Ibrahim Card Med J 2021; 11 (1): 71-78

Comparative Study between Oxytocin and Carbetocin for the prevention of Primary Postpartum Hemorrhage following Caesarean Section

Nurjahan Akter,[1] Shahela Jesmin,[2] Mosammat Nargis Shamima,[3] Nargis Zahan,[4] Farhana Naznin,[5] Susmita Sharmin [6]

ABSTRACT

Background & objective: Of the many pharmacological options for the management of postpartum hemorrhage, oxytocin is the first line of treatment. The newer drug carbetocin is getting popularity among obstetricians, although there is as yet not enough evidence about its safety and efficacy. The present study attempted to compare oxytocin with carbetocin for the routine prevention of postpartum hemorrhage (PPH) following caesarean section.

Methods: The present comparative clinical trial was conducted in the Department of Obstetrics and Gynaecology in Rajshahi Medical College Hospital (RMCH), Rajshahi over a period of one year between March 2017 to February 2018. Pregnant women undergoing cesarean section under regional anaesthesia and do not have known hypersensitivity to oxytocin and carbetocin and known bleeding disorders were included in the study. A total of 96 such subjects were consecutively included and were randomly assigned to either Oxytocin (n = 48) and Carbetocin (n = 48) Groups. The outcome was evaluated in terms of incidence of PPH (loss of blood > 1000 ml), blood transfusion needed to compensate for lost blood, additional oxytocics needed to manage PPH and adverse effects encountered by the subjects.

Result: The mean age of the subjects was around 25 years and the age distribution between the study groups was almost similar. In terms of obstetric characteristics multigravida was predominant in the Oxytocin group than that in the Carbetocin group. The current pregnancy profile like gestational age, ANC received, number of foetus in utero and placental position all were comparable between the groups. Antenatal conditions/diseases deemed to have influence on PPH were no different between the study groups. Past history of caesarean section was higher in Oxytocin group (43.8%) than that in the Carbetocin group (22.9%). There were negligible incidences of past PPH and myomectomy in either group. The mean haemoglobin level in the former and the latter groups were 9.5 and 10 gm/dl respectively with majority of the subjects being mildly anaemic. More than 80% of the subjects in either group underwent emergency caesarean section. The outcome showed that 83% in the Oxytocin group and 90% in the Carbetocin group did not develop PPH, but the difference was not significant. The mean blood lost was somewhat lower in the carbetocin group (630 ml) than that in the Oxytocin group (685 ml). The number of patients needed to be transfused and the mean amount of blood transfused to them in each group was fairly comparable. Oxytocin group received additional oxytocic drugs, such as, Metherspan and Misoprostol more frequently than the Carbetocin group did, but the differences did not turn significant. A few patients in both groups developed adverse effects but they were comparable. The mean 24-hours urine output was > 2000 ml in either group).

Conclusion: The study concluded that the incidence of PPH, the amount of blood lost, number of patients transfused, amount of blood transfused and the additional amount of oxytocics required for the prevention and treatment of PPH were broadly comparable between the two study groups.

Key words: Primary PPH, oxytocin, carbetocin, caesarean section etc.

ORIGINAL ARTICLE

Authors' information:

[1] ***Dr. Nurjahan Akter***, *MS, Medical Officer, Shaheed Sheikh Abu Naser Specialized Hispital, Khulna.*

[2] ***Dr. Shahela Jesmin***, *DGO, FCPS, MCPS, Professor and Head, Department of Obstetrics & Gynaecology, Barind Medical College, Rajshahi.*

[3] ***Dr. Mosammat Nargis Shamima***, *DGO, MS, Asst. Professor, Department of Obstetrics & Gynaecology, Rajshahi Medical College, Rajshahi.*

[4] ***Dr. Nargis Zahan***, *MS, Asst. Professor, Department of Obstetrics & Gynaecology, Rajshahi Medical College, Rajshahi.*

[5] ***Dr. Farhana Naznin***, *MS, Medical Officer, Jashore General Hospital, Jashore.*

[6] ***Dr. Susmita Sharmin***, *MBBS, Medical Officer, Tanore Upazilla Health Complex, Rajshahi.*

