Systematic Review and Meta-Analysis

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Carbetocin vs oxytocin for prevention of postpartum hemorrhage after vaginal delivery

A meta-analysis

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Abstract

Objective: To evaluate the efficacy and safety of carbetocin for prevention of postpartum hemorrhage in women undergoing vaginal delivery compared with oxytocin.

Methods: We conducted a systemic literature search in PubMed, the Cochrane Library, and Embase without language restrictions from inception of each of database to November 18th, 2018. Randomized controlled trials with outcome measure of blood loss ≥500 ml were eligible if they compared carbetocin with oxytocin to prevent postpartum hemorrhage during the third stage of labor in women undergoing vaginal delivery.

Results: This meta-analysis of 5 randomized controlled trials (30,314 women) indicated that there was no significant difference between carbetocin and oxytocin in blood loss ≥500 ml in women undergoing vaginal delivery (relative risks (RRs), 0.52; 95% confidence intervals (CIs), 0.24 to 1.15; $P = .11$; $I^2 = 69\%$). Sensitivity analyses showed the same results. No significant differences were found in blood loss ≥1000 ml, use of additional uterotonic agents, blood transfusion, uterine massage, flushing, vomiting, abdominal pain, nausea, dizziness, headache, palpitation, itching, and shivering.

Conclusions: This meta-analysis showed that carbetocin was as effective and safe as oxytocin for prevention of postpartum hemorrhage in women undergoing vaginal delivery, and the choice of carbetocin for routine prophylaxis will depend on cost-effectiveness.

Abbreviations: CI = confidence interval, IM = intramuscular, IQR = interquartile range, IU = international unit, IV = intravenous, PPH = postpartum hemorrhage, RR = relative risk, USD = United States dollar, WHO = World Health Organization.

Keywords: carbetocin, postpartum hemorrhage, vaginal delivery

1. Introduction

Although great effort has been made to reduce maternal mortality, postpartum hemorrhage remains to be the largest direct cause of maternal death, accounting for nearly one-fourth death worldwide and contributes to long term disability and severe maternal morbidity such as blood transfusion, emergency surgery, and admission to intensive care unit.[1,2] Postpartum hemorrhage is defined as blood loss at least 500 ml after vaginal delivery and blood loss more than 1000 ml after cesarean section.[3] The most common cause of postpartum hemorrhage is uterine atony, which results from poor contraction of the uterus after childbirth.[3] The incidence of postpartum hemorrhage has been increasing in developed countries including the USA and Europe for the past 15 years.[4]

Currently, the World Health Organization (WHO) recommends active management of the third stage of labor for prevention of postpartum hemorrhage.[3] Prophylactic administration of uterotonic agents is identified as the most important component of active management of the third stage of labor, which has reduced the incidence of postpartum hemorrhage nearly by 50%.[5] Oxytocin, which has a short half-life and duration of action, is the current standard therapy for the prevention of postpartum hemorrhage. However, as it is susceptible to heat, its efficacy cannot be assured in many low- and middle- countries where access to cold-chain transport and storage is unavailable, and quality issues such as impurity and insufficient active ingredients also compromise its efficacy.[6] In contrast, carbentocin, which is a long-acting oxytocin analogue, has been widely used in preventing postpartum hemorrhage since 1997, and heat-stable carbentocin, and has been shown to maintain active for more than 36 months at 30°C and 75% relative humidity.[7]

Clinical trials of carbetocin for postpartum hemorrhage prevention have focused mainly on cesarean delivery. A recent

Editor: Daryle Wane.

The authors have no conflicts of interest to disclose.

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How to cite this article: Jin XH, Li D, Li X. Carbetocin versus oxytocin for prevention of postpartum hemorrhage after vaginal delivery: a meta-analysis. Medicine 2019;98:47(e17911).

