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Original Articles

Efficacy and Safety of Carbetocin in Comparison to Oxytocin in the Active Management of Third Stage of Labour Following Vaginal Delivery: An Open Label Randomized Control Trial

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Abstract:

Objective(S):*This study was conducted to evaluate the efficacy and safety of carbetocin in comparison to oxytocin in the active management of third stage of labour following vaginal delivery.*

Methods:*A randomized-controlled trial was conducted in the Institute of Child and Mother Health (ICMH), Dhaka, Bangladesh over a period of nine months from January to September, 2015. Patients who got admitted in ICMH with labour pain were assessed by general examination, abdominal examination and labour status was confirmed by per vaginal examination. On the basis of selection criteria total 94 pregnant women who had undergone vaginal delivery were randomized for two groups of drugs. According to computer generated randomization sequential number was allocated for cases. One group of patients received intravenous 100 micro gram carbetocin and another group of patients received intramuscular 10 IU oxytocin in third stage of labour. Outcome measures such as amount of blood loss in 24 hours, primary PPH, massive blood loss, need of fundal massage, need for additional uterotonic therapy, blood transfusions as well as other adverse effects were all documented.*

Results: *In this study, massive blood loss did not occur in any of patients in carbetocin group. But massive blood loss occurred in 8.5% women of oxytocin group. Further fundal massage, immediate blood transfusion and additional uterotonics were not needed by any patient in carbetocin group. In oxytocin group, fundal massage required in 10.6% of women, blood transfusion was needed for 6.4% patients and additional uterotonics was needed for 10.6% women. Average amount of blood loss were 64 ml less in carbetocin group and adverse effects of drugs were almost similar in both groups. Primary PPH was developed 6.4% in oxytocin group but none of patients developed PPH in carbetocin group.*

Conclusion: *Carbetocin appears to be an effective new drug in the active management of third stage of labour in vaginal delivery. A single dose of 100 microgram IV carbetocin is more effective than oxytocin for maintaining adequate uterine tone, less blood loss and preventing postpartum bleeding in women undergoing vaginal delivery. So, carbetocin can be considered as a good alternative to oxytocin in the active management of third stage of labour in vaginal delivery.*

Key words: *Post-partum hemorrhage, uterotonic drugs, carbetocin, oxytocin.*

Introduction:

Active management of the third stage of labour (AMTSL) is a critical intervention for PPH prevention. AMTSL has become a central component for the PPH reduction strategies of governments around the world. In 2012, WHO has issued new recommendations regarding AMTSL, which can be used to strengthen and focus the implementation of this life saving

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intervention[1]. Anaemia after delivery of a child (postpartum anemia) is a common problem throughout the world[2,3].The prevalence of postpartum anaemia is highest in developing countries [2,3]where it is a major cause of maternal morbidity and mortality [4,5]. It has been estimated that of the 500,000 maternal death occurring each year on a global scale in association with delivery, 20% are caused by peripartum hemorrhage and anaemia[4,5,6] . However, postpartum anaemia also constitutes a significant and partly unrecognized problem even in developed countries[7,8]. The use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour is recommended for all births[1]. Postpartum haemorrhage is the single most important cause of maternal mortality worldwide. It is the leading cause of maternal deaths accounting for nearly one-quarter of all maternal death[9,10].The global prevalence of PPH is approximately 6% of all deliveries[11], whereas in low income countries the prevalence varies from 8.6 to 18.7% [9,12]. In developing countries, mortality from PPH remains high[13]. In low income setting, PPH accounting for 30% of maternal death [9,12], while in Bangladesh it is 31 % [14]. In 1990, the maternal mortality ratio was 574 per 100,000 live births. In 2001 the MMR was 322 per 100,000 live births. In 2010 the ratio was 194 per 100,000 live births. In 2015 the ratio was 176 per 100, 000 live births[15,16]. So far the picture is really looking promising for Bangladesh. The key contribution to this decrease was a drop in mortality risk mainly due to improved access and use of health facilities. Now, building on the momentum generated by MDG 5, the sustainable development goals (SDGs) establish a transformative new agenda for maternal health towards ending preventable maternal mortality; target 3.1 of SDG 3 is to reduce the global MMR to less than 70 per 100 000 live births by 2030.[17]

PPH may be primary that occur within 24 hours of delivery and secondary where bleeding appears after 24 hours. Primary PPH is the most common one and up to 80% cases it occurs due to uterine atony, [18] while secondary PPH related to infection.

