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Review Article

## Comparison of carbetocin with other uterotonic agents in preventing postpartum hemorrhage

Belinda Carlisa\*

Department of Obstetrics and Gynecology, Mauponggo Public Health Center, Nagekeo District, East Nusa Tenggara, Indonesia

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**\*Correspondence:**

Dr. Belinda Carlisa,

E-mail: [belinda.carlisa@gmail.com](mailto:belinda.carlisa@gmail.com)

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### ABSTRACT

Postpartum hemorrhage (PPH) is defined as blood loss of at least 500 ml or more after vaginal delivery and 1000 ml or more after abdominal delivery. It contributes up to 28% of maternal mortality worldwide and 30.3% of maternal death in Indonesia. 70% cases of PPH are caused by uterine atony. PPH can be prevented by doing routine use of uterotonic agents in active management of third stage of labour. Uterotonic agents that currently available are oxytocin, carbetocin, methylergometrine, syntometrine, misoprostol and carboprost. Carbetocin (a long-acting synthetic analogue of oxytocin) is a new drug which has stronger ability to induce uterine contraction than oxytocin. It does not induce hypertension like methylergometrine and syntometrine. Therefore, carbetocin can be considered as an alternative drug to oxytocin in women with severe preeclampsia. However, more studies are needed to assess the efficacy and safety of carbetocin for prevention of PPH in preeclamptic women. Compared to methylergometrine and syntometrine, carbetocin is more effective in reducing postpartum blood loss. Adverse effects like nausea and vomiting were lower in women treated with carbetocin. Compared to misoprostol, carbetocin is also superior in reducing blood loss. Adverse effects like shivering, fever and metallic taste were higher in women treated with misoprostol. Further studies are needed to assess the superiority between carbetocin and carboprost since there is no published literature yet regarding this topic. In conclusion, carbetocin is superior to other uterotonic agents in preventing postpartum hemorrhage with fewer adverse effects.

**Keywords:** Carbetocin, Postpartum hemorrhage, Uterotonic agents

### INTRODUCTION

Postpartum hemorrhage (PPH) is the most important cause of maternal morbidity and mortality worldwide, and it contributes up to 28% of maternal deaths.<sup>1</sup> In Indonesia, it is responsible for approximately 30.3% of maternal deaths.<sup>2</sup> PPH is defined as blood loss of greater than or equal to 500 ml after vaginal delivery and greater than or equal to 1000 ml after cesarean section, or any blood loss that cause hemodynamic instability after delivery.<sup>3-5</sup> The most common cause of PPH is uterine atony and it accounts for 70% of cases.<sup>5,6</sup> Uterotonic agents are routinely used in active management of third

stage of labour for preventing PPH. It acts by enhancing natural uterine contraction and retraction during third stage of labour.<sup>7</sup> Uterotonic agents that currently available are oxytocin, carbetocin, ergot alkaloids (such as ergonovine, syntometrine) and prostaglandins (such as misoprostol, carboprost).<sup>1,8,9</sup>

The most commonly used uterotonic agent for prevention of PPH is oxytocin. However, recently a lot of scientist showed interest to conduct research about carbetocin. It is a long-acting synthetic analogue of oxytocin which has a stronger ability to induce uterine contraction. Thus make it considered to be more effective than oxytocin in

preventing PPH.<sup>1</sup> Several studies have reported that carbetocin decreases the need for additional uterotonic agents compared to oxytocin.<sup>7,10,11</sup>

Moreover, studies from Reyes et al and Nucci et al showed that carbetocin had similar safety profile with oxytocin in preventing PPH in women with severe preeclampsia.<sup>12,13</sup> Therefore, the author is interested to write this review article to compare the efficacy of carbetocin with other uterotonic agents in preventing postpartum hemorrhage using recent evidence.

### POSTPARTUM HEMORRHAGE (PPH)

#### Definition

Postpartum hemorrhage (PPH) is defined as blood loss of greater than or equal to 500 ml after vaginal delivery and greater than or equal to 1000 ml after abdominal delivery or any blood loss that causes hemodynamic instability after delivery.<sup>3-5</sup> PPH that occurs in the first 24 hours after delivery is defined as primary PPH while between

24 hours and 6 weeks after delivery is defined as secondary PPH.<sup>14,15</sup>

#### Etiology

Etiology of PPH is often referred as the four T; tone (uterine atony), tissue (retained placenta), trauma (laceration of genital tract), and thrombin (coagulopathy).<sup>3,9</sup> Among these etiology, 70% of cases are caused by uterine atony.<sup>5,6</sup>

#### Prevention

Prevention of PPH can be done by doing active management of the third stage of labor routinely. This protocol consists of 3 procedures; the use of uterotonic agents just after the birth of baby, controlled cord traction and uterine massage.<sup>3,5,16</sup> Uterotonic agents that currently available for preventing PPH are oxytocin, carbetocin, methylergometrine, syntometrine, misoprostol and carboprost.<sup>7</sup> Pharmacology of these drugs is shown in Table 1.