Received: 6 April 2019 / Received in final form: 8 September 2019 / Accepted: 13 October 2019

http://dx.doi.org/10.1097/MD.0000000000017911

systematic review showed that carbetocin was more effective than oxytocin for reducing the need for additional uterotonic drugs and the need for uterine massage after cesarean delivery.[8] However, it is unclear whether carbetocin is more effective and tolerable than oxytocin for prevention of postpartum hemorrhage following vaginal delivery. Therefore, we found it necessary to evaluate the efficacy and safety of carbetocin in preventing postpartum hemorrhage in women undergoing vaginal delivery compared with oxytocin.

2. Methods

2.1. Search strategy

This meta-analysis was performed according to Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidlines.[9] We conducted a systemic literature search in PubMed, the Cochrane Library, and Embase without language restrictions from inception of each of database to November 18th, 2018. The search was undertaken in these databases using the following medical subject heading (MeSH) terms, keywords, and their combinations: carbetocin; oxytocin; postpartum hemorrhage("postpartum", "post partum","post-partum", "hemorrhage" and "haemorrhage"); labor stage third; third stage ("third", "3rd"). The reference lists of the initially identified articles, previously published systematic reviews and review articles were also manually searched for additional relevant publications. Ethical approval and patient written informed consent were not required, as all data were collected from previous published studies.

2.2. Study selection and data extraction

Randomized controlled trials with outcome measure of blood loss ≥500 ml were eligible if they compared carbetocin with oxytocin to prevent postpartum hemorrhage during the third stage of labor in women undergoing vagianl delivery. Quasi-randomized trials were excluded. Trials published in abstract only were also excluded. Two independent reviewers screened citations at title and abstract level to identify potentially eligible trials. Then the full texts of the relevant citations were retrieved and assessed for inclusion. The data extracted from these trials included the first author, publication year, population characteristics, intervention details, study design, and reported outcomes. Two of the reviewers extracted data from each trial independently. All disagreements between the 2 reviewers were resolved through discussion. The risk of bias in included trials was assessed by the use of criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[10] Assessments of the risk of bias for each of the included trial were completed according to the 7 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). This tool categorizes randomized trials by "low, unclear or high risk of bias" in each domain.

2.3. Outcomes

The primary outcome was blood loss of at least 500 ml after vaginal delivery. The secondary outcomes were blood loss of at least 1000 ml; use of additional uterotonic agents; blood transfusion; uterine massage; flushing; vomiting; abdominal pain; nausea; dizziness; headache; palpitation; itching; shivering.

2.4. Data synthesis

The dichotomous data results after pooling estimates across trials were reported as RR with 95% CIs. Heterogeneity of the results among the trials was assessed with the I^2 statistic. If significant heterogeneity was observed, the random-effects model was used. Otherwise, a fixed-effects model was employed. Sensitivity analyses were carried out to assess the effect of risk of bias on the overall results by excluding 1 trial at 1 time. All analyses were performed using Revman statistical software version 5.

3. Results

3.1. search results and characteristics of included studies

Our search strategy identified 211 citations, of which 64 were duplicates, and 142 were excluded based on title and abstract. After assessing full texts of the remaining 5 citations, we included 5 randomized controlled trials comparing carbetocin with oxytocin for prevention of postpartum hemorrhage in this meta-analysis.[11–15] The PRISMA flow diagram summarizing the selection procedure is shown in Figure 1.

Baseline characteristics of the 5 included trials are presented in Table 1.

