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Original Research Article

Study on Oxytocin Versus Carbetocin In Management of Third Stage of Labour In Vaginal Deliveries

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Abstract:

Background: Postpartum hemorrhage (PPH) is one of the primary causes of maternal illness and death globally. About 25% of female fatalities are caused by it with higher rates in developing countries like India. Blood loss of at least 500 milliliters within 24 hours of delivery is referred to as primary PPH, whereas secondary PPH happens between 24 hours and 12 weeks after delivery. Active management of the third stage of labour with uterotonics is the gold standard for prevention. Oxytocin is the first-line drug, while carbetocin, a longer-acting and heat-stable oxytocin analogue, has shown potential benefits but requires further evaluation.

Method: A randomized, double-blind controlled trial was conducted over 12 months at the Department of Obstetrics & Gynaecology, RIMS Ranchi, including 170 women having a typical vaginal birth. Following delivery, participants were randomized to receive intramuscular oxytocin 10 IU (n=85) or carbetocin 100 µg (n=85). Primary outcome was incidence of PPH (≥500 mL blood loss). Hemoglobin alteration, the requirement for extra uterotonics, blood transfusions, intensive care unit admission, and side effects were examples of secondary outcomes. SPSS was used for the statistical analysis, and $p<0.05$ was accepted as significant.

Results: Baseline demographic and obstetric characteristics were similar between groups. PPH occurred in 21.18% of the carbetocin group and 24.71% of the oxytocin group (p=0.584). Mean hemoglobin drop was similar (1.10 ± 1.11 g/dL vs 1.15 ± 1.14 g/dL; p=0.947). Additional uterotonics were required in 20.0% vs 24.71% (p=0.461), blood transfusion in 3.53% vs 7.06% (p=0.496), and ICU admission in 2.35% vs 1.18% (p=1.00) for carbetocin and oxytocin, respectively. Adverse-effect rates were low and comparable in both groups.

Conclusion: After vaginal delivery, carbetocin and oxytocin showed similar safety and effectiveness in preventing postpartum hemorrhage. The cases of PPH, hemoglobin drop, and need for additional uterotonics did not significantly differ between the groups. Blood transfusion, ICU admission, and adverse effects also showed no significant differences between the groups. Carbetocin remains a viable alternative to oxytocin, especially in resource-limited settings where its heat stability offers logistical advantages.

Keywords: Postpartum haemorrhage, Carbetocin, Oxytocin, Vaginal delivery, Uterotonics, Randomized controlled trial.

Introduction

Postpartum haemorrhage (PPH) is a major concern worldwide, associated with a significant morbidity and mortality. The World Health Organization (WHO) defines postpartum hemorrhage in vaginal deliveries as 500 milliliters or more of blood lost within 24 hours of delivery. Thousands of women die each year due to PPH. It is the main reason of maternal mortality that is responsible for almost 25% of female's deaths all over the world [1]. The estimated incidence of PPH, based on previous nationwide studies, ranges from 2.8% to 7.9% [2]. India contributes to nearly 20% of global maternal mortality. PPH is a frequent complication during delivery in India, with occurrence rates ranging from 2% to 6% after vaginal delivery and about 6% following caesarean section [3]. There are two types of postpartum hemorrhage (PPH): primary and secondary. Any bleeding from the birth canal that takes place between 24 hours and 12 weeks after delivery is referred to as secondary PPH, whereas

primary PPH is defined as blood loss of 500 ml or more within 24 hours of delivery. Based on the volume of blood loss, PPH is also classified as minor (500 ml to 1 liter) or major (more than 1 liter). Major PPH can be further specified as moderate (1 to 2 liters), severe (more than 2 liters), or a massive obstetric hemorrhage (more than 2.5 liters) [4,5].