**Table 1: Pharmacology of all uterotonic agents in preventing postpartum hemorrhage.**

Drug	Dose and route	Onset of action	Duration of action	Side effects	Contraindications
Oxytocin <sup>3,5,16,17</sup>	10 IU im or 5-10 IU by slow iv injection	2-3 minutes	15-30 minutes	Hypotension, myocardial ischemia, arrhythmias, nausea, vomiting, headache, flushing, and release of atrial and brain natriuretic	Unknown
Carbetocin <sup>5,8,18</sup>	100 µg iv or im	2 minutes	2-4 hours after iv injection, 6-120 minutes after im injection	Nausea, vomiting, abdominal pain, hypotension, headache, chilling and pyrexia	Uterine, vaginal or cervical rupture
Methylergometrine <sup>5,16</sup>	0.2-0.5 mg oral, im, or iv	5-15 minutes after oral, 2-5 minutes after im, instantaneous after iv	2-4 hours	Headache, nausea, vomiting, dizziness, hypertension, coronary artery spasm, intracerebral hemorrhage	Hypertension, heart disease, retained placenta, preeclampsia, and eclampsia
Syntometrine <sup>5,8,19</sup>	1 ml im (combination of 5 IU oxytocin plus 0.5 mg ergometrine)	2-3 minutes	3 hours	Same as oxytocin and ergometrine	Same as oxytocin and ergometrine
Misoprostol <sup>5,6,14</sup>	400-600 µg oral, sl, rectal	3-5 minutes	75 minutes	Shivering, pyrexia, nausea, vomiting and diarrhea	Unknown
Carboprost <sup>9,20</sup>	250 µg im	20 minutes	3 hours	Nausea, vomiting, diarrhea, headaches, hypertension and bronchial asthma	Cardiac and pulmonary disease

Abbreviations: IU=international unit; im=intramuscular administration; iv=intravenous administration; sl=sublingual administration.

## COMPARISON OF CARBETOCIN WITH OTHER UTEROTONIC AGENTS IN PREVENTING POSTPARTUM HEMORRHAGE

### *Carbetocin versus oxytocin*

Attilakos et al in 2010 conducted a double-blind randomised single centre study to compare the effectiveness of carbetocin with oxytocin for prevention of PPH in low risk patients following cesarean section. 377 women were recruited and divided into two groups. 188 women received 100 µg of intravenous carbetocin and 189 women received 5 units of intravenous oxytocin. The study found that carbetocin reduced the use of additional oxytocin when compared to oxytocin (33.5% vs 45.5%,  $p=0.023$ ). Adverse effects were similar between two groups.<sup>10</sup> This study is comparable to recent studies in 2016-2017.<sup>11,21-23</sup>

Mohamed Maged et al in 2015 conducted a prospective double-blind randomized study to compare the effectiveness of carbetocin with oxytocin for prevention of PPH in high risk patients following vaginal delivery. 200 women were recruited and divided into two groups. 100 women received 100 µg of intramuscular carbetocin and 100 women received 5 units of intramuscular oxytocin. Amount of blood loss, the incidence of PPH, and the need for additional uterotonic agents were significantly lower in carbetocin group than in oxytocin group (337.73±118.77 ml vs 378±143.2 ml, 4 vs 16%, 23 vs 37%,  $p=0.03$ ). Adverse effects such as nausea, vomiting, flushing, dizziness, headache, shivering, metallic taste, dyspnea, palpitation and itching were similar between two groups.<sup>11</sup>

Hassan et al in 2017 conducted a comparative prospective case-controlled single centre study to compare the effectiveness of carbetocin with oxytocin for prevention of PPH in high risk patients following cesarean section. 200 women were recruited and divided into two groups. 100 women received 100 µg of carbetocin intravenously and 100 women received 20 units of oxytocin in 500 ml of 0.9% NaCl solution as infusion (150 ml/hour). They found that amount of blood loss and the need for additional uterotonic agents were significantly lower in carbetocin group than in oxytocin group (557±304 ml vs 716±377 ml,  $p=0.005$ ; 18% vs 43%,  $p < 0.001$ ). Adverse effects were similar between two groups.<sup>21</sup>