We identified 5 trials that assessed the efficacy and safety of carbetocin vs oxytocin in preventing postpartum hemorrhage in women who delivered vaginally. Differences in baseline characteristics were noticed among these trials. Two trials[12,15] included women with a singleton gestation; 1 trial[14] recruited women with a singleton gestation and 1 risk factor such as prolonged labor >12 h and polyhydramnios; 1 trial[11] enrolled women with at least 1 risk factor including retained placenta and induction of labor; 1 trial[13] recruited women with at least 2 risk factors such as primipara >40 years of age and multiple pregnancy. Women with abnormal conditions such as cardiac, hepatic or renal disease, coagulopathy, and abnormal placenta were excluded. Maternal age was not stated in 1 trial,[11] but was comparable between the carbetocin and oxytocin groups in each trial; Maternal age in 1 trial[12] was much younger than the other 3 trials.[13–15] A standard dose of 100 μg carbetocin was administered across all the trials, while the dose of oxytocin varied from 5 to 10 IU across the trials. The administration route of carbetocin and oxytocin also varied across these trials. Women received a single intramuscular injection of either carbetocin or oxytocin in 2 trials[13,15]; women received a single intravenous injection of either carbetocin or oxytocin in 1 trial[14]; women received a single intramuscular injection of carbetocin or intravenous injection of oxytocin in 1 trial[11]; women received a single intravenous injection of carbetoin or intramuscular injection of oxytocin in the last trial.[12] Primary outcome was not stated in 2 trials,[13,14] and varied across the other 3 trials.[11,12,15] However, these trials all included blood loss at least 500 ml. Assessment of risk of bias is shown in Figure 2. Two trials[14,15] were assessed to be "low risk of bias" in 7 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias), 1 trial[11]

