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Carbetocin vs Oxytocin for Prevention of Postpartum Hemorrhage in Cesarean Delivery: A Systematic Review and Meta-Analysis

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ABSTRACT

Background & Objective: Postpartum Hemorrhage (PPH) is a leading cause of maternal mortality, primarily due to uterine atony. Oxytocin is commonly used to prevent PPH due to its rapid onset and safety. Carbetocin, a long-acting oxytocin analogue, offers a longer duration of action, reducing blood loss and the need for additional uterotonics in cesarean sections. The present study was conducted with aim to compare carbetocin and oxytocin in preventing PPH after elective cesarean delivery.

Materials & Methods: This systematic review and meta-analysis was conducted through a comprehensive literature search to identify Randomized Controlled Trials (RCTs), observational studies, and meta-analysis comparing carbetocin and oxytocin for prevention of PPH after cesarean delivery. A meta-analysis was conducted which calculate the pooled risk ratio in terms of postpartum blood loss and postpartum hemoglobin level.

Results: In this study, six RCTs with a total of 3,048 patients were included. There was significant difference between carbetocin and oxytocin in postpartum blood loss volume (RR, -47.71; 95%CI, -69.16- (-26.27); P<0.0001; I2=95%). Furthermore, there was no significant difference between carbetocin and oxytocin in postpartum hemoglobin level (RR, -0.03; 95%CI, -0.14-0.08; P=0.62; I2=91%).

Conclusion: This meta-analysis indicated that carbetocin is a viable alternative for preventing PPH after cesarean delivery; however, further clinical trials are necessary to validate its effectiveness.

Keywords: Carbetocin, Oxytocin, Prevention, PPH, Cesarean delivery

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1. Introduction

Postpartum Hemorrhage (PPH) is a significant cause of maternal mortality and need for postpartum hysterectomies. PPH is defined as a blood loss of at least 500 ml after vaginal delivery or over 1000 ml following a cesarean section **(1)**. Globally, PPH results in approximately 140,000 maternal deaths each year. Despite ongoing efforts to reduce maternal deaths, PPH remains the leading direct cause, accounting for about 25% of such fatalities. It also leads to long-term complications and severe maternal health issues, including need for blood transfusions, emergency surgeries, and intensive care units admissions **(2,3)**. A study by Hosseinzadeh et al. found that PPH occurred in 15.7% of cesarean deliveries, with common risk factors including preoperative BMI, a history of PPH, and anemia **(4)**.

Uterine atony is recognized as the primary cause of Postpartum Hemorrhage (PPH), responsible for up to 80% of cases **(5)**. It is recommended to administer uterotonics routinely right after delivery. Oxytocin, known for its rapid onset and good safety profile, is the most commonly used uterotonic agent. However, due to its short half-life of 4-10 minutes, it requires continuous or repeated dosing **(6)**. Carbetocin, a synthetic form of oxytocin with a longer duration of action, has a half-life of 85-100 minutes. This structural difference makes carbetocin more stable, protecting it from degradation by aminopeptidase and disulfide compounds **(7)**. Studies have shown that compared to oxytocin, carbetocin is more effective in reducing blood loss, minimizing the need for additional uterotonics, and lowering the risk of PPH, especially during cesarean deliveries **(7-9)**. Moreover, several clinical randomized trials have reported that carbetocin, compared to oxytocin, is linked to less postpartum blood loss and a smaller decrease in hemoglobin levels after cesarean deliveries **(10-15)**. Nevertheless, despite numerous studies on the topic, there is still a limited number of meta-analysis examining the effectiveness of carbetocin versus

oxytocin in cesarean sections. Therefore, this study was conducted with aim to systematically review and analyze the efficacy and safety of carbetocin versus oxytocin in preventing PPH after cesarean deliveries over the past 4 years.

2. Materials and Methods

This systematic review and meta-analysis study followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines **(16)**.

