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IMPLICATION OF HEAT STABLE CARBETOCIN IN PREVENTION OF POSTPARTUM HAEMORRHAGE

Obstetric & Gynaecology

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ABSTRACT

Background: The greatest cause of maternal death in low-income nations is postpartum haemorrhage (PPH), which also significantly contributes to severe maternal morbidity and long-term impairment. This paper describes the current research into carbetocin and compare the effectiveness of uterotonics to assist healthcare decision makers to provide an effective uterotonic for prevention of PPH.[1] **Aims and objectives :** The aims of the present study were: - to compare the haemodynamic effects of oxytocin and carbetocin , to assess the efficacy of these two drugs in terms of intraoperative blood loss and the additional uterotonic needed in caesarean section and vaginal delivery in cases of post-partum haemorrhage. **Material and methods :** This randomised control study was conducted on 100 antenatal women who came in OPD of obstetrics and gynaecology for delivery in Muzaffarnagar Medical College. It was conducted for a period of 6 months. **Conclusion:** Carbetocin was more efficacious than oxytocin in terms of hemodynamic stability, use of additional uterotonics, and women undergoing PPH.

KEYWORDS

Carbetocin, Uterotonics, PPH

INTRODUCTION:

One of the main causes of maternal mortality globally, postpartum haemorrhage (PPH), accounts for 27.1% of all maternal deaths[1,2] and complicates 11% of all deliveries. Target is to reduce the global maternal mortality ratio to less than 70 per 100 000 live births by 2030. Uterine atony is the most frequent cause of haemorrhage at time of delivery, hence its prevention calls for an efficient uterotonic. When blood loss exceeds 500 mL following vaginal delivery and 1000 mL following a caesarean section within the first 24 hours of delivery, the condition is referred to as primary PPH.

Subtypes of PPH identified with ICD-9 and ICD-10 diagnostic codes included: 1) PPH due to retained placenta, 2) PPH due to uterine atony (occurring within 24 hours following delivery), 3) delayed and secondary PPH (occurring after the first 24 hours following delivery) and 4) PPH due to a coagulation defects.[6,7]

Currently, the World Health Organization (WHO)[1,3]recommends Active Management of the Third Stage of Labour (AMTSL) to prevent PPH. AMTSL as a prophylactic intervention is composed of three components : 1) administration of a uterotonic, preferably oxytocin, immediately after birth of the baby and before delivery of placenta; 2) controlled cord traction (CCT) to deliver the placenta; and 3) massage of the uterine fundus after the placenta is delivered.[1,3]

The most crucial procedure is the giving of a uterotonic to the mother as soon as the baby is born.[3]. Oxytocin is the recommended uterotonic where its efficacy can be assured.[1] Ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension

Exposure to circumstances that cause the uterotonic to degrade can reduce the efficiency of uterotonics in causing the uterine contractions required to prevent haemorrhage.[1] The effectiveness of oxytocin cannot be guaranteed in many low- and middle-income nations where access to sustained cold-chain is unavailable, the efficacy of oxytocin cannot be assured because it is susceptible to heat degradation resulting in treatment failure.[1,4,5]

A synthetic oxytocin analogue with a lengthy half-life, carbetocin was first described in 1987. Due to its 40-minute half-life (about 4 to 10 times longer than oxytocin's), it promotes more contraction time[7] and has less side effects (like headache, tremor, hypotension, nausea, abdominal pain, and pruritus). It causes regular contractions by attaching to oxytocin receptors in the uterus myometrium.

The use of carbetocin led to the creation of a product that satisfies the ICH stability standards for hot and humid conditions (Zone IV A and B) for 36 months at 30 °C and 6 months at 40 °C. A safe and stable uterotonic could help reduce maternal mortality from PPH in nations where the cold chain is unreliable or unavailable.[1]

A 2012 Cochrane study found that carbetocin reduced the requirement for further uterotonics and uterine massage when compared to oxytocin[24]. In 2018, a meta-analysis showed that carbetocin was effective in reducing the need for additional uterotonics, postpartum haemorrhage, and the need for transfusion during Caesarean procedures.[25]

When a pregnant woman has one PPH risk factor and has undergone an elective caesarean delivery or a normal vaginal delivery, the Society of Obstetricians and Gynecologists of Canada (SOGC; 2009) 9 recommends carbetocin as a first-line medication for the prevention of PPH.[23]

AIMS AND OBJECTIVES:

1) To study the effectiveness of carbetocin in prevention of PPH
2) To compare the hemodynamic effects of carbetocin with oxytocin
3) Need of additional uterotonic drugs

MATERIALS AND METHODS

This is a randomisation controlled study conducted on 100 antenatal women coming for delivery via any mode (vaginal or caesarean) in department of obstetrics & gynaecology in Muzaffarnagar Medical college & Hospital. They were randomly divided into two groups receiving either 10IU oxytocin or 100mcg carbetocin irrespective of mode of delivery.