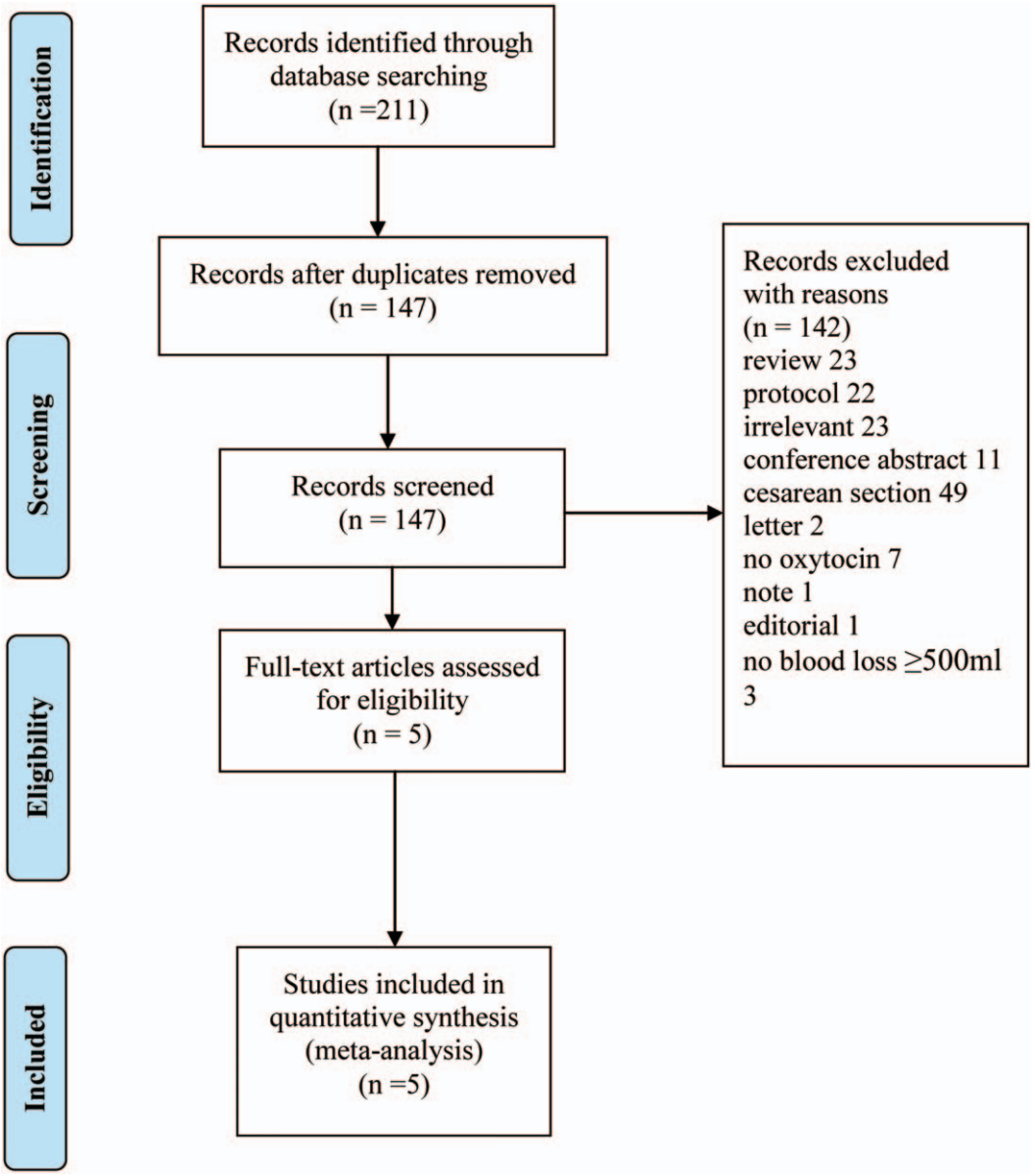

Figure 1. Study selection flow diagram.

was considered to be "unclear risk of bias" in 1 domain (incomplete outcome data) and "low risk of bias" in the other 6 domains, 1 trial[12] was assessed to be "unclear risk of bias" in 2 domains (allocation concealment, blinding of participants, and personnel) and "low risk of bias" in the other 5 domains, and 1 trial[13] was considered to be "unclear risk of bias" in 1 domain (blinding of participants and personnel) and "low risk of bias" in the other 6 domains.

3.2. Primary outcome: blood loss ≥500 ml

This meta-analysis of the 5 trials (30,314 women) showed there was no significant difference between carbetocin and oxytocin in blood loss ≥500 ml in women undergoing vaginal delivery (RR, 0.52; 95%CI, 0.24–1.15; $P=.11$; $I^2=69\%$)(Fig. 3). Due to the high heterogeneity, sensitivity analyses were performed to explore the cause of heterogeneity. The sensitivity analyses by excluding 1 trial at 1 time showed the same results.

3.3. Secondary outcome

No statistically significant difference was found between the carbetocin and oxytocin groups in blood loss ≥1000 ml (RR, 1.04; 95% CI, 0.86–1.26; $P=.67$; $I^2=0\%$), use of additional uterotonic agents (RR, 0.63; 95% CI 0.37–1.07; $P=.09$; $I^2=83\%$), blood transfusion (RR, 1.13; 95% CI 0.94–1.37; $P=.19$; $I^2=17\%$), uterine massage (RR, 0.40; 95% CI 0.06–2.58; $P=.34$; $I^2=53\%$), flushing (RR, 1.90; 95% CI 0.68–5.33; $P=.22$; $I^2=0\%$), vomiting (RR, 0.85; 95% CI 0.13–5.45; $P=.86$; $I^2=58\%$), abdominal pain (RR, 1.20; 95% CI 0.85–1.71; $P=.30$; $I^2=12\%$), nausea (RR, 0.95; 95% CI 0.37–2.44; $P=.91$; $I^2=29\%$), dizziness (RR, 1.56; 95% CI 0.71–3.42;

Table 1

Characteristics of included trials.