Literature search was conducted in databases such as PubMed, Scopus, and Cochrane looking for studies comparing the efficacy of carbetocin versus oxytocin for prevention of PPH following cesarean delivery during the last 4 years. The detailed keywords for each database are in Pubmed ("carbetocin"[All Fields] or carbetocin [Text Word]) and ("oxytocin"[MeSH Terms] OR oxytocin[Text Word]) and ("postpartum hemorrhage/prevention and control"[Mesh]) and (cesarean section or "Cesarean Section"[Mesh]), Scopus are TITLE-ABS-KEY ((carbetocin) and (oxytocin) and (postpartum and hemorrhage or postpartum and bleeding) and (cesarean and section)), and Cochrane are (carbetocin) and (oxytocin) and (postpartum hemorrhage or postpartum bleeding) and (cesarean section). Furthermore, an advanced search strategy was applied where necessary to narrow down the search procedure.

The following inclusion criteria were set by the authors: study type: randomized controlled trials; study population: postpartum patients; intervention: intravenous carbetocin infusion; comparison: intravenous oxytocin injection of the same form and dose with the intervention; results: effectiveness on postpartum hemoglobin level, postpartum blood loss volume, or hematocrit level. The exclusion criteria were as follows: case-controlled or retrospective study design, incomplete outcome data, full-text articles that cannot be retrieved, studies on vaginal deliveries, comparisons between carbetocin and other uterotonics, like ergometrine, and languages other than English. The study's eligibility criteria were created by 2 authors and consensus was made by third author whenever needed.

The main conclusions and important details from every included study were meticulously summarized by the author in this systematic review. The information below was taken out: (1) the author and the publishing year; (2) study features, such as the research's design and location; (3) study population, such as sample size and average age; (4) intervention, including the features of each intervention program; and (5) population, including sample size and mean age. When necessary, a third author reached a consensus when two authors developed the data extraction criteria.

The Cochrane Risk of Bias 2.0 for Randomized Controlled Trials was used to evaluate the quality of each research. The five dimensions of this instrument are: bias risk resulting from the randomization procedure, bias resulting from deviations from intended interventions, bias resulting from missing outcome data, bias in outcome assessment, and bias in choosing the reported result. The study's overall quality was then evaluated using the Agency for Healthcare Research and Quality's (AHRQ) criteria. The quality assessment was carried out by two authors, with a third author reaching an agreement as necessary.

Meta-analysis was performed using the RevMan 5.4. Pooled mean difference and 95% confidence intervals were obtained by using random-effects model. I2 statistic was used to quantify heterogeneity between the studies (I2<25%, no heterogeneity; I2 25-50%, moderate heterogeneity; and I2>50%, extreme heterogeneity).

3. Results

Study characteristics: All the six studies included were randomized controlled trials conducted in India, Sweden, Slovenia, China, Egypt, and Turkey (Figure 1) **(10-15)**. These studies were conducted during 2020-2023. The participants of the included studies were patients with maternal ages 18-40 years with singleton pregnancies and a gestational age greater than 37 weeks with cesarean delivery on the intervention group, the patients received carbetocin 100 µg/mL via intravenous infusion. On the other hand, the control group receives oxytocin 5 IU/mL intravenously. Primary outcomes measured were efficacy on postpartum blood loss and postpartum hemoglobin level. Meanwhile, the secondary outcomes measured were postpartum hematocrit level or the number of additional uterotonics medication. The detailed characteristics of included studies are shown in Table 2.

Risk of Bias Assessment

The results from bias assessment were shown in Figure 2. In summary, four studies included in this review have good quality in terms of AHRQ standards, while two studies remain unclear **(11,12)**. Therefore, four studies are categorized as having low risk of bias **(10,13-15)**.

Efficacy on Postpartum Blood Loss

Postpartum blood loss was reported by the study from Cetin et al., Ibrahim et al., Kang et al., and Vernekar et al., **(10,13-15)**. This meta-analysis, which included 4 trials with a total of 1,491 women, revealed a significant difference in postpartum blood loss between carbetocin and oxytocin in women undergoing cesarean delivery (RR, -47.71; 95% CI, -69.16; -26.27; P<0.0001; I2=95%) (Figure 3). Given the high heterogeneity, sensitivity analyses were conducted to investigate the source of this variability. However, excluding 1 trial at a time in the sensitivity analyses still yielded the same results.