Correspondence: ***Dr. Nurjahan Akter,*** *Phone: +8801712995374 E-mail: drnurjahan28@gmail.com*

INTRODUCTION:

Global efforts on maternal health have decreased maternal mortality.[1] with fewer than 83,052 maternal deaths estimated for the year 2013.[2] Primary PPH is the single leading cause of maternal mortality worldwide, accounting for nearly a fifth of all maternal deaths.[3] A population-based research study conducted in Bangladesh reported PPH as 6% of total maternal morbidities.[4] Primary postpartum hemorrhage (PPH) is a potentially life-threatening complication for both vaginal and cesarean delivery, although the risk of PPH in women who receive a caesarean section (CS) is higher than that in women who undergo a vaginal delivery and vaginal birth after previous cesarean section [VBAC].[5,6]

Primary PPH is one of the major contributors to maternal morbidity and mortality especially in developing countries.[3,7] Although there has been a remarkable improvement in the management of PPH in recent years, it still contributes to one-quarter of all maternal deaths worldwide.[8] The incidence of primary PPH has been reported to be 3.9% in women delivered vaginally and reaches up to 8% in women with cesarean section.[9] The most frequent cause of primary PPH is uterine atony, comprising up to 80% of the primary PPH cases.[10] The impact of primary PPH on maternal mortality and morbidity makes active management of the third stage of labour to a critical key.[11] To this end, uterotonic agents are administered immediately after delivery of the baby.[10] Oxytocin is currently the uterotonic of first choice. It has proven to decrease the incidence of primary PPH by 40% and has a rapid onset of action and a good safety profile.[10,12,13] A disadvantage of oxytocin is its short half-life of 4-10 minutes, requiring a continuous intravenous infusion or repeated intramuscular injections to maintain tonicity of uterus.[14] Another prophylactic medication currently used is syntometrine. It is a mixture of 5 IU oxytocin and 0.5 mg ergometrine which prompts the onset of oxytocin effect and sustains uterotonic effect of ergometrine. Although prophylactic use of syntometrine in the third stage of labour is effective in reducing blood loss due to primary PPH, cardiovascular and gastrointestinal side effects such as nausea, vomiting and raised blood pressure are considerably higher mainly due to stimulation of smooth muscle contraction and vasoconstriction by ergometrine.[15] Therefore, syntometrine is contraindicated in women with co-existing medical conditions, such as, cardiac disease, pre-eclampsia etc. These women are then administered oxytocin which is less effective in the prevention of primary PPH.

Faced with this backcloth, administration of prostaglandins, such as, misoprostol and carbeprost has been explored for several years. The use of misoprostol for the prevention of primary PPH demonstrates lower effect than injectable uterotonic agent following vaginal delivery and is associated with a higher incidence of severe primary PPH and need of additional uterotonics.[16] These factors make misoprostol unsuitable prophylactic agent for the prevention of excessive bleeding. Among the other agents that have been explored for the prevention of primary PPH, carbetocin appears to be a promising medication.[17] Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single dose injection in the route of intravenous or intramuscular. In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic contractions within 2 minutes, followed by rhythmic contractions for a further hour. Intramuscular injection of carbetocin produces tetanic contractions within 2 minutes, lasting about 11 minutes and followed by rhythmic contractions for an additional 02 hours. In comparison with oxytocin, carbetocin produces a prolonged uterine activity when administered postpartum, with respect to both frequency and amplitude of contractions.[17] Carbetocin is well tolerated and the safety profile is similar to that of oxytocin.[18,19] Studies have been performed to compare the efficacy of carbetocin with conventional oxytocins for the prevention of primary PPH in different countries but few studies have been done in our country in this field. So, the present study was intended to compare the

efficacy and safety between carbetocin and oxytocin with the hypothesis in mind that carbetocin is better than oxytocin in the prevention of primary PPH following cesarean section.

