Systematic Review

Carbetosine, a Long-acting Oxytocin Agonist, as a Uterotonic in the Prevention of the Occurrence of Postpartum Bleeding

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Abstract

Objective: To evaluate the comparative effect of carbetocin versus other uterotonic agents (misoprostol and oxytocin) in preventing postpartum bleeding.

Methods: Medical search engines such as Pubmed, Google Scholar, and Cochrane were used for literature searches. The literature covered the period from 2013 to 2023. Keywords used were "Carbetocin" or "long-acting oxytocin" and "uterotonic", "post-partum hemorrhage" or "post-partum bleeding." Data analysis was conducted using the RevMan 5.4 application.

Results: This study involved 12 clinical trials involving a total sample of 32,312 people. Based on forest plot analysis, it was found that patients receiving carbetocin therapy had a 0.42 times lower risk of developing postpartum compared to those receiving other uterotonic agents (misoprostol and oxytocin) (OR: 0.42; 95% CI: 0.26-0.68; p<0.0004; with heterogeneity p<0.00001, I2 85%)

Conclusion: Carbetocin, with its effectiveness and efficacy, can be considered as one modality for preventing postpartum hemorrhage in comparison to other uterotonic agents, such as misoprostol and oxytocin. In addition to that, it can benefit women at risk of having a major obstetric hemorrhage.

Keywords: carbetosin, clinical trial, meta-analysis, uterotonic.

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INTRODUCTION

Maternal deaths are estimated to occur at a rate of 140,000 annually, or 1 woman every 4 minutes, according to World Health Organization (WHO) data. Additionally, postpartum bleeding may cause up to 25% of maternal deaths. Estimated that 100,000 maternal deaths occur annually.[1] Nearly a quarter of all maternal deaths worldwide occur after childbirth, with postpartum hemorrhage being the leading cause in low-income nations like Indonesia.[2-4]

Postpartum hemorrhages are defined as blood losses of at least 500 mL and more than 1000 mL after vaginal and cesarean deliveries respectively.[5] The WHO's current recommendation for preventing postpartum hemorrhage involves aggressively managing the third stage of labor. The most important element of actively treating the third stage of labor is using uterotonic medicines beforehand, which has been found to prevent postpartum hemorrhage by up to 50%. Currently, oxytocin serves as the primary treatment for preventing postpartum hemorrhage. Nonetheless, challenges arise due to its short half-life and activity.[6] However, in many low- and middle-income nations, exposure to heat in areas without access to cold-chain transit and storage cannot ensure its efficacy. Quality issues like impurities and insufficient active ingredients are also mentioned as issues with using such oxytocin.[5]

Studies have investigated the efficacy of oxytocin and carbetocin in reducing postpartum hemorrhage. Since 1997, the long-acting oxytocin analog carbetocin has successfully stopped postpartum bleeding.[7,8] In previous research, the effects of carbetocin 100 mg intramuscularly (IM) and oxytocin 5 IU intramuscularly (IM) were compared. The carbetocin group required less uterotonics and had much less bleeding. After extensive research, it was shown that IM carbetocin reduced postpartum hemorrhage more effectively than oxytocin. Previous studies

have shown that uterine contractions can commence in less than two minutes after the initial carbetocin dose and persist for up to two hours.[2,7,8]

To date, only a limited number of meta-analyses and systematic reviews have addressed the role of carbetocin, a long-acting oxytocin agonist, in preventing postpartum hemorrhage. Therefore, further investigation is necessary to elucidate the role of carbetocin in reducing postpartum bleeding. This gap in research prompted the authors of this meta-analysis to examine the use of carbetocin, a long-acting oxytocin agonist, as a uterotonic agent in preventing postpartum hemorrhage.

METHODS

Search engines such as PubMed, Google Scholar, and Cochrane were utilized for literature searches spanning the years 2013 through 2023. Keywords included "Carbetocin" or "long-acting oxytocin" and "uterotonic," along with "postpartum hemorrhage" or "postpartum bleeding." Data analysis was performed using the RevMan 5.4 program. Inclusion criteria were as follows pregnant women with a higher risk of preterm labor who used carbetocin as a uterotonic to prevent postpartum hemorrhage; evaluation of the efficacy of carbetocin, a long-acting oxytocin agonist, as a uterotonic; and the availability of adequate odds ratio (OR) data accompanied by 95% confidence intervals. Reviews, case reports, correspondence, conference abstracts, and duplicated data were excluded from consideration.

RESULTS

Based on the quality assessment of the study using the New Ottawa Scale for the analysis of Randomized Control Trials, the fundamental research has good quality (Table 1.)

