Original Article

Comparative study of Efficacy and Safety of Carbetocin versus Oxytocin for Prevention of Postpartum Haemorrhage in Women Undergoing Normal Vaginal Delivery in Tertiary Care Centre of Bihar

Dr. Kanti Kumari, Dr. Arun Kumar, Dr. Mukesh Kumar, Dr. (Prof.) Asha Singh

1. Dr. Kanti Kumari, 2nd Year PG Student, Department of Pharmacology, Nalanda Medical College, Patna, Bihar, India.
2. Dr. Arun Kumar, Tutor (Senior Resident), Department of Pharmacology, Nalanda Medical College, Patna, Bihar, India.
3. Dr. Mukesh Kumar, Assistant Professor, Department of Pharmacology, Nalanda Medical College, Patna, Bihar, India.
4. Dr. (Prof.) Asha Singh, Professor & Head, Department of Pharmacology, Nalanda Medical College, Patna, Bihar, India.

***Corresponding author's E-mail:** arunakash71@gmail.com

Received: 12-03-2024; **Revised:** 26-04-2024; **Accepted:** 04-05-2024; **Published on:** 15-05-2024.

ABSTRACT

Introduction: Since oxytocin has a brief half-life and duration of action, it is currently the recommended treatment for avoiding postpartum haemorrhage. However, in numerous medium- to small-sized countries wherein cold chain transit and storage are not feasible, its effectiveness cannot be assured due to its heat sensitivity. On the other hand, the long-acting oxytocin analogue carbetocin is stable in the heat. Nevertheless, there is insufficient data to determine whether carbetocin or oxytocin is more effective and tolerable in preventing postpartum haemorrhage following vaginal birth.

Aims/objective: To evaluate and compare the safety and effectiveness of oxytocin and carbetocin in reducing postpartum haemorrhage in women undergoing normal vaginal delivery.

Materials and Method: Using randomly generated numbers from the internet, 100 women were split into groups C and O, each with 50 women. Women in group O received an intramuscular injection of oxytocin at a dosage of 10 IU, while women in group C received a single injection of heat-stable carbetocin at a dosage of 100 µg. The medications were started as soon as the baby was born. The mean blood loss following vaginal delivery served as the main outcome measure. Secondary outcome variables were the Proportion of women who lost more than 500 millilitres of blood, the need for additional uterotonic or surgical treatments, and the frequency of adverse events.

Results: Women receiving carbetocin experienced a mean blood loss that was comparatively lower to those receiving oxytocin, and the difference was of statistical significance ($p < 0.05$). In contrast, there was no discernible variation in the Proportion of women with PPH (blood loss greater than 500 millilitres). Although fewer women in the carbetocin group needed blood transfusions or extra uterotonic medications, this difference didn't appear to be of statistical significance ($p > 0.05$). There was not a significant difference ($p > 0.05$) between the two groups with respect to incidence of adverse events.

Conclusion: In women who have had a singleton vaginal delivery, carbetocin has been demonstrated to be more effective than oxytocin in avoiding postpartum haemorrhage. The government needs to take action to guarantee that carbetocin is affordable and readily available.

Keywords: Carbetocin, Oxytocin, Post-partum haemorrhage, Vaginal delivery, Uterotonic.

INTRODUCTION

Postpartum haemorrhage continues to be the most frequent primary reason of maternal mortality despite significant attempts to lower it. It is the cause of substantial maternal morbidity, such as blood transfusions, surgical emergencies, and ICU admissions, as well as about 25 percent of all deaths globally. [1, 2] One common consequence that is observed after between two and four percent of vaginal births and 6% of caesarean sections is post-partum haemorrhage. Around the world, it accounts for 35% of maternal mortality, making it the leading cause fatalities for mothers. [3] The cause of 38% of maternal mortality in India is postpartum haemorrhage.[4]

The term "postpartum haemorrhage" (PPH) refers to bleeding from the genital tract that is more than 500 mL following vaginal delivery and more than 1000 mL following caesarean section. The two types of PPH are primary (bleeding within the first 24 hours of delivery) and secondary (severe bleeding beyond 24 hours but inside 12 weeks).[5] When uterine muscles do not contract well after childbirth, it can lead to uterine atony, which is the most common cause of postpartum haemorrhage.[6]

In order to stop postpartum haemorrhage, the World Health Organization (WHO) currently advises aggressive treatment of the third stage of labour.[6] The most important aspect of actively managing the 3rd stage of labour is the preventative use of uterotonic drugs. Postpartum haemorrhage is about 50% less common when the uterotonic drug is used.[7]