METHODS:

This comparative clinical trial was conducted in the Department of Obstetrics and Gynaecology, RMCH, Rajshahi, Bangladesh over a period of one year from March 2017 to February 2018. Having obtained ethical clearance from the Institutional Review Board (IRB) of Rajshahi Medical College, Rajshahi, a total of 96 term pregnant women whose bleeding time and clotting time were within physiological range and who were scheduled for cesarean section under regional anaesthesia alone were included in the study. Hypersensitivity to oxytocin and carbetocin, known bleeding disorders, women unwilling to participate were excluded from the study. The included study subjects were randomly allocated between the two study groups. For random allocation there were two cards-one marked with 'O' (for oxytocin) and another with 'C' (for carbetocine). The first enrolled patient was asked to draw a card blindly. If she got the card marked with 'O' she went to oxytocin group and the second patient then automatically received carbetocine or vice-versa. In this way total patients were randomly and equally allocated into either oxytocin group (n=48) or carbetocin group (n = 48).

With informed written consent data were collected by a semi-structured questionnaire. The patients in the oxytocin group received Inj. oxytocin 05 IU intravenously (IV) immediately after delivery followed by 20 IU in 1 liter of Hartman's solution (125 ml/hr) over 8 hour, while the patients in the carbetocin group received Inj. carbetocin 100 microgram IV immediately after delivery of the baby. Blood loss was estimated by usual way with visual estimation, number of used mops, and number of used pads[20] and PPH was defined as blood loss of more than 500 ml after vaginal delivery and more than 1000 ml after cesarean section that occur in the first 24 hours after delivery. All patients have had a Foley catheter and urobag *in situ* for 24 hours after CS and amount of urine voided was monitored at 6 hourly intervals for 24 hours. Efficacy and adverse effect of both drugs assessed cautiously and included in the data sheet. All patients were followed up for 1st 24 hours. The outcome was evaluated in terms incidence of PPH, amount of blood lost, blood transfusion needed to compensate for blood lost due to PPH, additional amount oxytocics needed and adverse effects encountered by the study subjects. Data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 17. The test statistics used to analyze the data were descriptive statistics, Chi-square or Fisher's Exact Probability Test and Unpaired t-Test. While categorical data were compared between groups using Chi-square or Fisher's Exact Test, the continuous data were compared between groups using Unpaired t-Test. The level of significance was set at 5% and p-value < 0.05 was considered significant.

RESULTS:

The mean ages of the subjects in the Oxytocin and Carbetocin groups were almost similar (25.3 ± 4.9 vs. 24.1 ± 4.4, p = 0.190). The two groups were almost identical in terms of BMI, with majority of the subjects in either group being overweight or obese (p = 0.858) (Table I). Obstetric history shows that the proportion of multigravida was significantly higher in the Oxytocin group than that in the Carbetocin group (p = 0.004). The gestational ages of Oxytocin and Carbetocin groups at caesarean section were almost identical (38.7 ± 1.5 vs. 39.1 ± 1.8 weeks, p = 0.375). There was no significant difference between the study groups with respect to ANC received (p=0.342). Majority of the subjects in either group had single foetus in the utero with no significant intergroup difference (p = 0.552). In terms of placental position, anterior insertion was higher in both the groups (p = 0.739) (Table II).

Comparison of risk factors between the study groups revealed that none of the conditions shown in table III was any different between the study

ORIGINAL ARTICLE

groups (p > 0.05). Past history of CS was considerably higher in Oxytocin group (43.8%) than that in the Carbetocin group (22.9%) (p=0.030). There were negligible incidences of primary PPH and myomectomy in either group. Distribution of blood groupings among study population shows that 'B' group was the most common blood group followed by 'O', 'A' and the 'AB' in either group. Majority of the subjects in both Oxytocin and Carbetocin groups had Rh positive blood (97.9 vs. 97.9%, p = 0.753). The mean levels of haemoglobin in the former and the latter groups were 9.5 and 10 gm/dl respectively (p = 0.122). More than 80% of the subjects in either group underwent emergency caesarean section (p = 0.713) (table IV). The prime indication for the current CS is previous CS, severe preclampsia or eclampsia, prolonged labour, foetal distress, breech presentation, obstructed labour and placenta previa. None of the indications was any different between the study groups (p > 0.05) (Table V).

