Comparative Study between Oxytocin and Carbetocin in Prevention of Postpartum Hemorrhage

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Background: Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide. Uterotonic agents like oxytocin and carbetocin are used to prevent PPH by promoting uterine contractions. While oxytocin is widely used, carbetocin, a long-acting oxytocin analog, has gained attention for its sustained effects and potential to reduce the need for additional uterotonics.

Objective: To compare the efficacy and safety of oxytocin and carbetocin in preventing PPH in women undergoing vaginal delivery or caesarean section.

Methods: This review examines randomized controlled trials and observational studies comparing intravenous or intramuscular oxytocin and carbetocin. Outcomes assessed include postpartum blood loss, need for additional uterotonics, haemodynamic stability, and adverse effects.

Results:

- **Efficacy: Carbetocin demonstrates comparable or superior efficacy to oxytocin in reducing blood loss and the need for additional uterotonics.**
- **Haemodynamic Effects: Carbetocin is associated with more stable haemodynamic profiles due to its prolonged half-life, whereas oxytocin may cause transient hypotension or tachycardia.**
- **Safety: Both drugs have a low incidence of adverse effects, but carbetocin's single-dose administration offers practical advantages in resource-limited settings.**

Conclusion: Both oxytocin and carbetocin are effective in PPH prevention. Carbetocin's longer duration of action and stable haemodynamic effects make it a promising alternative to oxytocin, particularly in high-risk patients or where consistent monitoring is challenging. Further large-scale studies are needed to assess cost-effectiveness and long-term outcomes.

Keywords: postpartum hemorrhage, oxytocin, carbetocin, uterotonic agents, caesarean section, vaginal delivery.

The American College of Obstetricians and Gynaecologists (ACOG) defines postpartum hemorrhage (PPH) as a cumulative blood loss of 1,000 millilitres or more, accompanied by symptoms or signs of hypovolemia, occurring within the first 24 hours after childbirth.

Postpartum hemorrhage (PPH) remains the leading cause of maternal mortality and contributes significantly to maternal morbidity. It often necessitates blood transfusions, emergency surgical interventions, and intensive care unit (ICU) admissions. PPH accounts for approximately 25% of maternal deaths globally and is a common complication in childbirth, occurring in about 2–4% of vaginal deliveries and 6% of cesarean sections. Worldwide, PPH is responsible for 35% of maternal deaths, making it the primary cause of maternal fatalities. In India, this figure rises to 38%.

PPH is defined as excessive bleeding from the genital tract, exceeding 500 mL following vaginal delivery or 1,000 mL after a cesarean section. It is classified into two types:

1. Primary PPH, which occurs within the first 24 hours after childbirth.
2. Secondary PPH, which refers to severe bleeding occurring beyond 24 hours but within 12 weeks postpartum.

The leading cause of PPH is uterine atony, where the uterine muscles fail to contract adequately after childbirth. To prevent PPH, the World Health Organization (WHO) recommends a proactive approach during the third stage of labour. The cornerstone of this strategy is the use of uterotonic medications, which significantly reduce the risk of PPH by approximately 50%.

Oxytocin is currently the first-line treatment for PPH prevention due to its short half-life and rapid onset of action. However, its efficacy can be compromised in countries with limited access to cold-chain transportation and storage, as heat sensitivity and quality issues such as impurities or insufficient active components can affect its potency.

Since 1997, carbetocin, a long-acting analogue of oxytocin, has been used successfully to manage PPH.

Unlike oxytocin, thermostable carbetocin remains effective for over three years when stored at 30°C with a relative humidity of 75%. It can be administered via intravenous or intramuscular routes, with minimal side effects similar to oxytocin.

Carbetocin has shown superior safety compared to oxytocin, with its ability to remain stable at room temperature making it particularly suitable for use in developing countries like India. It is also the most cost-effective option for routine preventive treatment. However, the higher cost of carbetocin compared to oxytocin may limit its availability in remote healthcare facilities. It is crucial for the government to ensure that carbetocin is both affordable and readily accessible.

The short half-life of oxytocin, ranging from 1 to 6 minutes, is a significant limitation, as it often necessitates continuous intravenous infusion or repeated intramuscular injections.