Efficacy on Postpartum Hemoglobin Level

Furthermore, regarding the postpartum hemoglobin level parameter which were reported by Ibrahim et al., Kang et al., and Vernekar et al., **(10,13,14)**, there was no significant difference between carbetocin and oxytocin in postpartum hemoglobin level in women undergoing cesarean delivery (RR, -0.03; 95%CI, -0.14; 0.08; P=0.62; I2=91%) (Figure 4). Due to the high heterogenity, sensitivity analyses were conducted to identify the source of this variability. However, excluding 1 trial at a time in the sensitivity analyses produced consistent results.

Efficacy on Postpartum Hematocrit Level

The study by Cetin et al., also reported the decrease of hematocrit level post cesarean delivery in both groups of patients receiving carbetocin and oxytocin. The results indicated no significant difference in the reduction of hematocrit levels between pre and post intervention in either group. The decrease in hematocrit was 3.07±3.23 (P=0.726) in the carbetocin group and 3.55±2.44 (P=0.180) in the oxytocin group **(15)**.

Efficacy of Additional Uterotonics

Subsequently, additional uterotonics were also assessed by the study from Kang et al., **(15)** which reported that there are no significant differences in the number of patients that require additional uterotonics. In the carbetocin group, 80±18.2 patients require additional uterotonic medications, while in the oxytocin group, 89±22.9 patients require additional uterotonics (P>0.05).

Table 1. Table of keywords for literature search

Database	Keywords	Hits
Pubmed	("carbetocin"[All Fields] OR carbetocin[Text Word]) and ("oxytocin"[MeSH Terms] or oxytocin [Text Word]) and ("postpartum hemorrhage/prevention and control"[Mesh]) and (cesarean section or "Cesarean Section"[Mesh])	23
Scopus	TITLE-ABS-KEY ((carbetocin) and (oxytocin) and (postpartum and hemorrhage or postpartum and bleeding) and (cesarean and section))	58
Cochrane	(carbetocin) and (oxytocin) and (postpartum hemorrhage or postpartum bleeding) and (cesarean section)	115