Inclusion criteria:
All antenatal women with Singleton pregnancy coming to OPD /Emergency for delivery in Muzaffarnagar medical college

Exclusion criteria: Women with-
- Cardiovascular problems
- Thrombotic diseases
- Epilepsy
- Hypercoagulable state
- High blood pressure
- History of Hypersensitivity to carbetocin

A written informed consent was asked from eligible women on admission.

Firstly we recruited 50 women who received carbetocin **(group A)**, then we enrolled 50 women who received oxytocin **(group B)**. Women in the carbetocin group (group A) received a bolus of 100 µg i.m. after delivery of baby. Women in the oxytocin group (group B) received 10 IU of oxytocin i.m. after delivery of baby.

When the lady is admitted to the hospital for delivery, if she is in early labour, her vital signs are normal, and she is not under stress, she will be asked to participate in the trial.

To evaluate the haemodynamic effects between carbetocin and oxytocin we considered the drop in a blood pressure comparing the BP before administration of either uterotonic , 5 minutes and 2hrs after drug administration, The need for additional uterotonic agents or any blood transfusion , evaluation of the drop in haemoglobin level by comparing the pre and post delivery (12hrs) haemoglobin and number of patients underwent PPH.

Duration : 6 months

Sample size : 100

RESULTS :

All maternal subject characteristics were comparable in both the study groups.

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

Table 1: Maternal Age

Age	N =100	%
21-25	30	30
26-30	42	42
31-35	28	28

The maternal age in both groups was between 21-35yrs , most (42%) women being in the age group of 26-30 years

Table 2: Gestational Age

GESTATIONAL AGE	N=100	%
36-37.6 weeks	20	20
38-39.6 weeks	56	56
>=40 weeks	24	24

Most (56%) women delivered baby between gestational age 38-39.6 weeks

Table 3: Systolic Blood Pressure Before And After Delivery Via Any Mode

Category	Group A (SBP mmHg)	Group B (SBP mmHg)
Before administration	116	124
5 mins after administration	120	116
2 hrs after delivery	114	110

Table 4: Diastolic Blood Pressure Before And After Delivery Via Any Mode

Category	Group A (DBP mmHg)	Group B (DBP mmHg)
Before administration	68	70
5 mins after administration	64	62
2 hrs after delivery	70	64

Regarding the haemodynamic effects of carbetocin and oxytocin, both drugs have a hypotensive effect., but as seen in our study oxytocin is more hypotensive as compared to carbetocin both in systolic and diastolic B.P. but as a whole there is not much significant difference in BP measurements in both the groups.

Table 5: Outcome Of Third Stage Of Labor

Outcome	Group A		Group B	
	N=50	%	N=50	%
Primary PPH	4	8	8	16
Need for blood transfusion	6	12	10	20
Need for additional uterotonics	6	12	12	24

In present study it was observed that 8% patients from carbetocin group underwent primary PPH , all required blood transfusion and additional uterotonic drugs to control PPH. They were managed medically.

2 patient in carbetocin group was anaemic which required blood transfusion.

In oxytocin group , 16% patients underwent PPH, out of which 7 required blood transfusion and all 8 required additional uterotonic drugs. 7 were managed medically. 1 patient required bilateral uterine artery ligation to control PPH. 3 patients were anaemic which required blood transfusion.

Table 6: Haemoglobin Levels

Category	Group A	Group B
Pre delivery Hb	11.6 g/dl	11 g/dl
Post delivery Hb (12hrs)	11 g/dl	10 g/dl

Most of the women in the study group had haemoglobin in the range of 10-12 g/dl. In this study it was observed that there was more drop in haemoglobin in oxytocin group as compared to carbetocin group post delivery. 5% patients were anaemic in the study.

Uterine tone and uterine contractility were better in carbetocin group as compared to oxytocin group, fundus was significantly below 2 cm from the umbilical point in patients of group A after 2 and 12 hours post delivery.

Previous studies have shown that carbetocin could induce maternal tachycardia and facial flushing but no such side effects were seen in the present study.