Carbetocin, a long-acting analogue of oxytocin, is now recommended for the prevention of uterine atony following cesarean sections (CS) performed under epidural or spinal anesthesia. Carbetocin provides a rapid onset of action within 1–2 minutes and has a prolonged duration of effect, lasting approximately 1 hour. This results in stronger and more sustained uterine contractions compared to oxytocin. Additionally, carbetocin shares a similar safety profile with oxytocin, making it a safe and effective option for broader use.

Oxytocin plays a vital role in stimulating smooth muscle contractions. Postpartum, it is released to promote uterine contractions, helping to prevent excessive bleeding. Additionally, oxytocin triggers the milk let-down reflex, facilitating lactation.

In the uterus, oxytocin induces rhythmic contractions in the upper segment of the myometrium, leading to the constriction of spiral arteries and a reduction in uterine blood flow. This mechanism makes oxytocin an effective first-line treatment for postpartum hemorrhage (PPH).

Carbetocin operates similarly to oxytocin but offers distinct advantages. With a significantly longer half-life and the ability to produce stronger and more sustained contractions, carbetocin enhances the management of postpartum bleeding.

The primary objective of using uterotonic agents during the third stage of labor and after cesarean sections is to reduce postpartum and postoperative bleeding, respectively. Evidence from a cross-sectional study revealed that the postoperative blood loss in the carbetocin group was significantly lower compared to the oxytocin group. Furthermore, the incidence of hemorrhage was 12% in the carbetocin group versus 32% in the oxytocin group. This demonstrates that carbetocin is more effective than oxytocin in preventing uterine atony and, consequently, PPH.

Oxytocin injection (synthetic) acts on the smooth muscle of the uterus to stimulate contractions, with its efficacy depending on the uterine threshold of excitability. It specifically targets the uterine smooth muscle, particularly toward the end of pregnancy, during labor, and immediately after delivery. Oxytocin promotes rhythmic uterine contractions, increases the frequency of existing contractions, and enhances uterine muscle tone. However, it has a very short half-life of 4 to 10 minutes, limiting its duration of action.

Carbetocin, a long-acting synthetic analogue of oxytocin, was first described in 1987. Its half-life is approximately 40 minutes—4 to 10 times longer than that of oxytocin. Intravenous administration of an optimal dose of 100 μg has been shown to provide an effect comparable to a 16-hour intravenous infusion of oxytocin in terms of increasing uterine tone and reducing the risk of postpartum hemorrhage (PPH) in elective caesarean sections.

Carbetocin binds to oxytocin receptors on the uterine smooth muscle, stimulating rhythmic contractions, increasing the frequency of existing contractions, and enhancing uterine tone. During pregnancy, the number of oxytocin receptors in the uterus increases significantly, reaching its peak at the time of delivery. In the non-pregnant state, the uterine oxytocin receptor content is minimal.
We divided the participants into two groups, each consisting of 50 women. One group received an intramuscular injection of 10 IU of oxytocin, while the other group was administered 100 μg of heat-stable carbetocin intramuscularly. The drugs were promptly administered after the delivery of the baby, and the third stage of labor was managed in accordance with the World Health Organization's (WHO) recommendations.

The surgeon clamped and cut the umbilical cord and placed a plastic drape under the woman's buttocks to collect blood. If bleeding persisted beyond the first hour, blood was collected for an additional hour or two. The volume of collected blood was measured by weighing the drape before and after use on a digital scale, with the difference recorded in grams. The trial concluded when the women were discharged from the hospital, and adverse event data were collected from the time of informed consent until discharge.

The primary outcome measure was the average volume of blood loss from the vagina, recorded in milliliters. The secondary outcome measures included:

- The number of women who lost more than 500 millilitres of blood postpartum.
- The number of women requiring additional uterotonic drugs.
- The number of women needing blood transfusions.
- The number of women requiring manual removal of the placenta.
- The number of women undergoing hysterectomy or other surgical interventions.
- The number of new-borns requiring artificial respiration or resuscitation.
- The number of adverse events directly related to the administered drugs.