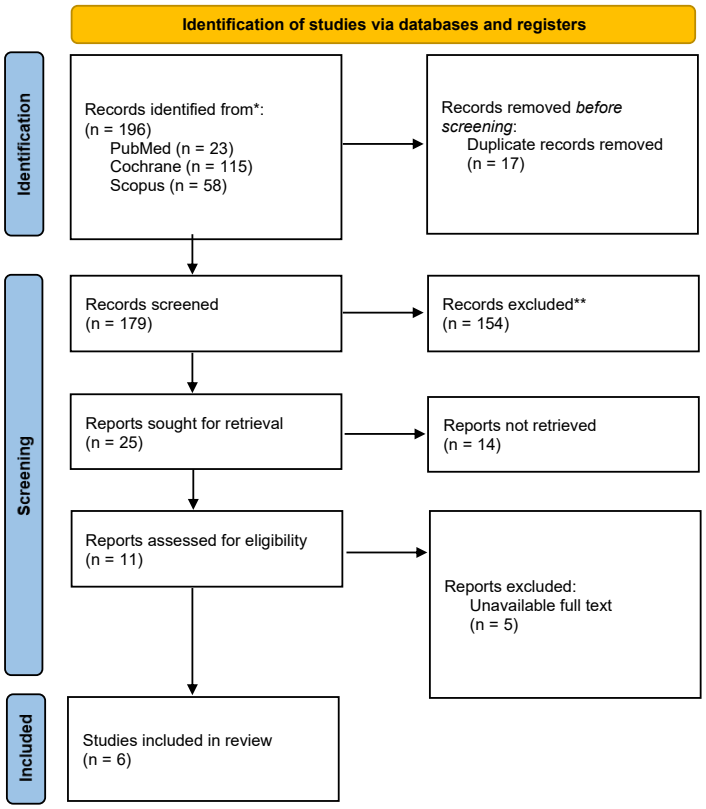


Figure 1. Diagram flow of literature search strategy

Table 2. Study characteristics and outcomes

Study	Location	Number of patients	Patient characteristics	Intervention group- Carbetocin (Dose, timing)	Control group - Oxytocin (Dose, timing)	Results
Cetin et al[14]., 2023	Turkey	150 patients Intervention: 75 Control: 75	Mean age: Intervention: 28.57±6.06 y Control: 28.33±5.67 y Patients with maternal ages 18-40 years with singleton pregnancies with a gestational week greater than 37 weeks were included.	Carbetocin 100 µg/mL (Pabal®; Ferring Pharma, Istanbul, Turkey) was intravenously administered immediately after the birth of the baby.	Oxytocin 5 IU/mL (Synpitan Forte®; Deva Pharma, Istanbul, Turkey) (n=75) oxytocin infusion consisting of 20 IU dissolved in 500 mL of normal 0.9% sodium chloride solution and infused at a rate of 125 mL/h was administered immediately after clamping the umbilical cord	**Decrease in hemoglobin concentration (g/dL)** Intervention: 1.03±1.04 (P=0.023) Control: 1.3±0.85 (p=0.835) **Decrease in hematocrit concentration (g/dL)** Intervention: 3.07±3.23 (P=0.726) Control: 3.55±2.44 (p=0.180) **Postpartum blood loss (mL)** Intervention: 277.19±208.10 (P=0.445) Control: 294.13±198.64 (P=0.445)
Rabow et al[10]., 2023	Sweden	59 patients Intervention: 30 Control: 29	Mean age: Intervention: 33.4 (4.0) y Control: 32.0 (3.8) y Healthy women 18-40 years old with singleton pregnancy planned for elective CS under spinal anesthesia at gestational week 35 or more	Carbetocin 1 mL (100 µg/mL) was administered intravenously after baby delivery and umbilical cord cutting	Oxytocin 1 mL (5 IU/mL) was administered intravenously after baby delivery and umbilical cord cutting	**Patients with blood loss >1000 mL** Intervention: 5 patients Control: 4 patients p-value not available
Kang et al[12]., 2022	China	827 patients Intervention: 439 Control: 388	Mean age: Intervention: 31.6±4.1 y Control: 31.7±3.8 y Women with one or more PPH risk factors, scheduled	Carbetocin 100 µg (H20070013, Ferring Pharmaceutical Co. Ltd., St-Prex, Switzerland) via intravenous injection over one minute	Oxytocin 10 IU (H31020850, Hefeng Pharmaceutical, Shanghai, China) via uterus body injection, followed by 20 IU oxytocin in 500 mL 5% glucose solution	**Postpartum blood loss after 2 hours (mL)** Intervention: 421.8±190.8 (P>0.05) Control: 456.8±331.7 (P>0.05) **Postpartum hemoglobin (g/L)**

			for cesarean section on term pregnancy. The indications for elective cesarean section and PPH risk factors included scarred uterus (the uterus of a woman that had undergone myomectomy or previous cesarean section), uterine fibroid, breech position, and age≥ 35 years		(H11020060, China Resources Zizhu Pharmaceutical Co., Ltd., Beijing, China) via intravenous drip over 1 hour	Intervention: 116.7±12.6 (P>0.05) Control: 116.9±12.6 (P>0.05) **Use of additional uterotonics** Intervention: 80±18.2 (P>0.05) Control: 89±22.9 (P>0.05)
Likar et al[11]., 2022	Slovenia	57 patients Intervention: 27 Control: 30	Mean age: Intervention: 33.5 (5.1) y Control: 31.9 (4.5) y Healthy women with uncomplicated singleton pregnancies at term (≥37 completed weeks of pregnancy) scheduled for elective cesarean section after one previous cesarean. All included women were not in labour	Carbetocin 100 µg intramuscularly	Oxytocin 5 IU in a 100 mL saline solution as an intravenous bolus	**Visual estimated blood loss during surgery (300–400 ml)** Intervention: 24 (80%) Control: 21 (77.8%) **Visual estimated blood loss during surgery (400 – 500 ml)** Intervention: 6 (22.2%) Control: 6 (20%)
Vernekar et al[9]., 2022	India	1795 patients Intervention: 897 Control: 898	Mean age: Intervention: 23 y Control: 23 y Healthy pregnant women with gestational age ≥37 weeks of pregnancy	Carbetocin 100 µg intramuscularly	Oxytocin 10 IU intramuscularly	**Post- delivery Hemoglobin (g/dL, mean, difference)** Intervention: 10.09 Control: 10.21 Difference or ratio: -0.128 (-0.251 to -0.004) P-value: 0.0432 **Postpartum blood loss (mL, median, ratio)** Intervention: 160.4 Control: 163.2 Difference or ratio: 0.98 (0.92–1.05) P-value: 0.6214