Conventional uterotonics like oxytocin has used for preventing PPH but it has some limitations like shorter half- life,[16,18] less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema. In addition, the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension[19]. Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability[20]. Bleeding due to uterine atony can be prevented by active management of third stage labour (AMTSL)[9]. Till now it is recommended that oxytocin should be used as oxytocic agent either in the form of intramuscular injection or intravenous infusion. But it's adverse effects limit its random use[20]. Moreover, oxytocin potency deteriorates when it is exposed to temperatures greater than 30°C for prolonged periods of time. For this reason, oxytocin should be distributed and stored along a cold chain[1].In our country cold chain is not properly maintained for oxytocin. So, there is a chance of lowering effectiveness and stability. As a result, treatment failure may occur.

Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties[21,22]. Carbetocin has prolonged duration of action (approximately 1 hour), which ensures more contraction time and less adverse effect[23,24]. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring 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. [20]

A single dose of carbetocin has been hypothesis to act as a 16 hours in comparison to intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section[19]. Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain, and pruritus[20].Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum haemorrhage[19,22,25]. We had conducted this clinical study to evaluate the efficacy and safety of carbetocin in the active management of third stage of labour following vaginal delivery.

Patients and methods:

This randomized control trial was done from January, 2015 to September, 2015 in the Department of Obstetrics and Gynaecology, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh. About 94 pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion criteria. According to computer generated randomization sequential number was allocated for cases. A written informed consent was taken from eligible women on admission. The study protocol was approved by the ethical committee of Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh.

Inclusion criteria were women with a single pregnancy undergoing vaginal delivery above 36 weeks of gestation (gestational age was recorded according to the last menstrual period and was confirmed by ultrasound report).

Exclusion criteria were placenta praevia, multiple gestations, and placental abruption (determined by history and ultrasound report) hypertensive disorders in pregnancy, preeclampsia, and known case of cardiac, renal, liver diseases, epilepsy, moderate anemia (Hb <9gm/dl), intrauterine foetal death and unwilling to participate in the study.

During study period we enrolled 47 women who received carbetocin 100 ìg I/V as a single dose and 47 women who received 10 IU of oxytocin after the delivery of the baby and prior to the delivery of the placenta. The primary outcome was measured by the amount of blood loss within 24 hours after delivery. Based on the experience of previous study[26], the research team was provided a pre-weighted standardized delivery mat (Quaiyum's mat) and pre-weighted sanitary pads for blood collection after delivery to each of the pregnant woman to measure blood loss in 24 hours postpartum period. We had measured the amount of blood loss in gram by digital postal scale. Then we multiplied the amount in gram by 1.06 to get the amount of blood loss in ml. It would be mentioned that 1000 gram is equivalent to 1056 ml. Primary PPH was considered when blood loss is 500 ml within 24 hours of delivery in both groups. The secondary outcomes were need for additional uterotonic therapy, massive blood loss, additional massage, blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation and by need of additional uterotonics to contract the uterus.

Statistical analysis:

Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were expressed as means ±SD. 95% confidence interval was calculated and p value of <0.05 was considered as significant.

Results:

A total of 110 pregnant women with a single pregnancy were initially recruited for inclusion in this study. Sixteen cases were excluded (5 had preeclampsia, 5 eclampsia, 2 placenta praevia, 2 placental abruption and 2 multiple gestation). Thus 94 women were recruited for final study and analysis. Mean age of study patients was 22.7 ± 3.2 and 22.1 ±3.2 years in carbetocin and oxytocin group respectively. Among study population 20 (42.6%) patients in carbetocin group and 23 (48.9%) patients in oxytocin group had mild anaemia. Mean systolic and diastolic BP was 110±9.6 mm of Hg and 73 ±5.3 mm of Hg in carbetocin group and 108±7.7 mm of Hg and 70±12.5 mm of Hg in oxytocin group. Mean gestational age at delivery was 39±1.1 and 39.09± 1.7 weeks in carbetocin and oxytocin group respectively.

It shows that baseline parameters are equal in both the groups (Table I).

Table-II.Shows that massive blood loss took place in 8.5% cases, fundal massage required by 10.6% patients, blood transfusion needed for 6.4% patients and additional uterotonic needed for 10.6% patients in oxytocin groupbut in carbetocin group there was no massive blood loss in any patient, fundal massage and blood transfusion was not needed for any patient and none of the patient required additional uterotonics.

The mean differences were statistically significant (P<0.05). Except abdominal pain in few cases (4 in carbetocin and 5 in oxytocin) no major adverse effects observed in any group.