The consequences of PPH extend beyond the immediate postpartum period, leading to significant morbidity. Chronic anemia, lactation failure, blood transfusion, prolonged hospital stays, increased risk of infection, ICU admissions, and impaired quality of life are among the potential sequelae. Psychosocial morbidity further compounds the impact of PPH on affected individuals and their families. Despite advancements in obstetric care, PPH continues to pose a challenge globally, emphasizing the ongoing need for effective prevention, timely intervention, and comprehensive management strategies [6,7,8]

Although PPH is a leading cause of maternal mortality, it can be effectively managed. The proactive control of the third stage of labor, which includes uterotonic medications, controlled cord traction, and uterine massage, is the gold standard for prevention. Oxytocin (10 IU IM) is the preferred drug, administered after the anterior shoulder is delivered. Carbetocin (100 µg IV or IM) is an alternative for elective cesarean sections. Since there is a greater chance of adverse effects, rgonovine is regarded as a backup option. [9,10].

Carbetocin, a synthetic oxytocin analog, has a four-fold prolonged half-life than oxytocin, eliminating the need for continuous infusion. It is particularly useful in areas without a cold chain, as it is more heat-stable than oxytocin.Compared to oxytocin, studies indicate that carbetocin may lessen the need for additional uterotonics and lower the incidence of PPH; however, further research is required to ascertain which medication is better [11,12].

Methods

Study design: Randomized controlled Double blinded Study

Study population: This study included women who underwent normal vaginal deliveries at Labour room emergency, Department of Obstetrics & Gynaecology, RIMS Ranchi.

Place of study: The study was conducted at Labour room emergency Department of Obstetrics &

Gynaecology, RIMS Ranchi

Duration of study: 12 months (March 2023 to March 2024)

Study Population and Sample Size: A minimum sample size of 85 patients per group was determined based on a prior study that revealed a primary PPH rate of 8.5% in the oxytocin group and 0% in the carbetocin group. This was evaluated using a standard formula to ensure the study had an 80% power and a 5% level of significance, resulting in a total sample size of 170 patients.

Blood loss measurement: Weighing soaked swabs or drapes after delivery is one technique that has been shown to be useful for the early diagnosis of PPH. Nevertheless, this approach significantly adds to the strain of medical personnel and might not be appropriate in a busy hospital environment. Another technique for measuring postpartum blood loss is the use of sterile under-buttock or postpartum drapes. This approach is affordable, practical, and simple to deploy, making it appropriate for hospitals with limited resources. This study employed this methodology.

Inclusion criteria

- Every female who choose to give a typical vaginal birth.

Exclusion criteria

- Women who underwent caesarean section.
- Women who have a history of oxytocin and carbetocin hypersensitivity.
- Women with epilepsy, liver or kidney disease, or cardiovascular disorders

Methodology: This study involved a detailed examination of patients, where all findings were recorded on a predesigned proforma. Following informed consent, patient data such as age, parity, gestational age, and medical history (including menstrual, obstetrical, and past medical/surgical history) were collected. A thorough physical and systemic examination was conducted, noting factors like pregnancy-induced hypertension, gestational diabetes, and mode of delivery. Relevant investigations, including a complete blood count, blood typing (ABO/Rh), and blood sugar, were also performed. The primary outcomes observed were the occurrence of PPH, the need for additional uterotonics, uterine massage, and blood transfusions, as well as the change in hemoglobin levels before and after delivery.

Block Randomization: The study used a double-blinded block randomization method to assign 170 women into two groups: an oxytocin group and a carbetocin group. The allocation was managed using a sealed envelope system, with 17 blocks, each containing 10 envelopes (5 for each group). Upon a patient's consent, an envelope was randomly selected to determine their group assignment. The first group received a 10 IU intramuscular injection of oxytocin, while the second group received a 100 mcg intramuscular injection of carbetocin immediately after delivery. Both the patients and the

investigator were unaware of the group assignments to ensure the study remained double-blinded.

Statistical Analysis: The study utilized various statistical methods to analyze the data. Quantitative data were displayed as means with standard deviations or as medians with interquartile ranges, whereas categorical variables were displayed as numbers and percentages. For quantitative data, For variables that were not normally distributed, the Mann-Whitney test was employed, and for variables that were normally distributed, the independent t-test. Chi-Square tests were employed for qualitative data, with Fisher's exact test used when expected values in a cell were less than five. SPSS software was used to analyze all of the data, and a p-value of less than 0.05 was deemed statistically significant.