Ibrahim et al[13]., 2020	Egypt	160 patients Intervention: 80 Control: 80	Mean age: Intervention: 30 y Control: 30 y Women aged 18–35 years, singleton pregnancy, scheduled for elective (with no evidence of labor pain) lower segment CS, gestational age of ≥37 weeks, and have one of the hypertensive disorders in pregnancy	100 µg carbetocin diluted in 10 ml of Ringer's lactate solution injected directly into the vein over 2 min (Pabal; Ferring, Langley, UK)	10 IU oxytocin (Syntocinon; Alliance, Chippenham, UK) in 1000 ringer lactate as IV drip at a rate of 125 ml/h	**Total blood loss (mL)** Intervention: 424.75±182.59 Control: 679.5±200.25 P<0.001 **Postpartum hemoglobin level (g/dL)** Intervention: 11.2±1.2 Control: 10.4±1.1 P<0.005 **Postpartum hematocrit level (%)** Intervention: 33.6±2.4 Control: 29.8±4.8 P<0.005

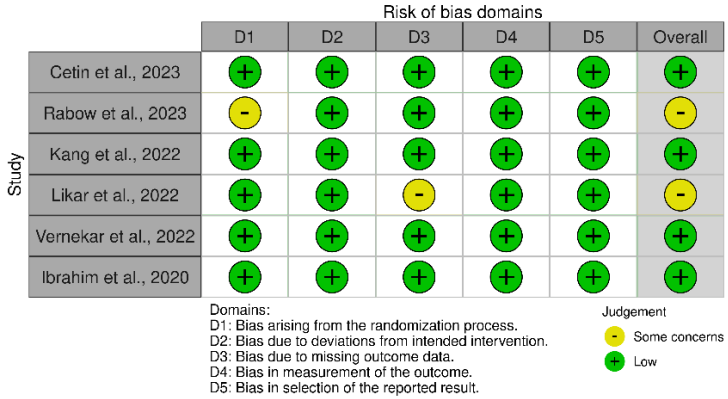


Figure 2. Summary of risk of bias assessment

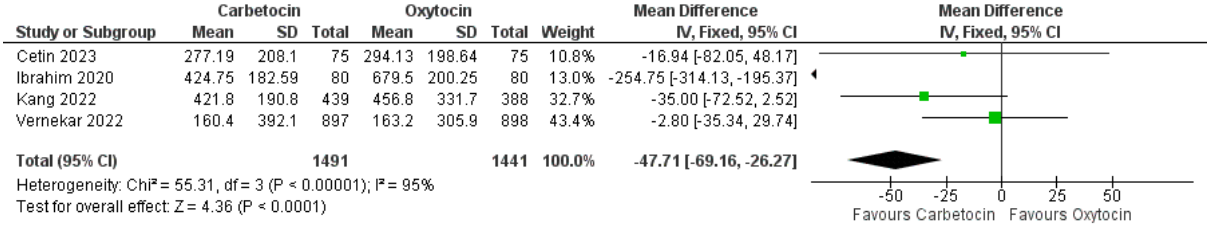


Figure 3. **Meta-analysis and forest-plot of postpartum blood loss**

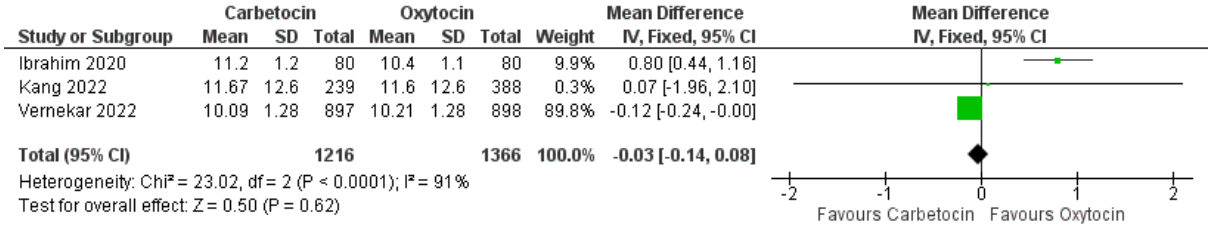


Figure 4. **Meta-analysis and forest-plot of postpartum hemoglobin level**

4. Discussion

PPH is a major cause of maternal death, accounting for approximately 25% of maternal fatalities worldwide and leading to significant morbidity. It causes around 140,000 maternal deaths each year and can result in long-term disabilities **(5)**. PPH is characterized by excessive blood loss following childbirth, with specific thresholds for vaginal and cesarean deliveries. Uterine atony is the primary cause of PPH, and the use of uterotonics right after delivery is recommended for PPH prevention. While oxytocin is effective and safe, it has a short half-life and requires repeated administration. Carbetocin, a longer-acting synthetic version of oxytocin, has demonstrated superior results in reducing blood loss and the need for additional uterotonics, especially in cesarean deliveries **(14)**.

This meta-analysis focused on women undergoing cesarean sections, comparing carbetocin to oxytocin for preventing PPH that evaluated postpartum blood loss, hemoglobin levels, additional uterotonic use, and transfusions. The results showed a significant decrease in postpartum blood loss, but no significant change in postpartum hemoglobin levels. Carbetocin is a medication that helps prevent PPH by promoting uterine contractions. As an oxytocin agonist, it mimics the natural hormone oxytocin, which plays a role in reducing blood loss after childbirth. Carbetocin binds to oxytocin receptors in the smooth muscles of the uterus, inducing rhythmic contractions, improving uterine tone, and increasing the frequency of contractions **(6)**.

