98.0%) and 50(100%) in carbetocin and oxytocin group respectively. After 45 minutes, 1 hour and 2 hours follow up all patients had contracted uterus. Table 9 shows that uterotonic drug were needed 7(14.0%) in carbetocin group and 27(54.0%) oxytocin group. Blood transfusion needed 8(16.0%) in carbetocin group and 17(34.0%) in oxytocin group. Uterotonic drug and blood transfusion were found significant ($p<0.05$) and higher in oxytocin group than carbetocin group.Table 10 shows the distribution of Hb% and HCT among patients. The mean pre-operative of Hb% was 10.89±1.39 gm/dl in carbetocin group and 11.19±1.02 gm/dl in oxytocin group. Mean post-operative Hb% was 10.77±1.07 gm/dl and 10.60±1.16 gm/dl in carbetocin and oxytocin group respectively. Mean pre-operative HCT was 34.19±3.80% in carbetocin group and 34.75±2.25% in oxytocin group. Mean post-operative HCT was 34.43±2.12% and 33.97±3.18% in carbetocin and oxytocin group respectively.

DISCUSSION

In this study majority patients belonged to age 21-30 years in both carbetocin and oxytocin group respectively. The mean age was found 25.20±5.43 years in carbetocin group and 25.90±5.83 years in oxytocin group [Table 1]. In the study (Fahmy *et al.*,) the mean age was found 25.4±4.0 years in carbetocin group and 24.5±3.0 years in oxytocin group, which is similar to our study [16]. Another study (Hassan *et al.*,) reported that the mean age was 29.7±7.9 years in carbetocin group and 29.5±6.5 years in oxytocin group [17]. Larciprete *et al.*, (2013) reported that the mean age was 37.1±5.7 years in carbetocin group and 36.1±4.1 years in oxytocin group [18]; Jenkumwong *et al.*, (2017) reported that the mean age was 29.20±5.856 years in carbetocin group and 29.46±6.508 years in oxytocin group. The mean age of two different groups is similar to other study groups [19]. In this study we found multigravida was 28(56.0%) in carbetocin group and 31(62.0%) in oxytocin group. Majority patients had gestational age 37-40 weeks in both groups. The mean gestational age was found 39.25±1.67 weeks in carbetocin group and 39.31±1.57 weeks in oxytocin group [Table 2]. In other study (Jenkumwong *et al.*,) compared the incidences of post-partum hemorrhage (PPH) and blood transfusion, additional uterotonic use, hemoglobin and hematocrit change within 24 h after cesarean section and side effects between each group23. There was no statistic difference in incidences of PPH and blood transfusion, hemoglobin and hematocrit change within 24 h after cesarean section and side effects in both groups [19]. We found majority (28.0%) patients had prolonged labour, 13(26.0%) had P/H/O C/S and 9(18.0%) had obstructed labour in carbetocin group. In oxytocin group majority (38.0%) patients had P/H/O C/S, 14(28.0%) had obstructed labour and 8(16.0%) had prolonged labour [Table 3]. (Hassan *et al.*,) Found that the most frequently encountered risk factor was uterine over distension followed by prolonged labor trial. Uterine over distension was caused by polyhydramnios, twins or macrosomic fetus. History of PPH in a previous delivery was a common risk factor as well as antepartum hemorrhage in the current pregnancy. There was no significant difference between the two groups in history of P/H/O C/S [17]. In our study we found the mean±SD of post-operative blood loss in 15 minutes was (899.0±591.8) & (943.0±596.2); in 30 minutes was (41.6±48.8) & (45.8±58.2); in 45 minutes was (87.9±63.4) & (73.7±44.7) among carbetocin & oxytocin groups [Table 4]. In other study (Whigham *et al.*,) compared the efficacy of Carbetocin (long-acting oxytocin receptor agonist) versus Oxytocin given at non-elective caesarean section [20]. Participants received either carbetocin of 100µg or oxytocin 5 international units. There were no significant differences in the fall in hemoglobin, estimated blood loss, rates of post-partum haemorrhage or blood transfusions. Oxytocin and carbetocin have similar requirements for additional uterotonics, estimated blood loss, hemoglobin drop and blood transfusions [21]. In our study we found post-operative systolic blood pressure significantly higher in Oxytocin than Carbetocin. After 2 hour the mean±SD of 116.6±7.17 & 117.8±7.4 in carbetocin & oxytocin group respectively [Table 5]. In study of (Behery *et al.*,) observed that the mean systolic blood pressure was 131.73±20.88 mm of Hg in carbetocin group and 130.10±18.90 mm of Hg in oxytocin group [20]. In our study we found the mean of post-operative diastolic blood pressure (DBP) was 75.0±5.80 & 77.0±10.1 among carbetocin and oxytocin [Table 6]. In study of

(Behery *et al.*,) observed that the mean diastolic blood pressure was 86.15±9.24 mm of Hg in carbetocin group and 83.69±10.59 mm of Hg in oxytocin group [20]. The post-operative mean pulse was found 71.6±7.3 beats/min in carbetocin group and 68.9±5.9 beats/min in oxytocin group at two hours respectively [Table 7]. After 15 minutes uterine tone was found contracted 42(84.0%) in carbetocin group and 43(86.0%) in oxytocin group. After 30 minutes uterine tone was found contracted 49(98.0%) and 50(100%) in carbetocin and oxytocin group respectively. After 45 minutes, 1 hour and 2 hours follow up all patients had contracted uterus [Table 8]. In other study (Fahmy *et al.*,) compared the effect of carbetocin and oxytocin on uterine contraction and though the use of other uterotonic drugs postoperative in multiple pregnancy patients undergoing elective Cesarean section. They found that 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 [16]. We found that uterotonic drug were needed 7(14.0%) in carbetocin group and 27(54.0%) oxytocin group. Blood transfusion needed 8(16.0%) in carbetocin group and 17(34.0%) in oxytocin group. Uterotonic drug and blood transfusion were found significant ($p<0.05$) and higher in oxytocin group than carbetocin group [Table 9]. In other study (Hassan *et al.*,) additional uterotonic drugs were administered to 43 women of oxytocin group compared to 18 women of carbetocin group ($p<0.001$). In their study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs. 18% and $p<0.001$) [17]. The mean pre-operative of Hb% was 10.89±1.39 gm/dl in carbetocin group and 11.19±1.02 gm/dl in oxytocin group. Mean post-operative Hb% was 10.77±1.07 gm/dl and 10.60±1.16 gm/dl in carbetocin and oxytocin group respectively. Mean pre-operative HCT was 34.19±3.80% in carbetocin group and 34.75±2.25% in oxytocin group. Mean post- operative HCT was 34.43±2.12% and 33.97±3.18% in carbetocin and oxytocin group respectively [Table 10].

Conclusion and Recommendations

In our study, it can be concluded that Carbetocin is as effective and safe as Oxytocin in the prevention of PPH following caesarean section. The amount of blood loss, need of blood transfusion and the additional amount of uterotonics (Oxytocin 20 IU in 1 litter Hartman's solution and Misoprostol 800 µg per rectally) required for the prevention of PPH, pre and post-operative Hb% and HCT levels were almost comparable between the two study groups. There are no differences regarding adverse effects between two groups. Carbetocin is more heat stable than oxytocin which is of crucial importance to resource poor settings like us. So use of Carbetocin is more beneficial than oxytocin in prevention of PPH. So further study with a prospective and longitudinal study design needs to be done to identify the preventions of Oxytocin and Carbetocin in PPH following caesarean section by health professionals.

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