Average blood loss in carbetocin group was 325 ml and oxytocin group was 389 ml. Average 64 ml more blood loss was observed in oxytocin group. The mean differences were statistically significant (P<0.05) (Table III).

No patient developed PPH in carbetocin group. But 3 (6.4%) patients developed PPH in oxytocin group, though it is not statistically significant (P>0.05) (Table IV).

Table-I

Baseline characteristics of study patients (n=94)

Characteristics	Carbetocin Group (47)		Oxytocin Group (47)		
	Mean	± SD	Mean	± SD	P value
Age (Yrs)	22.7±	3.2	22.1±	3.2	0.439
Systolic BP (mm Hg)	110±	9.6	108±	7.7	0.210
Diastolic BP (mm Hg)	73±	5.3	70±	12.5	0.509
Gestational Age (Weeks)	39.01±	1.1	39.09 ±	1.7	0.799
Mild Anemia	N	%	N	%	
	20	42.6%	23	48.9%	0.386

Table-II

Outcome of Third stage of Labour (n = 94)

Outcome of 3rd stage of Labour	Carbetocin Group (47)		Oxytocin Group (47)		P value
	No.	(%)	No.	(%)	
Massive blood loss	0	0	4	8.5%	0.002
Fundal massage required	0	0	5	10.6%	0.002
Blood transfusion requirement	0	0	3	6.4%	0.07
Need for additional uterotonics	0	0	5	10.6%	0.002

Table-III

Blood loss in 24 hours (n = 94)

Amount of blood loss	Carbetocin group (47)	Oxytocin group (47)	Difference	P Value
Average blood loss in 24 hours (in ml)	325 ml (306 g)	389 ml (366gm)	64 ml	0.003

Table-IV

Outcome of the patient: Primary PPH (n = 94)

Outcome (Primary PPH)	Carbetocin group (47)		Oxytocin group (47)		P Value
	N	%	N	%	
Yes	0	00	3	6.4	0.07
No	47	100	44	93.6	

Discussion:

Active management of 3rd stage of labour significantly reduces 3rd stage haemorrhage. Active management includes application of uterotonics just after delivery of the head of the baby. Oxytocin has been using widely for long time. Now a days carbetocin, which is also a oxytocic drug has gained popularity due to its more potentiality in comparison to oxytocin. We compared the effect of two drugs in terms of controlling postpartum bleeding.

Our results had shown that carbetocin is superior in comparison to oxytocin in the reduction of blood loss during the active management of third stage of labour. Carbetocin also decreased the need for additional uterotonics, uterine massage and massive blood loss in the active management of third stage of labour after vaginal delivery. None of the patients in carbetocin group needed blood transfusion but in oxytocin group blood transfusion was needed in 6.4% patients. A similar study showed that none of the woman in carbetocin group required blood transfusion, while 15.5% in oxytocin group required it [27]. Agnes et al [28] investigated carbetocin versus oxytocin for the prevention of postpartum hemorrhage following vaginal delivery among high risk women and found that fundal massage was needed for 10% patients in carbetocin group and 83% patients in oxytocin group. In our study, none of patients in carbetocin group needed fundal massage but in oxytocin group fundal massage was needed in 10.6% patients.

A single dose of oxytocin is not adequate and it always follows by additional uterotonics to keep the uterus contractile. But a single dose of carbetocin is enough for controlling bleeding by keeping the uterus contractile for long time. Ortiz et al. [29] showed that only 1.5% patients needed additional uterotonics in carbetocin group and 5.8% patients in oxytocin group. Another study [27]showed that none of the patient in carbetocin group required additional uterotonics while as high as 71.5% of women in oxytocin group needed additional oxytocin to ensure adequate uterine contraction for long period [27]. Prophylactic use of carbetocin and oxytocin after an elective caesarean section showed significantly diminished need for additional uterotonics in carbetocin group [30]. Similar result shown by Debbie et al [31] where 5.7% patients needed additional uterotonics in carbetocin group whereas, 34.3% patients needed in oxytocin group. In our study, none of patients of carbetocin group required additional uterotonic but in oxytocin group additional uterotonics was needed for 10.6% patients.