When comparing the efficacy of 10 IU oxytocin and 100 μg carbetocin in preventing postpartum hemorrhage in women who had a full-term vaginal birth of a single baby, we observed a significant reduction in postpartum hemorrhage rates in the carbetocin group. Women treated with oxytocin had a higher incidence of postpartum hemorrhage within 1–3 hours after delivery and required more subsequent interventions.

he short half-life of oxytocin, ranging from 1 to 6 minutes, presents a limitation as it often necessitates continuous intravenous infusion or multiple intramuscular injections.

Carbetocin,a long-acting analogue of oxytocin, is now recommended for preventing uterine atony following cesarean sections (CS) performed under epidural or spinal anesthesia. Carbetocin induces a sustained uterine response, resulting in stronger and more frequent contractions. It has a rapid onset of action within 1–2 minutes and a prolonged duration of effect, lasting approximately 1 hour, making it more effective than its parent drug, oxytocin. Moreover, carbetocin's safety profile is comparable to that of oxytocin, supporting its broader use in clinical practice.

When comparing blood loss and hemoglobin (Hb) levels as parameters, there was a statistically significant difference between the carbetocin and oxytocin groups. Blood loss was notably lower in the carbetocin group compared to the oxytocin group. Blood loss was calculated using gravimetric measurement.

Hemoglobin (Hb) and hematocrit (HCT) levels were evaluated preoperatively and postoperatively in both groups. Preoperative Hb and HCT levels showed no significant differences between the groups. However, postoperative Hb and HCT levels were significantly higher in the carbetocin group than in the oxytocin group. These findings indicate that carbetocin was more effective in controlling blood loss and maintaining Hb and HCT levels.

Furthermore, the changes in Hb and HCT levels from preoperative to postoperative measurements were significantly smaller in the carbetocin group compared to the oxytocin group, further supporting the superior efficacy of carbetocin in minimizing blood loss and preserving blood parameters. The difference in hemoglobin (Hb) levels suggests significantly higher blood loss in the oxytocin group, indicating that carbetocin was more effective in controlling blood loss and in maintaining higher levels of Hb and hematocrit (HCT) values. These findings conclude that carbetocin showed superior results in minimizing blood loss and preserving blood parameters compared to oxytocin.

The carbetocin group demonstrated a lower need for additional uterotonic agents, with only (20%) requiring further administration, compared to (32%) in the oxytocin group. However, this difference was not statistically significant

In terms of severe anemia, the carbetocin group showed 10% incidence, while the oxytocin group had 20%. There was no statistically significant difference between the groups (P value = 0.161).

Similarly, regarding the need for blood transfusions, 6% of the carbetocin group required transfusions,

compared to 10% in the oxytocin group, but again, no statistically significant difference was observed.

Carbetocin is more effective than oxytocin in preventing postpartum hemorrhage in women who have undergone a vaginal delivery of a single baby. It also demonstrated superior safety compared to oxytocin. Its ability to remain stable at room temperature makes it particularly suitable for use in developing countries like India. While carbetocin is the most cost-effective choice for routine preventive treatment, its higher cost compared to oxytocin could limit its availability in remote healthcare facilities. Therefore, it is essential for the government to ensure that carbetocin is affordable and easily accessible.

Adverse reactions to carbetocin may include nausea, vomiting, abdominal pain, itching, increased body temperature, trembling, and weakness, affecting 10.0% to 40.0% of patients. In addition, 1.0% to 5.0% of patients may experience more severe side effects, such as back and chest pain, dizziness, anemia, chills, sweating, a metallic taste, tachycardia, and respiratory distress.

Carbetocin was found to be more effective than oxytocin in reducing postpartum blood loss, minimizing the need for uterine massage following vaginal births, and maintaining stable hemoglobin levels, according to research conducted among pregnant women with at least two risk factors for postpartum hemorrhage (PPH). Several previous studies also indicated that, compared to oxytocin, carbetocin reduced blood loss and the risk of postpartum hemorrhage after cesarean sections.
However, postpartum hemoglobin levels, blood transfusion rates, the use of hemostatics, the need for additional surgical procedures, uterine massage, and postpartum blood loss were not significantly different between the two groups. Potential reasons for the discrepancy between our results and those of other studies may include differences in the study populations and variations in the methodology used to calculate blood loss after cesarean sections. In this study, blood loss was assessed through the volume in suction bottles and the absorption in surgical drapes, gauzes, and pads.