Trial (year)	Region	Inclusion criteria	Exclusion criteria	Age (carbetocin vs oxytocin)	Intervention	Control	Primary outcome
Boucher, 2004	Canada	Women who delivered vaginally with at least 1 risk factor, including history of PPH or retained placenta; grand multiparity (>5);uterine overdistention, fetal macrosomia, or polyhydramnios; chorioamnionitis; antepartum hemorrhage;induction or augmentation of labor; prolonged labor rapid-excessive labor	Women younger than 18 years of age, or with coagulopathy; history of heart disease or cardiac arrhythmia; history or evidence of liver, renal, or endocrine disease; or hypersensitivity to study drugs	Comparable age between 2 groups	100 μg carbetocin IM	10 IU oxytocin IV	Additional uterotonic medication
Kabir, 2015	Bangladesh	Women with a singleton pregnancy undergoing vaginal delivery above 36 weeks of gestation	Placenta praevia; multiple gestations; placental abruption; hypertensive disorders; preeclampsia; known cardiac, renal, liver disease; epilepsy; moderate anemia; intrauterine fetal death	22.7 ± 3.2 vs 22.1 ± 3.2	100 μg carbetocin IV	10 IU oxytocin IM	Blood loss in 24 hours
Maged, 2016	Egypt	Women at 37–40 weeks of gestation with at least 2 risk factors, including previous PPH; primipara >40 years of age; BMI >35; multiple pregnancy; prolonged labor >12 h;ultrasound estimated fetal weight >4 kg	Women with placenta previa; coagulopathy; preeclampisa; cardiac, renal, liver disease; epilepsy; known hypersensitivity to study drugs	32.84 ± 7.52 vs 33.87 ± 7.6	100 μg carbetocin IM	5 IU oxytocin IM	Not stated
Amornpetchakul, 2018	Thailand	Women ≥20 years old with a singleton gestation ≥34 weeks and 1 risk factor, including history of PPH; induction of augmentation of labor >4 h; tocolytic agent exposure within 4 h prior to delivery; prolonged labor > 12 h;precipitated labor; grand multipara; polyhydramnios; uterine leiomyoma;	Women with active labor upon admission; bleeding disorders; thrombocytopenia; cardiovascular, liver, renal disease; asthma; epilepsy; migrane; study drug allergy; preeclampsia; abnormal placenta	28.5 ± 6.2 vs 28.9 ± 6.5	100 μg carbetocin IV	5 IU oxytocin IV	Not stated
Widmer, 2018	Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and The United Kingdom	Women with a singleton pregnancy and cervical dilatation of 6 cm or less	Women with cervical dilatation >6 cm; without informed consent; known allergy to study drugs; serious cardiovascular, hepatic, renal disease; epilepsy	Median (25 vs 25) IQR (22–30 vs 22–30)	100 μg carbetocin IM	10 IU oxytocin IM	Blood loss ≥ 500 ml or use of additional uterotonic agents; blood loss ≥1000 ml

IM = intramuscular, IQR = Interquartile Range, IU = international unit, IV = intravenous, PPH = postpartum hemorrhage.

$P = .27$; $I^2 = 0\%$), headache (RR, 0.76; 95% CI 0.22–2.63; $P = .66$; $I^2 = 43\%$), palpitation (RR, 2.48; 95% CI 0.49–12.70; $P = .27$; $I^2 = 0\%$), itching (RR, 0.52; 95% CI 0.02–14.52; $P = .70$; $I^2 = 58\%$), and shivering (RR, 1.31; 95% CI 0.54–3.22; $P = .55$; $I^2 = 0\%$)(Table 2).

4. Discussion

This meta-analysis of 5 randomized trials including 30,314 women showed that there was no significant difference between carbetocin and oxytocin in blood loss ≥500 ml in women undergoing vaginal delivery. Sensitivity analyses showed the same results. This meta-analysis also indicated that there were no significant differences between carbetocin and oxytocin in blood loss ≥1000 ml, use of additional uterotonic agents, blood transfusion, uterine massage, and adverse effects.

Access to effective uterotonic agents is the key to prevent atony postpartum hemorrhage. However, quality issues of uterotonic agents are prevalent in low- and middle-income countries.[16] According to latest evidence, due to insufficient amounts of active ingredient, nearly 45.6% to 74.2% of oxytocin samples failed quality tests in these countries.[6,17] Therefore, improving the quality and efficacy of uterotonic agents for prevention of postpartum hemorrhage becomes a critical issue. Carbetocin has advantages over oxytocin for prevention of postpartum hemorrhage. Compared with oxytocin, heat-stable carbetocin, does not need cold-chain transport and storage. Therefore, it is convenient to be stored in facilities at room temperature in low