Since oxytocin has a brief half-life and duration of action, it is currently the recommended treatment for avoiding postpartum haemorrhage. Its efficacy is nevertheless not assured across numerous medium- and small-sized countries wherein cold chain transit and storage are not feasible because to its heat sensitivity and quality issues like contaminants and inadequate active components also have an impact on its effectiveness.[8]

On the other hand, since 1997, postpartum haemorrhage has been effectively controlled with the administration of carbetocin, a long-lasting oxytocin analogue. It has been demonstrated that thermostatic carbetocin maintains its action for over three years at 30 degrees Celsius and 75 percent relative humidity.[9] It is possible to administer carbetocin intravenously or intramuscularly. Like oxytocin, the rate of side effects is minimal. It is also ideal for usage in primary or remote health centres because it requires fewer extra uterotonics.

The majority of carbetocin's postpartum haemorrhage prevention clinical trials have been conducted on caesarean procedures. According to a recent comprehensive review, carbetocin was found to be more efficacious than oxytocin in minimizing the requirement for extra uterotonics and post-partum uterine massage.[10]

Nevertheless, there is insufficient data to determine whether carbetocin or oxytocin is more effective and tolerable in preventing postpartum haemorrhage following vaginal birth. Consequently, we believed it was crucial to evaluate the effectiveness and safety of oxytocin and carbetocin in reducing postpartum haemorrhage in women having a typical vaginal delivery. We examined the volume of blood lost following vaginal delivery and the Proportion of women who lost more than 500 millilitres of blood between those who received oxytocin or carbetocin as a PPH preventive.

MATERIALS AND METHODS

The study involved a one-year open label randomised controlled trial conducted at a tertiary care centre located in eastern India, using a parallel 1:1 allocation of subjects. The Helsinki Declaration and good clinical practice recommendations were followed in the conduct of the study. Every study participant received a Participant Information Sheet, and signed written informed consent was obtained.

Inclusion criteria: Eligible women were those between the ages of 18 and 35 who were planned to undergo vaginal delivery and were having a singleton pregnancy with a gestational age of 37 to 40 weeks and a cervical dilatation of no more than 6 cm.

Exclusion criteria: Women with history of LSCS (lower segment caesarean section), women with requirement of instrumental vaginal delivery such as forceps or vacuum; women suffering from perineal or cervical tears at the time of labour and delivery; women with history of antepartum haemorrhage because of placenta praevia or abruptio placentae, women with history of preeclampsia or eclampsia or GDM (gestational diabetes mellitus) or multiple gestations or polyhydramnios; women with history of gynaecological problems like myomas; Women with history of coagulopathy; women with history of hypersensitivity to intervention drugs; women with history of hepatic, renal or cardiovascular disorders.

When a vaginal delivery was about to occur, women were randomized. Using randomly generated numbers from the internet, 100 women were split into groups C and O, each with 50 women. Women in group O received an intra-muscular injection of oxytocin at a dosage of 10 IU, while women in group C received an intra-muscular injection of heat-stable carbetocin at a dosage of 100µg. Following delivery of the infant, the medications were started right away, and the 3rd stage of labour was managed in accordance with WHO guidelines.[11] Following the clamping and cutting of the umbilical cord, the woman's buttocks were covered with a plastic drape intended to collect blood.

Blood was drawn either for one hour or for two hours if the bleeding continued beyond that time. After deducting the total weight of the drape at the beginning, the volume (millilitres) of the drape containing the gathered blood was calculated by weighing it on a digital scale and recording the weight in grams.

The trial's participation came to an end when the women were allowed to leave the hospital. Data on adverse events was documented from the point of informed consent until the point of release.

Primary Outcome Measure: Mean vaginal blood loss in millilitres.

Secondary Outcome Measures:

- Proportion of women who lose more than 500 millilitres of blood after giving birth
- Proportion of females in need of extra uterotonic drugs
- Proportion of women in need of blood transfusions
- Proportion of women who need the placenta to be manually removed
- Proportion of women in need of a hysterectomy or other extra surgical procedure
- Proportion of new-borns in need of artificial breathing or resuscitation
- Proportion of women whose adverse events were directly caused by interventional medications
- Proportion of women who had adverse event causally related to interventional drugs

Statistical Analysis: A tabular representation of the collected data was created using Microsoft Excel 2019. After that, the data was moved to graph pad version 8.4.3 for additional statistical analysis. The statistical significance of the differences in mean blood loss, women's age, and gestational age represented in mean ± standard deviation (SD) was assessed using an unpaired t test. To assess the statistical significance of variations in both primary and secondary outcome measures presented as proportions, Fisher's exact test was performed. The statistical significance threshold was set at a P-value of less than 0.05.