Results

A total of 170 women undergoing normal vaginal delivery were randomized equally to receive either intramuscular carbetocin 100 µg (n = 85) or intramuscular oxytocin 10 IU (n = 85). Baseline demographic and obstetric characteristics (age, parity, gestational age, booking status, PIH, gestational diabetes, previous cesarean, presentation and mode of labor) were similar between the two groups.

Table 1: Baseline demographic characteristics

Age category	Carbetocin (n = 85)	Oxytocin (n = 85)	Total (N = 170)	p-value
18–20 years	19 (22.35%)	17 (20.00%)	36 (21.18%)	0.884†
21–30 years	57 (67.06%)	60 (70.59%)	117 (68.82%)	—
31–40 years	9 (10.59%)	8 (9.41%)	17 (10.00%)	—
Mean ± SD	24.41 ± 4.38	24.60 ± 4.57	24.51 ± 4.46	0.784‡
Median (IQR)	24 (21–27)	24 (21–28)	24 (21–27.75)	—
Range	18–37	18–37	18–37	—

Primary outcome — Incidence of PPH: Postpartum hemorrhage (blood loss ≥ 500 mL) occurred in 18/85 (21.18%) patients in the carbetocin group and 21/85 (24.71%) in the oxytocin group; this difference was not statistically significant (p = 0.584).

Table 2: Incidence of postpartum hemorrhage (PPH)

Outcome	Carbetocin (n = 85)	Oxytocin (n = 85)	p-value
PPH ≥ 500 mL, n (%)	18 (21.18)	21 (24.71)	0.584
Blood loss 500–1000 mL*, n (%)	13 (72.22)	11 (52.38)	0.204
Blood loss 1000–1500 mL*, n (%)	5 (27.78)	10 (47.62)	0.204

Blood-loss distribution (among those with PPH): Among women who developed PPH, 500–1000 mL blood loss occurred in 13/18 (72.22%) in the carbetocin group versus 11/21 (52.38%) in the oxytocin group, while 1000–1500 mL occurred in 5/18 (27.78%) versus 10/21 (47.62%), respectively (p = 0.204).

Hemoglobin: Mean pre-delivery hemoglobin was 9.98 ± 1.08 g/dL (carbetocin) and 10.09 ± 1.14 g/dL (oxytocin) (p = 0.527). Mean post-delivery hemoglobin was 8.88 ± 0.63 g/dL versus 8.94 ± 0.57 g/dL (p = 0.499). The mean drop in hemoglobin was 1.10 ± 1.11 g/dL (carbetocin) and 1.15 ± 1.14 g/dL (oxytocin); median drop was 0.6 g/dL in both groups (p = 0.947).

Table 3: Comparison of hemoglobin between Carbetocin and Oxytocin

Variable	Carbetocin (n = 85)	Oxytocin (n = 85)	p-value
Pre-delivery Hb (g/dL), mean ± SD	9.98 ± 1.08	10.09 ± 1.14	0.527
Post-delivery Hb (g/dL), mean ± SD	8.88 ± 0.63	8.94 ± 0.57	0.499
Hb drop (g/dL), mean ± SD	1.10 ± 1.11	1.15 ± 1.14	0.947

Need for additional uterotonics: Additional uterotonic agents were required in 17/85 (20.0%) of the carbetocin group and 21/85 (24.71%) of the oxytocin group; this difference was not statistically significant (p = 0.461).

Blood transfusion and ICU admissions: Blood transfusion was required in 3/85 (3.53%) of the carbetocin group and 6/85 (7.06%) of the oxytocin group (p = 0.496). ICU admission occurred in 2/85 (2.35%) versus 1/85 (1.18%) respectively (p = 1.00).