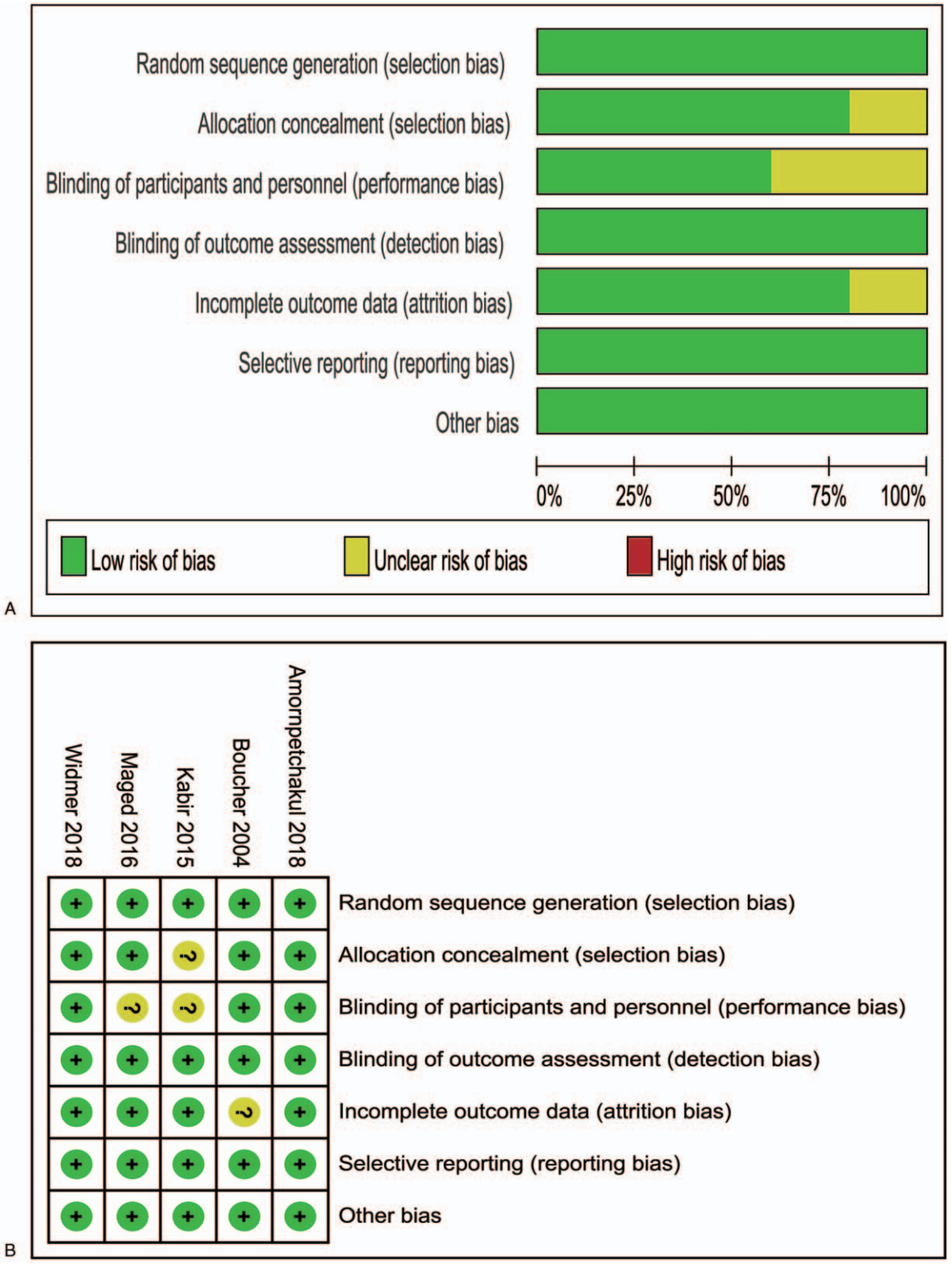

Figure 2. a. Risk of bias graph, b. risk of bias summary ("+" low risk; "?" unclear risk; "-" high risk).

and middle income countries where cold-chain transport and storage are not available. The half-life of carbetocin is 40 minutes, which is 4-10-fold longer than that of oxytocin, and the duration of action is 2 hours after an intramuscular injection,[14] avoiding side effects of intravenous injection. Nevertheless, there is a disparity in price between carbetocin and oxytocin. A vial of carbetocin is 18.20 USD, while a vial of oxytocin is only 0.18 USD, which could be a major barrier for carbetocin to be widely