Ortiz et al [29] also showed the mean amount of blood loss in carbetocin group was 366 ml and in oxytocin group was 400 ml when compared the efficacy of carbetocin with oxytocin. Average 34 ml more blood loss was observed in oxytocin group. Similar results shown by other two studies that average blood loss was more in oxytocin group than carbetocin group [32,33]. In this study average blood loss in carbetocin group was 325 ml and oxytocin group was 389 ml. Average 64 ml more blood loss was observed in oxytocin group. This fact can be explained by the known longer half-life of carbetocin. Carbetocin is effective in preventing postpartum hemorrhage in both high- and low-risk groups.[33]

Maged et al.[32] also showed the occurrence of PPH were 4% in carbetocin group and 16% in oxytocin group. In this study, occurrence of PPH in oxytocin group was 6.4% but in carbetocin group none of patients developed PPH. Primary postpartum haemorrhage is the most common form of major obstetric hemorrhage.[34] It is the most common cause of maternal morbidity in developed countries and a major cause of death worldwide [35,36]. The most common point at which PPH occurs is during the third stage of labour, when the uterus may suddenly loss its ability to contract. Around 80% cases of postpartum hemorrhage are due to uterine atonicity[30,37]. Bleeding due to uterine atonicity, can be prevented by active management of third stage labour (AMTSL)[10,26].

In conclusion the promising findings of this study suggested that carbetocin appears to be an effective new drug in the active management of third stage of labour in vaginal delivery. A single dose of 100 microgram IV carbetocin is more effective than oxytocin for maintaining adequate uterine tone, decreased blood loss and preventing postpartum hemorrhage in women undergoing vaginal delivery. Carbetocin can be considered as a good alternative to oxytocin in managing third stage of labour in vaginal delivery.

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Conflict of interest:

The authors declare that there is no conflict of interests regarding the clinical trial.

References:

1. WHO recommendations for the prevention and treatment of postpartum haemorrhage. WHO: Geneva, Switzerland, 2012.
2. Milman N. Postpartum anemia : definition, prevalence, causes and consequences. Ann Hematol 2011; 90:1247–1253.
3. Milman N. Anemia—still a major health problem in many parts of the world! Ann Hematol 2011; 90:369–377. http://dx.doi.org/10.1007/s00277-010-1144-5.
4. World Health Organization. Reduction of maternal mortality.A joint WHO/UNFPA/UNICEF/ World Bank statement. World Health Organization, Geneva, 1999.
5. Potts M, Campbell M .Three meetings and fewer funerals: misoprostol in postpartum hemorrhage. Lancet 2004; 364:1110–1111.
6. Tsu VD, Shane B. New and underutilized technologies to reduce maternal mortality: call to action from a bellagio workshop. Int J Gynecol Obstet 2004; 85(Suppl 1):S83–S93.
7. Bodnar LM, Siega-Riz AM, Miller WC, Cogswell ME, McDonald T. Who should be screened for postpartum anemia? An evaluation of current recommendations. Am J Epidemiol 2002; 156:903– 912.
8. Bergmann RL, Richter R, Bergmann KE, Dudenhausen JW. Prevalence and risk factors for early postpartum anemia. Eur J Obstet Gynecol Reprod Biol 2010; 150:126–131.
9. Derman R, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, Patted SS, Patel A, Edlavitch SA, Hartwell T, Chakraborty H, Moss N.Oral misoprostol in preventing post partum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet. 2006; 368:1248-53.
10. M Banu, S Nahar and HE Nasreen: Oral administration of misoprostol reduces postpartum haemorrhage.Global Health Action.2013; 4:10-25.

11. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM . Epidemiology of postpartum haemorrhage: a systematic review. Best Practice Res Clin Obstet Gynaecol 2008; 22(6):999-1012.

12. Dolea C, AbouZahr C and Stein C .Global burden of maternal haemorrhage in the year Global Burden of disease. 2000. http"//www/whoint/ healthinfo/statistics/bod_maternalhaemorrhage. pdf.(Accessed on 07 March 2011).

13. Bugalho A, Daniel A, Faundes A, Cunha M. Misoprostol for prevention of postpartum haemorrhage. Int J Gynecol Obstet 2001; 73:1-6.

14. National Institute of Population Research and Training (NIPORT), MEASURE Evaluation, UNC-CH, USA, ICDDR, B., 2011.

15. Bangladesh demographic and health survey, 2011.

16. Bangladesh Maternal Mortality Survey by National Institute of Population Research and Training (NIPORT), 2010.

17. WHO, UNICEF, UNFPA, The World Bank, and the United Nations Population Division. Trends in Maternal Mortality: 1990 to 2015. Geneva, World Health Organization, 2015

18. Oyelese Y, Scorza WE, Mastrolia R, Smulian JC.Post- partum hemorrhage. Obstet Gynecol Clin N Am 2007; 34(3):421–441.

19. G Larciprete, C Montagnoli, M Frigo, V Panetta J, Prenat et al Carbetocin versus oxytocin in caesarean section with high risk of post-partum haemorrhage Med. 2013; 7(1): 12–18.