Investigating outcome revealed that about 17% of the patients in Oxytocin group and 10.4% of the patients in Carbetocin group developed PPH, but the difference was not statistically significant (p=0.371). The average amount of blood lost was considerably higher in the former group (685 ml) than that in the latter group (630 ml) (p = 0.272). The number of patients needed to be transfused and the average number of units of blood transfused to the patients in each group was almost identical (p=0.972 and p=0.975 respectively) (Table VI). Additional oxytocic drug, such as, Metherspan and Misoprostol both were given more often in the Oxytocin group patients than in the Carbetocin group patients, although the differences were not statistically significant (p=0.217 and p = 0.218 respectively) (Table VII). None of the adverse effects like nausea/vomiting, palpitation, hypotension, headache, chills, tremor, chest-pain, hot sensation, sweating was significantly different between the groups. The average 24-hours urine output was > 2000 ml in either group (p = 0.679) (Table VIII).

Table I. Comparison of demographics and anthropometrics between groups

Demographic & anthropometric characteristics	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Age (years)#	25.3 ± 4.9	24.1 ± 4.4	0.190
BMI range (kg/m2)*			
18.5-24.9 (Normal)	9(18.8)	7(14.6)	
≥ 25.0 (Overweight & obese)	39(81.2)	41(85.4)	0.858

Figures in the parentheses indicate corresponding %; ***Chi-squared Test** (χ^2) was done to analyzed the data. #Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table II. Comparison of history of current pregnancy between groups

History of current pregnancy	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Gravida			
Primigravida	13(27.1)	27(56.3)	0.004
Multigravida	35(72.9)	21(43.7)	
Gestational age (weeks)#	38.7 ± 1.5	39.1 ± 1.8	0.375
ANC visit*			
Not received	3(6.3)	5(10.4)	
Regular	14(29.2)	19(39.6)	0.342
Irregular	31(64.6)	24(50.0)	
No of fetus in utero*			
Single	43(89.6)	45(93.8)	0.552
Twin	5(10.4)	3(6.2)	
Placental position*			
Anterior	18(37.5)	18(37.5)	
Posterior	13(27.1)	17(35.4)	0.739
Fundal	13(27.1)	9(18.8)	
Placenta previa	4(8.3)	4(8.3)	

Figures in the parentheses indicate corresponding %; * χ^2 was done to analyzed the data. # Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table III. Comparison of suspected risk factors between groups

Risk factors	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Antepartum hemorrhage*	8(16.7)	5(10.4)	0.486
Anaemia*			
Mild	26(54.2)	26(54.2)	
Moderate	7(14.6)	4(8.3)	0.580
No	15(31.3)	18(37.5)	
Chronic hypertension**	4(8.3)	1(2.1)	0.181
Preeclampsia*	9(18.8)	12(25.0)	0.459
Polyhydramnios**	0(0.0)	2(4.2)	0.247
Macrosomia**	4(8.3)	3(6.3)	0.500
Heart disease**	1(2.1)	0(0.0)	0.500
Past history of CS*	21(43.8)	11(22.9)	0.030
Past history pf primary PPH**	2(4.2)	1(2.1)	0.500
History of Myomectomy**	0(0.0)	1(2.1)	0.500

Figures in the parentheses indicate corresponding %; ***Chi-squared Test** (χ^2) was done to analyzed the data. ****Fisher's Exact Test** was done to analyzed the data.

Table IV. Laboratory investigation findings & operative details between groups

Laboratory investigation findings & Operative details	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
ABO blood grouping*			
A	9(18.8)	13(27.1)	0.313
B	22(45.8)	14(29.2)	
AB	2(4.2)	4(8.3)	
O	15(31.3)	17(35.4)	
Rh typing**			
Positive	47(97.9)	47(97.9)	0.753
Negative	1(2.1)	1(2.1)	
Hb (gm/dl)#	9.5 ± 1.7	10.0 ± 1.1	0.122
Type of C/S*			
Elective	10(20.9)	8(16.7)	0.713
Emergency	38(80.1)	40(83.3)	

Figures in the parentheses indicate corresponding %;
*__Chi-squared Test__ (χ^2) was done to analyzed the data.
**__Fisher's Exact Test__ was done to analyzed the data.