OBSERVATIONS AND RESULTS

Table 1: Comparison of baseline demographic and clinical characteristics between two groups

Variables	Group C (n = 50)	Group O (n = 50)	P-Value
Age in years (Mean ± SD)	26.94 ± 2.28	27.13 ± 2.01	0.66*
Number of primi-gravida	23	21	0.84**
Gestation age years (Mean ± SD)	38.94 ± 0.95	39.08 ± 1.04	0.48*
Number of women in which labour was induced	9	11	0.80**
Number of women in which labor was augmented	20	18	0.84*
Number of women with previous postpartum haemorrhage	2	1	>0.99**
*Unpaired t-test **Fisher's exact test			

In terms of baseline clinical and demographic traits, both groups were comparable. With regard to parity, duration of gestation, induction or augmentation of labor, or previous history of PPH, there was no statistically significant variance among the carbetocin and oxytocin group ($p > 0.05$).

Table 2: Comparison of efficacy of Carbetocin and oxytocin in post-partum haemorrhage

Outcome Measures	Group C (n = 50)	Group O (n = 50)	P-Value (Fisher's exact test)
Mean blood loss in ml ± SD	359.42 ± 39.82	391.77 ± 48.23	**0.0004** (Unpaired t test)
Number of women with post-partum blood loss > 500 ml	7	12	0.31
Number of women requiring additional uterotonic agents	9	12	0.62
Number of women requiring blood transfusion	1	4	0.36
Number of women requiring manual removal of placenta	0	1	>0.99
Number of women requiring additional surgical procedure	1	3	0.62
S- Significant NS- Non-Significant			

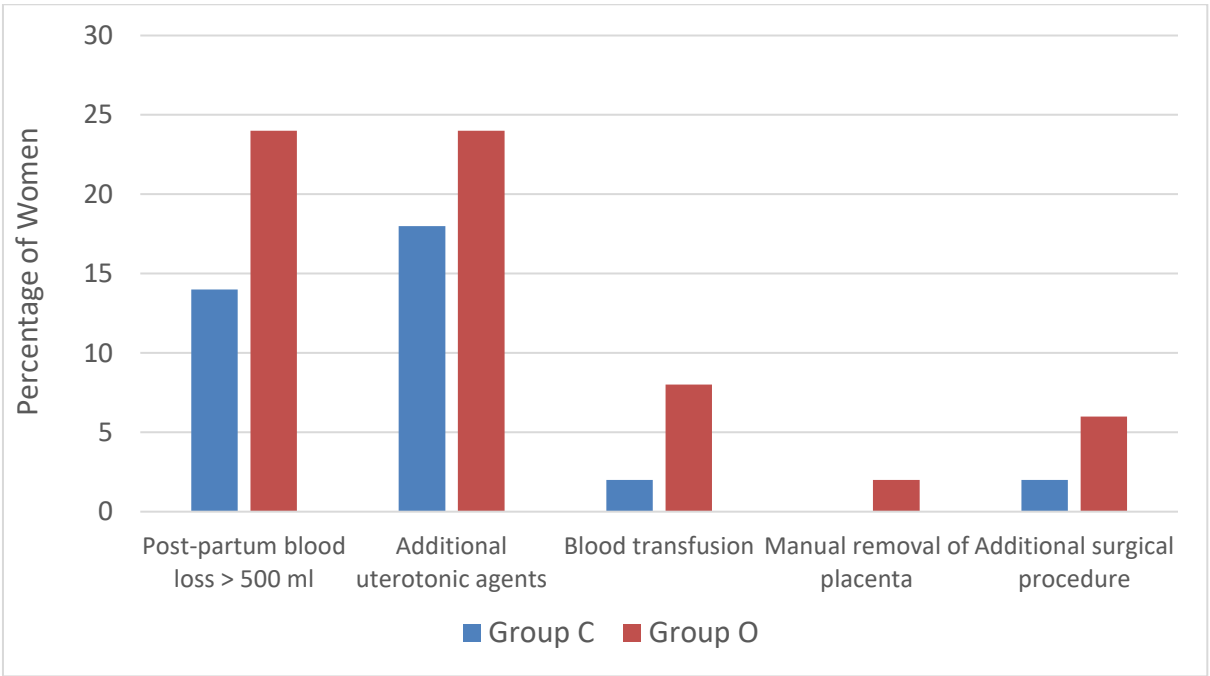

Figure 2: Comparison of efficacy of Carbetocin and oxytocin in post-partum haemorrhage

Table 3: Comparison of neonatal outcomes between two groups

Outcome	Group C (n = 50)	Group O (n = 50)	P-Value (Fisher's exact test)
Number of new-borns requiring resuscitation	3	5	0.72
Number of new-borns requiring mechanical ventilation resuscitation	1	3	0.62

There was no significant difference between carbetocin and oxytocin group with respect to neonatal outcomes (p>0.05).