Other interventions and safety: Balloon tamponade was needed in 1.18% of patients in each group (p = 1.00). No patient in either group required hysterectomy and there were no maternal deaths. Adverse-effect rates were similar between groups (nausea 8.24% vs 11.76%, p = 0.443; vomiting 2.35% vs 8.24%, p = 0.168; shivering 4.71% vs 3.53%, p = 1; hypotension 3.53% vs 4.71%, p = 1; fever 3.53% vs 3.53%, p = 1)

Table 4: Adverse effects

Adverse effect	Carbetocin (n = 85)	Oxytocin (n = 85)	p-value
Nausea, n (%)	7 (8.24)	10 (11.76)	0.443
Vomiting, n (%)	2 (2.35)	7 (8.24)	0.168
Shivering, n (%)	4 (4.71)	3 (3.53)	1.000
Hypotension, n (%)	3 (3.53)	4 (4.71)	1.000
Fever, n (%)	3 (3.53)	3 (3.53)	1.000

Overall interpretation of results: In this randomized double-blind trial of 170 women undergoing vaginal delivery, prophylactic intramuscular carbetocin demonstrated comparable efficacy and safety to intramuscular oxytocin to prevent PPH and related outcomes; no statistically significant differences were observed for the primary outcome (PPH), hemoglobin drop, need for additional uterotonics, blood transfusion, ICU admission, or adverse-effect rates.

Discussion

Management of third stage of labor remains a significant concern on account of occurrence of PPH which remains a significant cause of morbidity not only for the mother but even for the child in obstetrics and gynecology practice [13]. In this regard we conducted this study wherein we tried to examine the effect of carbetocin against oxytocin use for preventing occurrence of PPH and managing the third stage of labor in women undergoing vaginal deliveries in a hospital. Among 170 women enrolled in the present study, 85 were given carbetocin and 85 were given oxytocin. The women were randomized into the two groups. The randomization study design ensured that the two groups were comparable in the form of age of the women, parity of the women, gestational age of the women, booking status of the women and other risk factors such as PIH, gestational diabetes or previous C-section among the women; and any outcomes in the form of incidence of PPH among the two groups could be ascribed to the use of different intervention rather than the effect of any confounding factors [14].

The mean age of the study patients in the carbetocin group was 24.41 ± 4.38 while in the oxytocin group was 24.6 ± 4.57 with P is equal to 0.784. The study groups had similar age distribution. This was in accordance with the study by Tai et al. who compared the efficacy of intravenous carbetocin (n=100) and oxytocin (n=100) in managing vaginal delivery, and found similar mean age in both groups (23.07±4.69 vs. 22.80±4.48 years, P=0.678). The gestational age at which the women presented to the hospital was predominantly 37- 40 weeks (75.29% in Carbetocin vs. 72.94% in oxytocin). In carbetocin and oxytocin group, few women presented as preterm (9.41% vs. 5.88%), or postdated (15.29% vs. 21.18%) [14]. Other studies also reported similar results. Korb et al. found that compared to oxytocin, carbetocin had comparable gestational age (<37 weeks: 11.1% vs. 10.8%; 37–40 weeks: 48.8% vs. 47.5%; ≥40 weeks: 40.1% vs. 41.7%, p=0.518) [15].

The risk factors in the study groups were found to be comparable. In the carbetocin group, PIH was present in 16.47% of cases, while in the oxytocin group it was 22.35%. Other risk factors like IUD insertion, gestational diabetes, previous C-section, and a history of PPH were similarly distributed, with no significant statistical differences. These findings are consistent with other studies that have also reported similar distributions of risk factors and labor characteristics between carbetocin and oxytocin groups [16]. Compared to oxytocin group, carbetocin group had comparable need of episiotomy (68.24% vs. 65.88%, P=0.744) and instrument use in delivery (5.88% vs. 5.88%, P=1). Similarly, Korb et al. reported that compared to oxytocin, carbetocin had similar rate of episiotomy (17.1% vs. 19%, P=0.075) and instrumental delivery (20.9% vs. 20.7%, P=0.848) [15].