Table V. Comparison of indications of caesarean section between groups

Indications	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Placenta previa*	6(12.5)	5(10.4)	0.799
Abruptio placenta**	3(6.3)	1(2.1)	0.308
Prolong labour*	4(8.3)	10(20.8)	0.083
Subfertility**	1(2.1)	4(8.3)	0.181
Previous C/S*	21(43.8)	13(27.1)	0.088
Obstructed labour*	5(10.4)	6(12.5)	0.749
Twin pregnancy**	4(8.3)	4(8.3)	0.643
Severe preeclampsia or eclampsia*	10(20.8)	11(22.9)	0.805
Fetal distress*	5(10.4)	8(16.7)	0.371
Bad obstetric history**	1(2.1)	1(2.1)	0.753
Breech presentation*	8(16.7)	3(6.3)	0.109
Transverse lie**	1(2.1)	4(8.3)	0.181
Macrosomic baby**	3(6.3)	4(8.3)	0.500

Figures in the parentheses indicate corresponding %;
*__Chi-squared Test__ (χ^2) was done to analyzed the data.
**__Fisher's Exact Test__ was done to analyzed the data.

Table VI. Comparison of outcome between groups

Outcome	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
PPH developed*	8(16.7)	5(10.4)	0.371
Amount of blood lost (ml)#	685 ± 267	630.0 ± 225	0.272
Blood transfusion*			
Needed	13(27.1)	11(22.9)	0.972
Not needed	35(72.9)	38(77.1)	
No. of units needed#	7.1 ± 3.2	7.1 ± 3.3	0.975

Figures in the parentheses indicate corresponding %; * χ^2 was done to analyzed the data. # Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table VII. Comparison of additional oxytocic drug required between groups

Additional oxytocic drug required	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Metherspan*	8(16.7)	4(8.3)	0.217
Misoprostol**	5(10.4)	2(4.2)	0.218
Both oxytocics*	8(16.7)	5(10.4)	0.329

Figures in the parentheses indicate corresponding %;
*__Chi-squared Test__ (χ^2) was done to analyzed the data.
**__Fisher's Exact Test__ was done to analyzed the data.

Table VIII. Comparison of adverse effects between groups

Adverse effect	Group		p-value
	Oxytocin (n = 48)	Carbetocin (n = 48)	
Nausea/vomiting**	3(6.33	3(6.1)	0.661
Palpitation**	1(2.1)	2(4.2)	0.500
Hypotension**	2(4.2)	0(0.0)	0.247
Headache**	0(0.0)	1(2.1)	0.500
Chills**	4(8.3)	1(2.1)	0.181
Tremor**	1(2.1)	0(0.0)	0.500
Chest pain**	2(4.2)	0(0.0)	0.247
Hot sensation*	3(6.3)	1(2.1)	0.308
Sweating*	4(8.3)	2(4.2)	0.339
24 hours urine output#	2086 ± 322	2057 ± 362	0.679

Figures in the parentheses indicate corresponding %; * χ^2 was done to analyzed the data. # Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

DISCUSSION:

Of the many pharmacological options for the management of postpartum hemorrhage, oxytocin is the first line of treatment. The newer drug carbetocin is getting popularity among

ORIGINAL ARTICLE

obstetricians, although there is as yet not enough evidence about its safety and efficacy. That purpose, the present study attempted to compare oxytocin with carbetocin for the routine prevention of postpartum hemorrhage following caesarean section. In the present study, the mean age of the subjects was around 25 years and the age distribution between the study groups was almost identical. In terms of obstetric characteristics multigravida demonstrated their significant presence in the Oxytocin group than that in the Carbetocin group. The current pregnancy profile like gestational age, ANC received, number of foetus in utero and placental position all were almost similar between the groups. Antenatal conditions/diseases that are supposed to have influence on PPH were no different between the study groups. Past history of caesarean section was considerably higher in Oxytocin group (43.8%) than that in the Carbetocin group (22.9%), though the difference did not turn to significant. The mean levels of haemoglobin in the former and the latter groups were 9.5 and 10 gm/dl respectively with majority of the subjects being mildly anaemic. More than 80% of the subjects in either group underwent emergency caesarean section.