Table 1. Quality of the Study

Author, year	1	2	3	4	5	6	7	8	Criteria
Amornpetchakul, 2017	√	-	√	√	√	√	√	√	Good
Elbohoty, 2016	√	√	√	-	√	√	√	√	Good
Elgaforelsharkwy, 2013	√	√	√	√	√	√	-	√	Good
Hsu, 2021	√	√	-	√	√	√	√	√	Good
Ibrahim, 2020	√	√	√	√	-	√	√	√	Good
Maged, 2015a	√	-	√	√	√	√	√	√	Good
Maged, 2015b	√	√	√	√	√	-	√	√	Good
Razali, 2016	√	√	√	-	√	√	√	√	Good
Salem, 2019	√	-	√	√	√	√	√	√	Good
Taheripanah, 2017	√	√	√	√	√	-	√	√	Good
Whigham, 2018	√	-	√	√	√	√	√	√	Good
Widmer, 2018	√	√	√	-	√	√	√	√	Good

All included studies in this meta-analysis had a low risk of bias, according to Cochrane's review of the risk of bias using a risk of bias checklist (Table 2).

Table 2. Risk of Bias Analysis

Author, year	Signaling question			Default risk of bias
	1.1	1.2	1.3	
Amornpetchakul, 2017	Y	PY	N	Low
Elbohoty, 2016	Y	Y	N	Low
Elgaforelsharkwy, 2013	Y	PY	NI	Low
Hsu, 2021	PY	Y	N	Low
Ibrahim, 2020	Y	PY	N	Low
Maged, 2015a	Y	PY	PN	Low
Maged, 2015b	PY	PY	N	Low
Razali, 2016	Y	PY	N	Low
Salem, 2019	Y	Y	N	Low
Taheripanah, 2017	PY	PY	PN	Low
Whigham, 2018	Y	PY	N	Low
Widmer, 2018	PY	PY	N	Low

*Y/PY = "Yes" or "Probably yes"; N/PN = "No" or "Probably no"; NI = "No information"

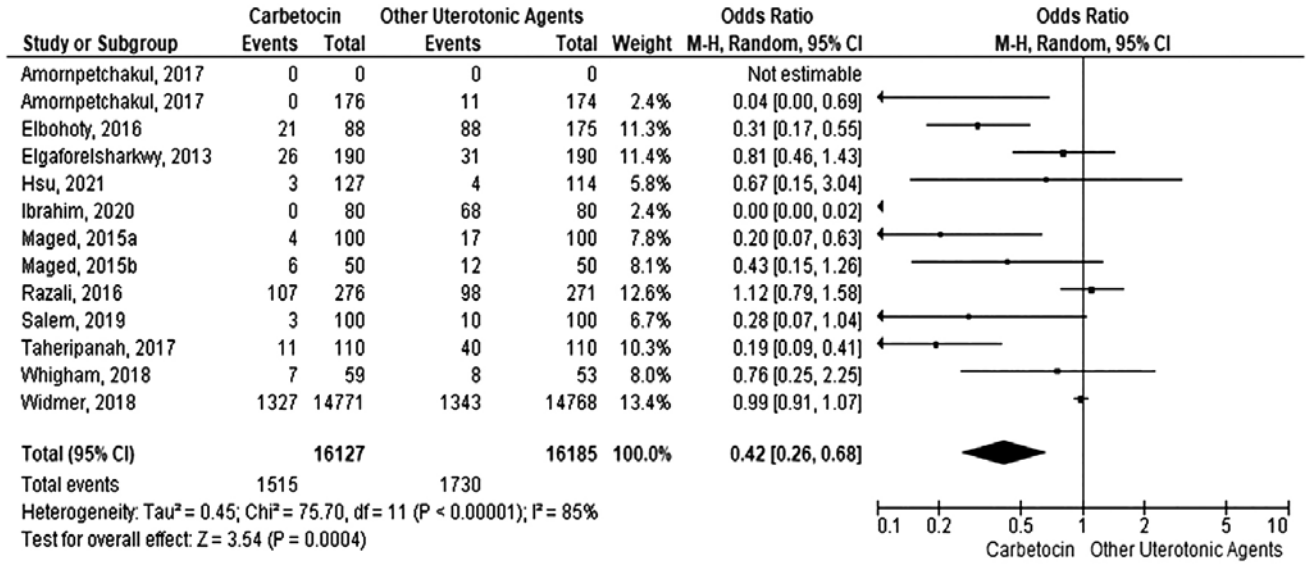

Figure 1. Forest plot for carbetocin vs. other uterotonic agents

This study involved 12 clinical trials involving a total sample of 32,312 people. Based on forest plot analysis, it was found that patients receiving carbetocin therapy had a 0.42 times lower risk of developing postpartum compared to those receiving other uterotonic agents (misoprostol and oxytocin) (OR: 0.42; 95% CI: 0.26-0.68; p<0.0004; with heterogeneity p<0.00001, I2 85%) (Figure 1).

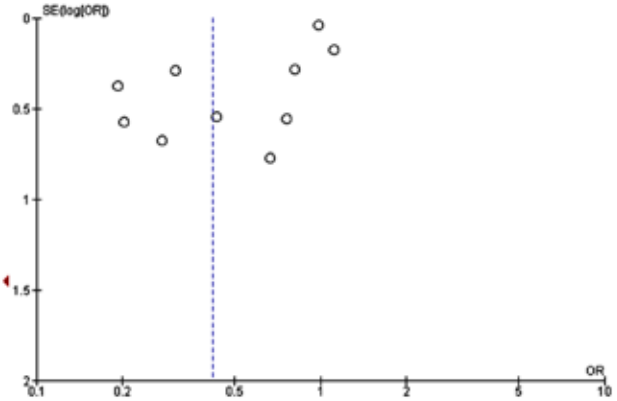

Figure 2. Tunnel plot for carbetocin vs. other uterotonic agents in preventing post-partum hemorrhage.