REFERENCES

[1] Mishra A, Singh RP, Pandey D, Singh KP. A comparative study on prophylactic use of oxytocin and carbetocin in cesarean delivery to prevent primary postpartum hemorrhage in tertiary care centre, Sitapur. Int J Life Sci Biotech Pharm Res. 2024;13(7):105. doi: 10.69605/ijlbpr_13.7.2024.105.

[2] Sinha M, Prabha R. Efficacy and Safety of Carbetocin Vs. Oxytocin in Preventing Postpartum Hemorrhage in Vaginal Deliveries: A Comparative Study. Azerbaijan Pharmaceutical and Pharmacotherapy Journal. 2024 Jul;23(3):1-None.

[3] Rao, Yarramsetti V.; Sravanthi, Thumpati Sai[1]; Kummarapurugu, Srividya[1]; Prasanna, Battula Lakshmi; Kuppili, Satwik[1]. Comparison of Carbetocin and Oxytocin Efficacy in Preventing Postpartum Hemorrhage after C-Section. Journal of Obstetric Anaesthesia and Critical Care 14(2):p 126-130, Jul–Dec 2024. | DOI: 10.4103/JOACC.JOACC_59_23

[4] Elomda, Fahd Abdelaal; Said, Ahmed Mohamed; and Sahloul, Wesam Hamdy (2023) "Comparison between oxytocin intravenous bolus, oxytocin intravenous bolus and infusion, rectal misoprostol and carbetocin infusion for the control of blood loss at elective cesarean section," Al-Azhar International Medical Journal: Vol. 4: Iss. 2, Article 3.

[5] MRH K, CK D, RA S. Haemodynamic effects of intravenous bolus of carbetocin and oxytocin on women undergoing caesarean section. Bangladesh Medical College Journal.28(1): 2023

[6] Bansal DrK, Sharma DrP, Jain DrS. INJECTION OXITOCIN VS INJECTION CARBETOCININ REDUCTION OF POSTPARTUM BLOOD LOSS IN CAESAREAN SECTION -A RANDOMIZED CONTROL STUDY. Journal of Cardiovascular Disease Research. 11(4):0976-2833.

[7] Tai K, Barman K, Das R, Mili T. Comparison of intravenous carbetocin versus intramuscular oxytocin in management of third stage of labour in vaginal delivery. The New Indian Journal of OBGYN. 10(2)(2454-2334).

[8] Choudhury FH, Noor MS, Tanzin ST. Comparison of Complication and Post-Operative Infection Rate Between Application of Carbetocin and Oxytocin during Management of Post-Partum Hemorrhage after Caesarean Section. Bangladesh Journal of Infectious Diseases. Volume 10,:Page 59-64.

[9] Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012;2:301-5.
[10] Moertl MG, Friedrich S, Kraschl J, Wadsack C, Lang U, Schlembach D. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: A randomised trial. BJOG 2011;118:1349-56.
[11] Hummel P, Holleboom CAG, Bolte AC, Creutzberg EC, Bruinse HW. Carbetocin for the Prevention of Fluxus Postpartum after a Caesarean section: Efficacy and Safety in Dutch Practice. Proceedings of the European Congress of Perinatal Medicine, 2010. p. 609-13.
[12] Fda.govn.d.Availablefrom: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/018261s031lbl.pdf. [Last accessed on 2023 July 13].. Chow R, Li A, Wu N, et al. Quality appraisal of systematic reviews on methods of labour induction: a systematic review. Arch Gynecol Obstet. 2021;304:1417e1426.
[13] Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Global Health. 2014; 2:e323ee333.
[14] Yaliwal RG, Biradar AM, Dharmarao PS, et al. A randomized control trial of 3 iu iv oxytocin bolus with 7 iu oxytocin infusion versus 10 iu oxytocin infusion during cesarean section for prevention of postpartum hemorrhage. Int J Wom Health. 2020; 12:1091.
[15] Charles D, Anger H, Dabash R, et al. Intramuscular injection,intravenous infusion, andintravenous bolus of oxytocin in the third stage of labor for prevention of postpartum hemorrhage:a three-arm randomized control trial. BMC Pregnancy Child birth. 2019;19:1e8.