Two other studies by Taheripannah et al and Khalafalah et al also reached similar results. Taheripannah et al recruited 220 women following cesarean section to receive either 100 µg of carbetocin intravenously or 30 units of oxytocin as infusion. Amount of blood loss, decrease in hemoglobin level and the need for additional uterotonic agents were significantly higher in oxytocin group than in carbetocin group (552.6 ml vs 430.68 ml,  $p < 0.001$ ; 2.05 vs 1.01,  $p=0.01$ ; 36.4% vs 10%,  $p < 0.05$ ).<sup>22</sup> Khalafalah et al recruited 88 women following cesarean section to receive either 100 µg of carbetocin intravenously or 20

units of oxytocin in 1000 ml of 0.9% NaCl solution as infusion (150ml/hour). They found that blood loss was significantly higher in oxytocin group than in carbetocin group (434.706 ml vs 366.477 ml,  $p=0.013$ ).<sup>23</sup>

### *Carbetocin versus oxytocin in severe preeclampsia*

Reyes et al in 2011 conducted a prospective double-blind randomized controlled trial to compare the use of oxytocin with carbetocin for prevention of PPH in women with severe preeclampsia. 60 women were recruited and divided into two groups to receive either carbetocin (100 µg diluted in 10 ml of Ringer's lactate solution) or oxytocin (20 units diluted in 1000 ml of Ringer's lactate solution) intravenously following either vaginal delivery or cesarean section. The study found that carbetocin had similar efficacy and safety with oxytocin in preventing PPH in women with severe preeclampsia. It did not induce hypertension or oligouria.<sup>12</sup> These findings are in accordance with the recent study by Nucci et al in 2016.<sup>13</sup>

### *Carbetocin versus methylergometrine*

A quasi experimental study by Boonkoonchanok et al in 2017 compared the effectiveness between 0.1 mg of intravenous carbetocin and 0.2 mg of intravenous methylergometrine maleate for prevention of PPH in low risk patients following vaginal delivery. 64 women were recruited, 32 in each group. They found that postpartum blood loss was significantly lower in carbetocin group than in methylergometrine maleate group (246.91 ml vs 312.53 ml,  $p=0.038$ ). Adverse effects like nausea and vomiting were found only in methylergometrine maleate group but none in carbetocin group.<sup>24</sup>

### *Carbetocin versus syntometrine*

Askar et al in 2011, conducted a prospective double-blind randomized controlled study to compare the effectiveness between 100 µg of intramuscular carbetocin and 1 ml of intramuscular syntometrine (containing 5 units of oxytocin and 0.5 mg ergometrine) for prevention of PPH in low risk patients following vaginal delivery. 240 women were recruited, 120 in each group. They found that postpartum blood loss was significantly lower in carbetocin group than in syntometrine group (224.6±110.6 ml vs 306.1±95.65 ml,  $p < 0.01$ ). Adverse effects like nausea and vomiting were significantly lower in carbetocin group than in syntometrine group ( $p < 0.05$ ) while hypertension was found only in syntometrine group but none in carbetocin group.<sup>25</sup>

Those findings are comparable with another study by Samimi et al. in 2013. They recruited 200 women following vaginal delivery to receive either 100 µg of intramuscular carbetocin or 1 ml of intramuscular syntometrine (containing 5 units of oxytocin and 0.2 mg ergometrine). The study found that mean value of hemoglobin drop and the need for additional uterotonic

agents were significantly lower in carbetocin group than in syntometrine group (0.39 g/dl vs 1.04 g/dl,  $p < 0.001$ ; 1% vs 11%,  $p = 0.002$ ). Adverse effects like nausea, abdominal pain and chill were lower in carbetocin group although the differences were not statistically significant.<sup>8</sup>

Mohamed Maged et al in 2016 conducted a double-blind randomized study to compare the effectiveness between carbetocin and syntometrine for prevention of PPH in 300 women following cesarean section. 150 women received 100 µg of intravenous carbetocin and 150 women received 1 ml of intramuscular syntometrine (containing 5 units of oxytocin and 0.2 mg ergometrine). They found that the incidence of PPH and the need for additional uterotonic agents were significantly lower in carbetocin group than in syntometrine group (2.7% vs 10%,  $p < 0.001$ ; 3.3% vs 17.3%,  $p < 0.001$ ). But, there were no significant difference regarding side effects like nausea, vomiting and shivering between two groups.<sup>26</sup>