DISCUSSION

Although oxytocin is the first-line agent in the prevention of postpartum haemorrhage, carbetocin has found its place in modern obstetrics. Our study compared the efficacy and safety of use of carbetocin and oxytocin for prevention of PPH.

A recent study of Moertl et al. showed that patients treated with oxytocin have more pronounced hypotension than patients treated with carbetocin,[7,16].So does this study reports a good haemodynamic profile in carbetocin group with substantially unmodified levels of systolic and diastolic blood pressure with respect to the BP levels in the group B in almost all the study times after drug administration.

Su et al. in the Cochrane of 2007 regarding "*Oxytocin agonists for preventing postpartum haemorrhage*" and in the Cochrane 2012 regarding *"Carbetocin for preventing postpartum haemorrhage"*, conclude that the use of carbetocin is more effective than oxytocin for preventing PPH in women undergoing caesarean section.[7-15]

Maged et al. studied high-risk pregnant women with PPH, and in another study, Maged et al. presented that carbetocin had significant advantages in preventing PPH incidence compared with oxytocin.[18-20]

In both study groups haemoglobin levels before and after 12 hours of delivery had no significant difference in both the groups, although there was a tendentially lower Hb decrease at 12 hours from delivery in the carbetocin group.

In our study , carbetocin group (12%) versus oxytocin group (24%), oxytocin group required additional uterotonics. Danzereau et al. firstly described a less additional uterotonic need for treatment of uterine atony in women who took carbetocin soon after delivery.[7,17]

Borruto et al. described a lower rate of additional oxytocic need in women undergoing carbetocin administration during CS[7,13] and we also reached on the same conclusions as many other researches.

At the same, there was a significant difference in the uterine tone and in the fundal height. The uterine contractility was better in the carbetocin group at 2, 12 and 24 hours after caesarean section and vaginal delivery. The fundus was significantly below 2 cm from the umbilical point in patients of group with respect to patients undergoing oxytocin administration.[7] Hence, suggesting the effectiveness of carbetocin compared to oxytocin regarding the uterine contraction and tonicity.

Despite being a synthetic oxytocin analogue, carbetocin may have stronger uterotonic effects and prevent PPH because of a small chemical structure variation.

Additionally, it was shown that although the oxytocin group experienced less postpartum blood loss than the carbetocin-treated group did, the incidence of postpartum anaemia was lower in the carbetocin-treated group.[20]

Pregnancy outcomes in our study showed that the carbetocin group had PPH in 8% of patients compared to oxytocin group which had PPH in

16% patients. In present study, blood loss was calculated by measuring the volume in the suction bottle and the absorption in the surgical drapes, gauzes, and pads.

Askar et al. compared the effect of 100 mcg of intramuscular carbetocin to syntometrine following vaginal delivery among 240 term low-risk pregnant women in a double-blind randomized controlled trial.[22,23]The authors concluded that intramuscular carbetocin was superior to syntometrine, as carbetocin caused less blood loss, less postpartum anemia, and fewer side effects than syntometrine; however, the authors found the two agents to be comparable in terms of the need for additional uterotonic drugs.

Carbetocin was considered safe for breast feeding because only a small amount of carbetocin passes into the breast milk after a single intravenous injection and does not cause side effects or clinical changes in the baby.

CONCLUSION:

Therefore, we draw the conclusion that a single carbetocin injection appears to be more efficient than oxytocin to maintain adequate uterine tone, with a similar safety profile in the third stage and in the first 24 hours following delivery, which are referred to as the "fourth stage of labour," and could be regularly used to prevent PPH.

Nelson et al. [20,21]considered that the effect of carbetocin was not inferior to oxytocin in the prevention of PPH, and the incidence of side effects was similar.

In terms of maternal outcomes, neither the carbetocin nor the oxytocin groups experienced any negative effects, such as organ damage (heart, lung, brain, liver, or kidney), the requirement for ventilator support, hemofiltration, or plasmapheresis.

But , Carbetocin is a relatively more expensive drug than conventional synthetic oxytocin (eg, Syntocinon), and there has not been sufficient evidence from cost-effectiveness studies to support its use in all patients. Still carbetocin proves to be more efficacious than the traditional oxytocin.