Compared to Oxytocin, Carbetocin had a comparable occurrence of PPH (21.18% vs 24.71%, p =0.584). This was in line with study by Kabir et al. who found that compared to oxytocin group, carbetocin group had lower but statistically insignificant PPH (0% vs. 6.4%, P=0.07). In relation to the blood loss when we compared the decrease in the hemoglobin levels, we found that compared to oxytocin group, carbetocin group had statistically similar fall in the hemoglobin with median values of 0.6 in both the groups P is equal to 0.947 [17]. According to Tai et al. there was significantly more mean fall in hemoglobin level (gm/dl) in oxytocin group than carbetocin group (1.05±0.78 vs. 0.70±0.58, P=0.0002). Compared to Oxytocin, Carbetocin had a comparable need for other uterotonics (20% vs 24.71%, p value=0.461) [14]. Similar to this, Tai et al. compared carbetocin and oxytocin and found that there was significantly more requirement of uterotonics in oxytocin group than carbetocin group (35% vs. 21%, P=0.040) [14].

Compared to Oxytocin, Carbetocin had a comparable rate of ICU admissions (2.35% vs 1.18%, p value=1). Till date this is the first study that compared Oxytocin and Carbetocin in terms of ICU admission. Carbetocin may be better in decreasing ICU admissions because of its prolonged action and decreased requirement of additional doses or interventions. Compared to Oxytocin, Carbetocin

had a comparable requirement of blood transfusions (3.53% vs 7.06%, p value=0.496)

This was in line with the study by Korb et al. who reported that compared to oxytocin, carbetocin had similar blood transfusions (1.45% vs. 1.36%; P = 0.799) [15]. Compared to Oxytocin, Carbetocin had a comparable distribution for adverse effects: Nausea: - 8.24% vs 11.76%; p=0.443, Vomiting:- 2.35% vs 8.24; p=0.168, Shivering: - 4.71% vs 3.53%; p=1, Hypotension:- 3.53% vs 4.71%; p=1, Fever:- 3.53% vs 3.53%; p=1). None of the patients in both groups underwent hysterectomy and none of the mothers in any group died. In others studies, Tai et al. reported that carbetocin and oxytocin groups had similar nausea (7% vs. 10%), vomiting (5% vs. 6%), shivering (4% vs. 4%), pyrexia (4% vs. 3%), and diarrhoea (2% vs. 3%) (P=0.619) [14]. Nirmala et al. found that compared to oxytocin group, carbetocin group had comparable side effects such as abdominal pain (2% vs. 5%), back pain (0% vs. 2%), headache (3% vs. 2%), and nausea (0% vs. 2%), and vomiting (0% vs. 3%) (P>0.05) [16].

Strengths

The key strengths of this study are its contribution to a previously under-researched area in India, as few studies have compared oxytocin and carbetocin for preventing PPH in normal vaginal deliveries within this context. The findings are well-supported by a substantial sample size and align with existing international literature, validating the use of carbetocin as a potent alternative to oxytocin, especially in settings without a reliable cold chain. The study's robust design, including the matching of demographic and gynecological characteristics, minimizes confounding factors and enhances the reliability of its results.

Conclusion

It can be concluded that the efficacy of carbetocin was equivalent to oxytocin in reducing the PPH as the occurrence of PPH was comparable in the two groups with 21.18% in carbetocin group and 24.71% in oxytocin group. Moreover, even the amount of blood loss was comparable among the two groups. After the blood loss, other parameters like falling hemoglobin, need for other uterotonics, need for ICU admissions, need for blood transfusions were also comparable among the two groups. Both oxytocin and carbetocin were associated with minimal and mild side effects like nausea, vomiting, shivering, hypertension and fever which were managed without any significant mortality in the mother or the child. Overall, carbetocin is a noble, safe and efficacious drug in comparison to oxytocin for prevention of PPH. Though Carbetocin holds equivalent efficacy in prevention of PPH, it must be mentioned here that it had advantage of being heat stable and not requiring cold chain – making it to be used widely in resource poor settings as well, barring it's cost effectivenss

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