The comparative evaluation of outcome of intervention (incidence of PPH) demonstrated that 17% in the Oxytocin group and 10% in the Carbetocin group developed PPH, although the difference was not statistically significant. The average amount of blood lost, the number of patients needed to be transfused and the average number blood units transfused to them in each group were all fairly comparable between the groups. Oxytocin group received additional oxytocic drugs, such as, Metherspan and Misoprostol quite often than the Carbetocin group did, although the difference did not turn to significant. A few patients in both groups developed adverse effects (nausea/vomiting, palpitation, hypotension, headache, chills, tremor, chest-pain, hot sensation, sweating and so on) but they were all comparable. 24-hours urine output was on an average > 2000 ml in either group.

As all the baseline demographic, medical and obstetric characteristics (except parity and gravida) were almost comparable between the study groups, the outcome obtained could be attributed to intervention and comparatively better response in the carbetocin arm might be due the drug carbetocin itself. But as we compared the distribution of parity between patients with and without PPH, it was evident that multiparity was significantly associated PPH. Past history of C/S also demonstrated a predominance in those who have had PPH, but the difference was not statistically significant. So, these confounding variables might have influenced the outcome of intervention. But as the primary outcome variable, PPH was not significantly different between the Oxytocin and Carbetocin groups, binary logistic regression analysis could not be contemplated to find the independent predictors of PPH. Attilakos and colleagues[20] conducted a similar study in the UK on 377 women (189 received Oxytocin and 188 received Carbetocin) for prevention of PPH following caesarean section (elective or emergency). The study demonstrated that there were no significant differences in the estimated blood loss, uterine tone at the end of the operation, number of women with major PPH (blood loss >1000 ml) or number of women requiring blood transfusions. A significantly more women in the oxytocin group (45.5%) required additional oxytocics than that in the carbetocin group (33.5%) ($p = 0.023$).[20] The findings are quite consistent with findings of the present study. Reyes & Gonzalez in a prospective double-blind randomized controlled trial in 60 women with severe preeclampsia, found Carbetocin to be as effective as oxytocin in the prevention of postpartum hemorrhage in women with severe preeclampsia. Carbetocin had a safety profile similar to that of oxytocin, and it was not associated with the development of oliguria or hypertension in this cohort.[21] In the present study as well Carbetocin was found as safe as Oxytocin.

Another study compared carbetocin with oxytocin as a prophylactic agent to prevent postpartum hemorrhage in the grand multiparous patients. Carbetocin was found to be as effective as oxytocin. Moreover, it was significantly associated with a reduced need to explore the uterine cavity manually for persistent bleeding.[21]

Several studies have shown the efficacy and safety of carbetocin in various clinical scenarios. A single intravenous dose of 100 µg of carbetocin has been shown to be as effective as a 16-hour infusion of oxytocin in preventing intraoperative blood loss after caesarean section.[18] Another study reached a similar conclusion when a single dose of carbetocin was found to have similar efficacy to a two-hour infusion of oxytocin in controlling intraoperative blood loss after removal of placenta. Carbetocin could be preferred to oxytocin because of dose convenience.[18] When outcome was considered in terms of adverse effects, the two drugs are fairly comparable to each other. However, two studies have shown that carbetocin was associated with a significantly lower incidence of nausea and vomiting.[22,23] Butwick and associates[22] also showed that carbetocin was associated with a lower incidence of hypertension at 30 and 60 minutes but a higher incidence of maternal tachycardia.

CONCLUSION:

Summarizing the findings of the present study and discussion thereof, it can be stated that Carbetocin is as effective and safe as Oxytocin in the prevention of PPH following CS. The incidence of PPH, the amount of blood lost and the additional oxytocics required for the treatment of PPH all were, although, to some extent higher in the Oxytocin arm than in the Carbeocin arm, the difference was not statistically significant and as such they were considered equally effective and safe in the management of primary PPH. The adverse effects were also no different. However, carbetocin has dose convenience compared to oxytocin. As the primary outcome, PPH is not a common occurrence, the sample size was deemed inadequate to test the hypothesis that carbetocin is better than oxytocin in the prevention of primary PPH. So, caution should be exercised to generalize the findings to reference population. A large-scale, multicenter study is recommended so that the findings derived from the study could be generalized and have policy implication.