DISCUSSION

Our current meta-analysis compared the effectiveness of carbetocin as a uterotonic drug in reducing the risk of postpartum hemorrhage. Patients administered carbetocin exhibit a significantly lower risk of bleeding compared to those receiving other uterotonic treatments.

Previous research involved a comparison between carbetocin and oxytocin to prevent postpartum hemorrhages. This study revealed that carbetocin reduced the necessity for uterotonics particularly those who underwent cesarean deliveries. However, vaginal delivery did not yield the same outcomes. The study found no significant difference between using carbetocin, oxytocin, or another control in terms of reducing the risk of postpartum hemorrhage, which is defined as any blood loss greater than 500 ml, or the threat of severe PPH, which is defined as a condition of blood loss greater than 1000 ml.[9]

The uterine tone can be improved with carbetocin, a synthetic long-analog of oxytocin. According to a prior study, intravenous carbetocin administration to postpartum individuals can induce tetanic uterine contractions that start after two minutes and persist for six. The rhythmic contraction was then generated for 60 minutes following the carbetocin injection.[10] Carbetocin has a half-life of 40 minutes, approximately four to ten minutes longer than oxytocin, with an optimal dosage of 100 µg intravenously.[11] The oxytocin receptor (OXTR) in the uterine smooth muscle can specifically bind carbetocin. The rhythmic contractions of the uterus can be induced by this method. Additionally, it might intensify prior contractions and raise the uterine muscular tone. Following intramuscular injection of carbetocin, the intravenous administration of the drug can trigger contractions for 60 and 120 minutes.[12]

Carbetocin is equally effective as syntometrine but has fewer adverse effects in preventing primary PPH after vaginal birth. A different study showed that a single injectable carbetocin dosage of 100 g decreased postpartum blood loss more efficiently and with fewer side effects. There was no difference between intramuscular carbetocin

and intravenous oxytocin in a randomized study between the frequency and severity of PPH in high-risk women. The prevention of PPH in high-risk women after vaginal birth was demonstrated in a more recent trial to be more successful with injectable carbetocin than oxytocin. Carbetocin outperforms syntometrine in avoiding PPH after vaginal delivery, according to a thorough review of 11 research.[12]

A prior study comparing intravenous administration of carbetocin and oxytocin in a hypertensive pregnant woman who underwent elective cesarean section demonstrated that carbetocin was more effective in reducing both intraoperative and postoperative blood loss compared to oxytocin. Additionally, the postoperative hemoglobin levels in the carbetocin group did not significantly differ from the preoperative levels, while the oxytocin group showed a decrease in hemoglobin levels.[13] However, recent research has shown minimal disparity in the efficacy of carbetocin and oxytocin solutions for manual placental removal. Similarly, there were no significant differences in the need for blood transfusions between the two groups.[14]

Carbetocin was compared with other control agents, including misoprostol. According to the previous study, carbetocin exhibited a more beneficial effect than misoprostol in reducing the risk of postpartum hemorrhage. Various factors were analyzed in the study, including decreased hemoglobin levels, the requirement for additional oxytocic substances, uterine massages, blood pressure monitoring, and adverse drug effects for each intervention. The study findings revealed that, compared to carbetocin, misoprostol significantly lowered hemoglobin levels after delivery ($p=0.025$). Additionally, the third stage of labor was shorter ($p=0.001$), and there was less blood loss ($p<0.001$) in the misoprostol group. Moreover, individuals in the carbetocin group required fewer additional oxytocic medications and uterine massages. Furthermore, the study indicated that misoprostol led to more adverse medication responses than carbetocin ($p<0.001$). Notably, the misoprostol group experienced significantly higher incidences of fever, shivering, and diarrhea with p-values of 0.006, 0.050, and 0.028, respectively. Additionally, blood pressure levels among individuals administered misoprostol were notably higher at 30 and 60 minutes post-delivery compared to those receiving carbetocin, extending up to 60 minutes after delivery.[15]

Despite its effectiveness, the cost of using carbetocin warrants consideration. In comparison to alternative treatments like oxytocin, carbetocin incurs higher costs. An earlier study demonstrated that oxytocin exhibited a higher mean cost-effectiveness than carbetocin. Specifically, the mean cost-effectiveness ratio for oxytocin was 4944 USD, whereas for carbetocin, it was 3874 USD.[13]

The limitation in this study is that we did not perform a sub-group analysis on the factors that are likely to influence the occurrence of postpartum bleeding, as in patients with differences in bleeding risk.

CONCLUSION

Due to its effectiveness and efficiency, carbetocin stands as a viable method in preventing postpartum hemorrhage. Moreover, it holds promise in benefiting women at high risk of experiencing significant obstetric bleeding.

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