Table 4: Comparison of frequency of different adverse events between two groups

Adverse Events	Group C (n = 50)	Group O (n = 50)	P-Value (Fisher's exact test)
Abdominal pain	2	6	0.27
Nausea & Vomiting	3	8	0.20
Chest pain	2	1	>0.99
Flushing	4	7	0.52

Women receiving carbetocin experienced a mean blood loss that was comparatively lower to those receiving oxytocin, and the difference proved to be of statistical significance ($p < 0.05$). However, the percentage of subjects with PPH (blood loss greater than 500 ml) did not change significantly, despite the carbetocin group showing marginally superior results. Although fewer women in the carbetocin group needed blood transfusions or extra uterotonic medications, this difference was not of statistical significance ($p > 0.05$). Compared to 4 women in the oxytocin group, just 1 woman in the carbetocin group needed surgical intervention or manual placenta removal.

Carbetocin and oxytocin were found to be equivalent with respect to safety. There was no statistically significant difference between carbetocin and oxytocin with respect to incidence of adverse events (P>0.05).

DISCUSSION

The purpose of this study was to examine the safety and effectiveness of 10 IU oxytocin and 100 mcg carbetocin in preventing postpartum haemorrhage in women who had singleton vaginal delivery at term. Compared to the oxytocin group, we found that the prevalence rates of postpartum haemorrhage were lower in the carbetocin group. This demonstrates that carbetocin is more effective than oxytocin when it comes to preventing postpartum haemorrhage.

The oxytocin group had a greater rate of PPH within 1-3 hours of birth and a higher requirement for other uterotonics for PPH prophylaxis. These findings are consistent with the research of Rath W et al., which found that the prolonged duration of carbetocin's effect contributed to similar incidence rates.[12] The women who received carbetocin had lower blood loss following delivery; this difference was shown to be of statistical significance. It was discovered that the safety profiles of oxytocin and carbetocin were comparable, and neither group experienced any severe adverse events during the first 24 hours following the drug's administration.

Therefore, convenience should be the key consideration when deciding whether to utilize carbetocin in a particular scenario, especially in primary and rural health centres. In developing nations like India, atonic postpartum haemorrhage is the main cause of mother mortality. 4 According to Jackson Jr. KW et al.'s research, uterotonics is the most effective way to manage and avoid postpartum haemorrhage, which has resulted in the widespread use of oxytocin.[13] But keeping up the cold chain required for oxytocin function is difficult in India, especially in rural regions. Under such conditions, heat-stable carbetocin can be especially lifesaving.

Furthermore, it was found in the research of Maged AM et al. that a single intramuscular or intravenous dosage of carbetocin is equally beneficial.[14] Carbetocin has also been shown in the research of Malm M et al. to have a satisfactory safety profile when injected through IV or IM route, with a very low frequency of adverse events. This makes it possible to employ it in basic healthcare settings.[15] Carbetocin costs more than oxytocin in India. However, carbetocin is a useful medication in the Indian environment due to its one-dose effectiveness and without a cold chain necessity.

There was no statistically noteworthy difference in blood loss above 500 ml between women with vaginal delivery and those given carbetocin or oxytocin, according to a meta-analysis of five randomized studies including 30,314 women. The results of the sensitivity studies were comparable. Additionally, according to the meta-analysis, there were not any statistically significant variations between the groups of women getting oxytocin or carbetocin in terms of blood loss exceeding 1000 ml, the requirement of extra uterotonic medication, the demand for blood transfusion, the necessity of uterine massage, or complications.[16]

The ability to obtain strong uterotonic drugs is essential for avoiding atony postpartum haemorrhage. However, according to the Theunissen FJ et al. research, low- and middle-income countries frequently have issues with the quality of uterotonic agents.[17] The latest data indicates that in these countries, insufficient quantities of the active component resulted in quality testing failures for 45.6% to 74.2% of oxytocin specimens.[8, 18] As a result, improving the potency and calibre of uterotonic medications is essential to halting postpartum haemorrhage.