REFERENCES:

1. Fiona J. Theunissen et al. Current research on carbetocin and implications for prevention of postpartum haemorrhage. Theunissen et al. Reproductive Health 2018, 15(Suppl 1):94
2. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323–33.
3. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization; 2012. p. 4.
4. Hogerzeil HV, GJA W, de Goeje MJ. Stability of injectable oxytocics in tropical climates: WHO report; 1993. WHO/AP93.6.
5. Mullany L, Newton S, Afari-Asiedu S, et al. Cumulative effects of heat exposure and storage conditions of oxytocin-in-Uniject in rural Ghana: implications for scale up. Global Health Sci Pract. 2014;2(3):285–94.
6. Knight M, Callaghan WM, Berg C, Alexander S, Bouvier-Colle MH, Ford JB, et al. Trends in postpartum hemorrhage in high resource countries: a review and recommendations from the International Postpartum Hemorrhage Collaborative Group. BMC Pregnancy Childbirth 2009; 9:55.
7. Giovanni Larciprete et al, carbetocin versus oxytocin in caesarean section with high risk of post-partum haemorrhage. Journal of Prenatal Medicine 2013: 7 (1): 12-18
8. Su LL, Chong YS, Samuel M. Oxytocin agonists for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007; 3:CD005457.
9. Leduc D, Senikas V, Lalonde AB. Clinical Practice Obstetrics Committee; Society of Obstetricians and Gynaecologists of Canada. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can 2009; 31:980-983.
10. Sweeney G, Holbrook AM, Levine M, Yip M, Alfredson K, Cappi S, et al. Pharmacokinetics of carbetocin, a long acting oxytocin analogue, in nonpregnant women. Curr Ther Res 1990; 47:528-540.
11. Boucher M, Horbay GL, Griffin P, Deschamps Y, Desjardins C, Schulz M, et al. Double-blind randomised comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing caesarean section. J Perinatol 1998; 18:202-207.
12. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C,Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section:the results of a double-blind randomised trial. BJOG 2010;117:929-936.
13. Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum haemorrhage after caesarean section: a randomized clinical trial. Arch Gynecol Obstet 2009; 280:707-712.
14. Boucher M, Nimrod CA, Tawagi GF, Meeker TA, Rennicks White RE, Varin J. Comparison of carbetocin and oxyocin for the prevention of postpartum haemorrhage following vaginal delivery: a double-blind randomized trial. J Obstet Gynaecol .Can 2004; 26:481-488.
15. Su LL, Ching YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012;15:CD005457
16. Moertl MG, Friedrich S, Krashl J, Wadsack C, Lang U,Schlembach D. Haemodynamic effects of carbetocin and oxytcin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. B J Obstet and Gynaecol 2011; 118:1349-1356.
17. Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR,Luther ER, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after caesarean section. Am J Obstet Gynecol 1999 Mar; 180 (3Pt 1):670-676.
18. A. M. Maged, A. M. Hassan, and N. A. Shehata, "Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women," The Journal of Maternal-Fetal & Neonatal Medicine, vol. 29, no. 4, pp. 532–536, 2016.
19. A. M. Maged, A. M. Hassan, and N. A. Shehata, "Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal delivery: a randomised controlled trial," Archives of Gynecology and Obstetrics, vol. 293,no. 5, pp. 993–999, 2016.
20. Xiaojuan Huang et al. Effect of Carbetocin on Postpartum Hemorrhage after Vaginal Delivery: A Meta-Analysis. Computational and Mathematical Methods in Medicine Volume 2022, Article ID 6420738, 6 pages
21. H. van der Nelson, S. O'Brien, S. Burnard et al., "Intramuscular oxytocin versus Syntometrine® versus carbetocin for prevention of primary postpartum haemorrhage after vaginal birth:a randomised double- blinded clinical trial of effectiveness,side effects and quality of life," BJOG, vol. 128, no. 7,pp. 1236–1246, 2021.
22. Askar AA, Ismail MT, El-Ezz AA, Rabie NH (2011) Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. Arch Gynecol Obstet 284:1359–1365
23. Paweena Amornpetchakul et al . Intravenous carbetocin versus intravenous oxytocin for preventing atonic postpartum hemorrhage after normal vaginal delivery in high-risk singleton pregnancies: a triple-blind randomized controlled trial. Archives of Gynecology and Obstetrics 2017
24. Su LL, Chong YS, Samuel M (2012) Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. https ://doi.org/10.1002/14651 858.CD005 457.pub4
25. Tse KY, Yu FNY, Leung KY. Comparison of carbetocin and oxytocin infusions in reducing the requirement for additional uterotonics or procedures in women at increased risk of postpartum haemorrhage after Caesarean section. Hong Kong Med J. 2020 Oct;26(5):382-389. doi: 10.12809/hkmj208683. Epub 2020 Oct 8. PMID: 33028723.