REFERENCE:

1. United Nations, 2000, United Nations Millennium Declaration. U.N. document A/RES/55/2,adopte.htm [accessedSeptember8.http://www.un.org/millennium/declaration/ares552e.htm[accessed September 2014] 2000.
2. Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS, Shackelford KA, Steiner C, Heuton KR et al. Global, regional, and national levels and cause of maternal mortality during 1990-2013pp. a systematic analysis for the Global Burden of Disease study 2013. *Lancet* 2014;384(9947):980-1004.
3. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van LOOK PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367(9516):1066-74.
4. WHO, 2000, UNICEF, & UNFPA. Maternal mortality in 2000: Geneva.
5. Farchi S, Polo A, Franco F. Severe postpartum morbidity and mode of delivery: a retrospective cohort study. *Acta Obstet Gynecol Scand* 2010;89:1600-3.
6. Leth RA, Moller JK, Thomsen RW, et al. Risk of selected postpartum infections after cesarean section compared with vaginal birth: A five year cohort study of 32,468 women. *Acta Obstet Gynecol Scand* 2009;88:976-83.
7. World Health Organisation. The World health report 2005: make every mother and child count. Geneva 2005.
8. Carroli G, Cuesta C, Abalos E, Glumezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Practice and Research. *Clinical Obstetrics and Gynaecology* 2008;22:999–1012.
9. Naef RW, Chauhan SP, Chevalier SP, et al. Prediction of hemorrhage at cesarean delivery. *Obstet Gynecol* 1994;83:923-6.
10. Dutch Association of Obstetricts and Gynaecology (NVOG). Guideline postpartum hemorrhage.http://www.nvog.nl.Accesed 1 Sept 2012, 2006:1-9.
11. Prendivile WJ, Elbourne D, McDonalds. Active versus expectant management in the third stage of labour. *Cochrane Database Syst Rev* 2000;3:CD000007.

12. American College of Obstetricians and Gynecologist (ACOG). ACOG educational bulletin. Postpartum hemorrhage. *Int J Gynaecol Obstet* 1998;61(1):79-86.

13. NICE Clinican Guideline Caesarean Section. http://www.nice.org.uk/guidance/cg132/evidence/cg132-caesarean-section-fullguideline-3 , 2011.

14. Oyelese Y, Scorza WE, Mastrolia R, Smulian JC. Postpartum hemorrhage. *Obstet Gynecol Clin N Am* 2007;34(3):421-41.

15. Carey M. Adverse cardiovascular sequelae of ergometrine. *Br J Obstet Gynaecol* 1993;100:865.

16. Tuncalp O, Hofmeyr GJ, Gumezoglu AM. Prostaglandins for preventing postpartum hemorrhage. Cochrane *Database Syst Rev* 2012;8:CD000494.

17. Chong YS, Su LL. Misoprostol for preventing PPH: some lessons learned. *Lancet* 2006;368:1216–7.

18. Boucher M, Horbay GL, Griffin P, et al. Double blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. *J Preinatol* 1998;18:202-7.

19. Dansereau J, Joshi AK, Helewa ME et al. Double blind comparison of carbetocinversus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol* 1999;180:670-6.

20. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage following cesarean section: the result of a double blind randomized trial. *BJOG* 2010;117:929-36.

21. Reyes OA, Gonzalez GM. Carbetocin Versus Oxytocin for Prevention of Postpartum Hemorrhage in Patients With Severe Preeclampsia: A Double-Blind Randomized Controlled Trial. *J Obstet Gynaecol Can* 2011;33(11): 1099–104.

22. Butwick AJ, Coleman L, Cohen SE, Riley ET, Carvalho B. Minimum effective bolus dose of oxytocin during elective Caesarean delivery. *Br J Anaesth* 2010;104: 338–43.

23. Abdul-Karim RW, Rizk PT. The effect of oxytocin on renal hemodynamics, water, and electrolyte excretion. *Obstet Gynecol Surv* 1970;25:805–13.