### Carbetocin versus misoprostol

In 2016 Elbohoty et al conducted a double-blind randomized controlled trial to compare the effectiveness and safety of carbetocin, misoprostol, and oxytocin for prevention of PPH following cesarean section. 263

women were recruited and divided into three groups; Group I (88 women received 100 µg of carbetocin in 1000 ml of 0.9% NaCl solution administered intravenously), Group II (89 women received 400 µg of sublingual misoprostol tablets) and Group III (86 women received 10 units of oxytocin in 1000 ml of 0.9% NaCl solution administered intravenously and additionally received 20 units of oxytocin in 500 ml of 0.9% NaCl solution as infusion over 4 hours). The study found that the incidence of PPH and decrease in hemoglobin level were highest in misoprostol group (both  $p = 0.001$ ), while the use of additional uterotonic agents was lowest in carbetocin group ( $p = 0.004$ ). Adverse effects such as heat sensation, metallic taste, fever, and shivering were all highest in misoprostol group ( $p < 0.05$ ).<sup>7</sup> These findings are in accordance with another study by Ibrahim et al. in 2017 that compares the use of 100 µg of intravenous carbetocin with 600 µg of sublingual misoprostol for prevention of PPH in women with severe preeclampsia following vaginal delivery. 60 women were recruited, 30 in each group. The study found that the incidence of PPH was significantly lower in carbetocin group than in misoprostol group (3% vs 20%,  $p = 0.04$ ). Adverse effects such as abdominal pain, fever, metallic taste and shivering were also significantly lower in carbetocin group than in misoprostol group ( $p < 0.05$ ).<sup>27</sup>

**Table 2: Comparison of carbetocin with oxytocin in preventing postpartum hemorrhage.**

Author	Sample	Delivery route	Drugs	Outcome
Attilakos et al <sup>10</sup>	377	CS	Carbetocin 100 µg iv Oxytocin 5 IU iv	The need for additional uterotonic agents was significantly lower in carbetocin group ( $p = 0.023$ ). Adverse effects were similar between two groups.
Maged M et al <sup>11</sup>	200	VD	Carbetocin 100 µg im Oxytocin 5 IU im	Amount of blood loss, the incidence of PPH, and the need for additional uterotonic agents were significantly lower in carbetocin group ( $p = 0.03$ ). Adverse effects were similar between two groups.
Hassan et al <sup>21</sup>	200	CS	Carbetocin 100 µg iv Oxytocin 20 IU in 500 ml of 0.9% NaCl iv (150ml/hour)	Amount of blood loss and the need for additional uterotonic agents were significantly lower in carbetocin group ( $p = 0.005$ , $p < 0.001$ ). Adverse effects were similar between two groups.
Taheripanah et al <sup>22</sup>	220	CS	Carbetocin 100 µg iv Oxytocin 30 IU in 1000 ml of 0.9% NaCl iv	Amount of blood loss decrease in hemoglobin level and the need for additional uterotonic agents were significantly lower in carbetocin group ( $p < 0.001$ , $p = 0.01$ , $p < 0.05$ )
Khalafalah et al <sup>23</sup>	88	CS	Carbetocin 100 µg iv Oxytocin 20 IU in 1000 ml of 0.9% NaCl iv (150ml/hour)	Amount of blood loss was significantly lower in carbetocin group ( $p = 0.013$ ).
Reyes et al <sup>12</sup>	60	CS VD	Carbetocin 100 µg in 10 ml Ringer's lactate iv Oxytocin 20 IU in 1000 ml of Ringer's lactate iv (125ml/hour)	Carbetocin had similar efficacy and safety with oxytocin in preventing PPH in women with severe preeclampsia.
Nucci et al <sup>13</sup>	60	CS	Carbetocin 100 µg iv Oxytocin 5 IU iv	Carbetocin had similar efficacy and safety with oxytocin in preventing PPH in women with severe preeclampsia.

Abbreviations: CS=cesarean section; VD=vaginal delivery; IU=international unit; im=intramuscular administration; iv=intravenous administration; sl=sublingual administration.