Carbetocin has an advantage over oxytocin in avoiding haemorrhage after childbirth. Unlike oxytocin, carbetocin doesn't need cold-chain transportation or storage because it is heat-resistant. For this reason, it is easy to maintain carbetocin at room temperature in nations with low or middle incomes where cold-chain transit and storage are not available. Half-life of carbetocin is 40 minutes which is 4 to 10 times greater than that of oxytocin. According to studies by Amornpetchakul P et al., intramuscular administration of carbetocin can be utilized to prevent the adverse effects of IV injection; the duration of action is120 minutes following intramuscular administration.[19]

According to a survey conducted by Combs CA et al., the following conditions increase the risk of postpartum haemorrhage: placenta retention in uterus, polyhydramnios, multiple pregnancies, or past experiences with prolonged labour.[20] It is unclear if women obtained a dose of carbetocin that prevented PPH in an effective manner. Subpopulations such as women with polyhydramnios, twin pregnancies, or past experiences of prolonged labour should be the focus of future research. Subsequent research endeavours ought to explore the ideal dosage, regimen, and mode of administration of carbetocin for the aforementioned subgroups.

CONCLUSION

In women who have had a singleton vaginal delivery, carbetocin has been demonstrated to be more effective than oxytocin in avoiding postpartum haemorrhage. Safety of carbetocin was also found to be better than oxytocin. Its room temperature stability makes it suitable for use in developing nations like India. The most economical option for routine prophylaxis is carbetocin. Currently, carbetocin is more expensive than oxytocin, which may restrict its application in outlying health centres. The government needs to take action to guarantee that carbetocin is affordable and readily available.

Acknowledgement: We are thankful to the healthcare workers of Nalanda Medical College, Patna, Bihar, India

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Global Health 2014;2:e323–33.
2. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980-2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet (London, England) 2010;375:1609–23.
3. Trends in maternal mortality: 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: World Health Organization; 2019.
4. Postpartum haemorrhage. National Health Portal of India. Available from: https://www.nhp.gov.in/disease/gynaecology-and-obstetrics/postpartumhaemorrhage Accessed on 3 May 2022
5. Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2016;198:12-21.
6. Heneghan C, Ward A, Perera R, et al. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. Lancet (London, England) 2012;379:322–34.
7. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev 2013;Cd001808.
8. Torloni MR, Gomes Freitas C, Kartoglu UH, et al. Quality of oxytocin available in low- and middle-income countries: a systematic review of the literature. BJOG 2016;123:2076–86.
9. Malm M, Madsen I, Kjellstrom J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. J Peptide Sci 2018;24:e3082.
10. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database SysReviews (Online) 2012;4:CD005457.
11. WHO recommendations on prevention and treatment of postpartum haemorrhage. Geneva: World Health Organization, 2012.
12. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):15-20.
13. Jackson Jr KW, Allbert JR, Schemmer GK, Elliot M, Humphrey A, Taylor J. A randomized controlled trial comparing oxytocin administration before and after placental delivery in the prevention of postpartum hemorrhage. Am J Obstet Gynecol. 2001;185(4):873- 7.
14. Maged AM, Hassan AM, Shehata NA. Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery in high risk women. J Matern Neonat Med. 2015;29(4):532-6.
15. Malm M, Madsen I, Kjellström J. Development and stability of a heat-stable formulation of carbetocin for the prevention

of postpartum haemorrhage for use in low and middle-income countries. J Pep Sci. 2018:e3082.

16. Jin XH, Li D, Li X. Carbetocin vs oxytocin for prevention of postpartum hemorrhage after vaginal delivery: A meta-analysis. Medicine (Baltimore). 2019 Nov;98(47):e17911. doi: 10.1097/MD.0000000000017911. PMID: 31764790; PMCID: PMC6882650.

17. Theunissen FJ, Chinery L, Pujar YV. Current research on carbetocin and implications for prevention of postpartum haemorrhage. Reprod Health 2018;15.

18. Anyakora C, Oni Y, Ezedinachi U, et al. Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits. BMC Preg Childbirth 2018;18:44.

19. Amornpetchakul P, Lertbunnaphong T, Boriboonhiransarn D, 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. Arch Gynecol Obst 2018;298:319–27.

20. Combs CA, Murphy EL, Laros RK., Jr Factors associated with postpartum hemorrhage with vaginal birth. Obst Gynecol 1991;77:69–76.