The findings of this study is supported by the similar meta-analysis which indicated a lower risk of PPH. Study by Voon et al., in 2018 has found that carbetocin caused a significant reduction in the rates of PPH (RR 0.79; 95%CI: 0.66 to 0.94; P=0.009), use of additional uterotonics (RR 0.57; 95% CI 0.49 to 0.65; P<0.001) and transfusion (RR 0.31; 95% CI 0.15 to 0.64; P=0.002) rather than oxytocin **(16)**. Additionally, a large retrospective study involving more than 1000 patients confirmed a significant reduction in PPH with using carbetocin compared to oxytocin in cesarean sections (16.36% vs 30.45%) **(19)**, which aligns with our findings. The reduction in the need for blood transfusions with carbetocin was also significant and consistent with previous trends, highlighting its importance due to the risks and costs associated with transfusion processes.

Although there is consensus on the reduced need for additional uterotonics, the high level of heterogeneity suggests that combining these studies may not be appropriate. This is likely due to varying rates of additional uterotonic use, which depend on subjective assessments and different oxytocin dosages. The significant difference between the cost of oxytocin (USD 0.18 per 10 IU vial) and carbetocin (USD 18.20 per vial) highlights the need for local cost-effectiveness evaluations before adopting routine prophylaxis, potentially limiting carbetocin use to higher-risk bleeding situations. A heat-stable formulation of carbetocin, which, like oxytocin, currently requires refrigeration **(17)**. This meta-analysis supports carbetocin's effectiveness in reducing PPH in cesarean delivery.

This study has several strengths and limitations. To the best of our knowledge, this study is the most updated systematic review assessing the efficacy of carbetocin vs oxytocin for the prevention of PPH in

cesarean delivery. However, some limitations of this study are the small number of included studies and the heterogeneity of the included studies were classified as high heterogeneity. Therefore, further studies are recommended in the form of a Randomized Controlled Trials (RCT) with bigger sample size to conclude a solid recommendation for clinical settings.

5. Conclusion

This systematic review and meta-analysis highlighted the superiority of carbetocin compared to oxytocin for the prevention of PPH, especially in reducing postpartum blood loss, preventing large reduction of hemoglobin and hematocrit level, and reducing the use of additional uterotonic medications.

6. Declarations

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Ethical Considerations

Not applicable

Authors' Contributions

J. J., J. N., C. C., I. C. have been involved in drafting the manuscript. All authors read and approved the final manuscript

Conflict of Interest

None

Fund or Financial Support

None

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