**Table 3: Comparison of carbetocin with other uterotonic agents in preventing postpartum hemorrhage.**

Author	Sample	Delivery route	Drugs	Outcome
Boonkoonchanok et al <sup>24</sup>	64	VD	Carbetocin 100 µg iv Methylergometrine maleate 0.2 mg iv	Postpartum blood loss was significantly lower in carbetocin group (p=0.038).
Askar et al <sup>25</sup>	240	VD	Carbetocin 100 µg im Syntometrine 1 ml im	Postpartum blood loss was significantly lower in carbetocin group (p <0.01). Adverse effects were significantly lower in carbetocin group (p <0.05).
Samimi et al <sup>8</sup>	200	VD	Carbetocin 100 µg im Syntometrine 1 ml im	Mean value of hemoglobin drop and the need for additional uterotonic agents were significantly lower in carbetocin group (p <0.001, p=0.002). Adverse effects were lower in carbetocin group although the differences were not statistically significant.
Maged M et al <sup>26</sup>	300	CS	Carbetocin 100 µg iv Syntometrine 1 ml im	Incidence of PPH and the need for additional uterotonic agents were significantly lower in carbetocin group (both p <0.001). Adverse effects were similar between two groups.
Elbohoty et al <sup>7</sup>	263	CS	Carbetocin 100 µg in 10 ml of 0.9% NaCl iv Misoprostol 400 µg sl Oxytocin 10 IU in 10 ml of 0.9% NaCl iv	Incidence of blood loss and decrease in hemoglobin level were highest in misoprostol group compared to carbetocin and oxytocin group (both p=0.001). The need for additional uterotonic agents was lowest in carbetocin group (p=0.004). Adverse effects were all highest in misoprostol group (p <0.05).
Ibrahim et al <sup>27</sup>	60	VD	Carbetocin 100 µg iv Misoprostol 600µg sl	Incidence of PPH was significantly lower in carbetocin group (p=0.04). Adverse effects were also significantly lower in carbetocin group (p <0.05).
Ali et al <sup>15</sup>	150	CS	Carbetocin 100 µg iv Oxytocin 20 IU in 1000 ml of 0.9% NaCl iv Misoprostol 400µg rectal	Incidence of PPH, the need for additional uterotonic agents, blood transfusion, and decrease in hemoglobin level were all significantly lower in carbetocin group (p <0.001, p=0.02, p <0.0001, p <0.05).

Abbreviations: CS=cesarean section; VD=vaginal delivery; IU=international unit; im=intramuscular administration; iv=intravenous administration; sl=sublingual administration.

Latest study in 2018 by Ali et al compares the efficacy of carbetocin with oxytocin and rectal misoprostol for prevention of PPH in high risk patients following cesarean section. 150 women were recruited and divided into 3 groups; Group I (50 women received 100 µg of carbetocin intravenously), Group II (50 women received 20 units of oxytocin in 1000 ml of 0.9% NaCl solution as infusion) and Group III (50 women received 400 µg of misoprostol rectally). They found that the incidence of PPH, the need for additional uterotonic agents, blood transfusion, and decrease in hemoglobin level were all significantly lower in carbetocin group than in oxytocin group and misoprostol group (p < 0.001, p=0.02, p <0.0001, p <0.05).<sup>15</sup>

#### **Carbetocin versus carboprost**

There is no published literature yet regarding the efficacy comparison between carbetocin and carboprost. All studies regarding efficacy comparison of carbetocin to other uterotonic agents in preventing postpartum hemorrhage are summarized in Table 2 and Table 3.

#### **CONCLUSION**

Carbetocin is superior to oxytocin in reducing postpartum hemorrhage and the need for additional uterotonic agents. Regarding adverse effects, carbetocin has similar adverse effects and safety profile with oxytocin. Carbetocin is also reported to be more effective than methylergometrine, syntometrine, and misoprostol. Adverse effects are fewer compared to these drugs.

There is very limited published literature regarding the efficacy of carbetocin in preventing postpartum hemorrhage in women with severe preeclampsia. Two studies reported that carbetocin is not associated with the development of oliguria or hypertension. Thus, carbetocin may be considered as a good alternative drug to oxytocin in women with severe preeclampsia. However, more studies are needed to assess the efficacy and safety of carbetocin in preeclamptic women. The author has not found any study that compares the efficacy of carbetocin to carboprost. Further studies are needed to assess the superiority between carbetocin and carboprost.

Despite superiority of carbetocin to other uterotonic agents, oxytocin is still the drug of choice in preventing postpartum hemorrhage. This is due to its cost-effectiveness and availability in most of health services in Indonesia since Indonesia is a developing country where health budget and infrastructure is often limited.

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