20. Werner R. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. European Journal of Obstetrics and Gynecology and Reproductive Biology; 2009; 147 (1): 15-20.

21. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, Hunt L, Draycott T. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomized trial. BJOG. 2010; 117: 929–936.

22. Gazi R, Quaiyum, A, Islam, M, Hossain, S,Wirtz, A,L, Saha, , N, C, Jesmin, M. Post-Partum Excessive Bleeding among Bangladeshi Women: Determinants, Perceptions, Recognition, Responses. Centre for Equity and Health Systems, ICDDRB, Dhaka, Bangladesh. Published November 15, 2012

23. Sergio RO, RP Aguado et al. Carbetocin versus oxytocin for prevention of postpartum haemorrhage: a randomized controlled trial. Published Online February 26, 2014 School of Clinical and Experimental Medicine, University of Birmingham,Birmingham Women's Hospital, Birmingham, UK .

24. Tharakan T, Jha J Randomized double blind prospective trial of active management of the third stage of labor. Arch Med Sci 2008; 4(1):79–82.

25. Yuen PM.Oxytocic Agents for the Management of Postpartum Haemorrhage Drug Review. 2011; 16: (10) 1-2.

26. Chandhiok N, Dhillon BS, Datey S, Mathur A, Saxena NC.Oral misoprostol for prevention of postpartum haemorrhage by paramedical workers in India. Int J GynaecolObstet 2006; 92:170-75.

27. Manal M, El Behery, G Abbas, El Sayeda, Azza A et al: Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. J Matern Fetal Neonatal Med.2016; 29(8):1257-1260.

28. Agnes P, M Fenix , Trinidad R , Vera et al: Double-Blind Randomized Controlled Trial Comparing the Effect of Carbetocin and Oxytocin for the Prevention of Postpartum Hemorrhage Among High Risk Women Following Vaginal Delivery; Philippine Journal of Obstetrics & Gynecology.2011; 35(4):169-175.

29. Ortiz S R, Aguado R P, Hernandez RS, Castorena M et al: Carbetocin versus oxytocin for prevention of postpartum haemorrhage: a randomised controlled trial; The Lancet. 2014 ;383:51

30. Holleboom CA, van Eyck J, Koenen SV, Kreuwel IA, Bergwerff F, Creutzberg EC, Bruinse HW. Carbetocin in comparison with oxytocin in several dosing regimens for the prevention of uterine atony after elective caesarean section in the Netherlands. Arch Gynecol Obstet 2013; 287:1111–1117.

31. Iynuy D, Atherinep N et al: Carbetocin versus Oxytocin for the Prevention of Postpartum Hemorrhage Following Elective Cesarean Section: Rizal Medical Center Experience; Philippine Journal of Obstetrics & Gynecology. 2013; 37 (2):71-79

32. Maged AM, Hassan AM, Shehata NA: Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women; J Matern Fetal Neonatal Med. 2016; 29(4): 532–536.

33 Mohammed S. E. Elsafty, Alaa S. Hassanin, M Laban, Ahmed M, Ibrahim et al: Intravenous carbetocin shot is superior to oxytocin infusion for placental delivery in second trimester abortion: a pilot randomized controlled trial: Fetal Neonatal Med. Early Online: 1–5, 2015 Informa UK Ltd. DOI: 10.3109/14767058.2015.1021673.

34. Bayev O.R. Use of carbetocin for preventing postpartum hemorrhage Department of Obstetrics, Gynecology, Perinatology, and Reproductology; Faculty for Postgraduate Training of Physicians, I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia 2013:Vol-7.

35. The Prevention and Management of Postpartum Haemorrhage: Report of Technical Working Group, Geneva 3–6 July 1989. Geneva: World Health Organization, 1990.

36. Bais JM, Eskes M, Pel M, Bonsel GJ, Bleker OP. Postpartum haemorrhage in nulliparous women: incidence and risk factors in low and high risk women. A Dutch population-based cohort study.Eur J Obstet Gynecol Reprod Biol. 2004; 115:166–72.

37. Dutch Association of Obstetrics and Gynaecology (NVOG). Guideline postpartum haemorrhage. 2012;1–9.