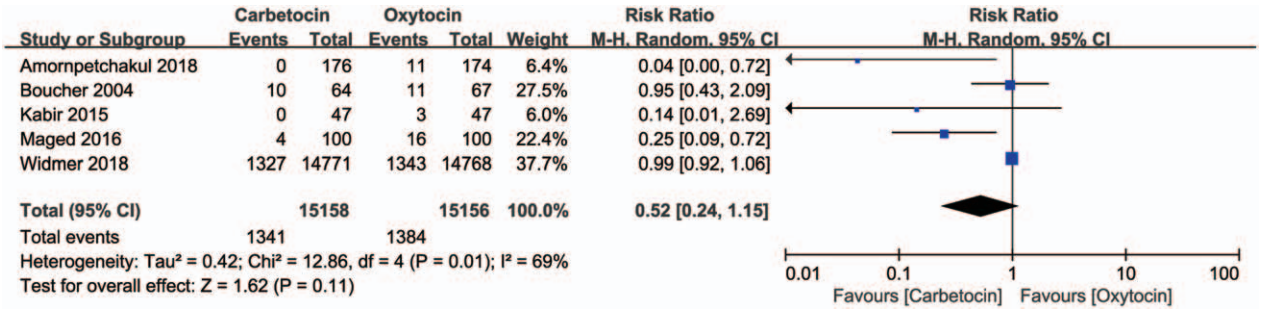

Figure 3. Carbetocin vs oxytocin for blood loss ≥500 ml in women undergoing vaginal delivery.

used in low- and middle-income countries. Currently, the WHO does not include a recommendation for carbetocin in preventing postpartum hemorrhage. However, the result of this meta-analysis indicated that there was no significant difference between carbetocin and oxytocin for prevention of postpartum hemorrhage in women undergoing vaginal delivery, and there was a non-significant trend in favor of carbetocin. Although the heterogeneity was high, sensitivity analyses by excluding 1 trial at 1 time showed the same results. No significant differences were found between carbetocin and oxytocin in blood loss ≥1000 ml, use of additional uterotonic agents, blood transfusion, uterine massage, and side effects such as abdominal pain, vomiting, dizziness, and palpitation. Therefore, according to the results of this meta-analysis, it is reasonable that professional organizations might consider to revise their clinical guidelines to clinicians and recommend heat- stable carbetocin as first line treatment for prevention of postpartum hemorrhage in women undergoing vaginal delivery especially in low- and middle-income countries, if carbetocin is proven to be cost-effective.

This meta-analysis has its limitations. First, most of the trials included in this meta-analysis were small, with likely biases, which could hinder the validity of research of carbetocin compared with oxytocin. Second, baseline characteristics of these women in these trials were different from each other. Two trials[12,15] included women with or without risk factors; 1 trial[14] only recruited women with 1 risk factor; 1 trial[11] only enrolled women with at least 2 risk factors; the last trial[13] only included women with at least 2 risk factors. Third, different dosage and administration routes of carbetocin and oxytocin were used in these trials. All the aspects mentioned above might contribute to the inconsistence of trials leading to the high heterogeneity of this meta-analysis. Fourth, we did not conduct an individual patient data (IPD) meta-analysis, which allows for evaluating the efficacy and safety of carbetocin in subpopulation such as women with different maternal age and risk factors. Therefore, we were unable to explore potential sources of heterogeneity and to perform subgroup analyses.

Table 2

Carbetocin vs oxytocin for secondary outcomes in women undergoing vaginal delivery.

Secondary outcome	Trials	Carbetocin (Events/Total)	Oxytocin (Events/Total)	RR (95%CI)	*P* value	I^2
Blood loss ≥1000 ml	Amornpetchakul (2018), Maged (2016), Widmer (2018)	222/15047	213/15042	1.04 (0.86–1.26)	.67	0%
Use of additional uterotonic agents	Amornpetchakul (2018), Boucher (2004), Kabir (2015),Maged (2016), Widmer (2018)	1584/15177	1630/15166	0.63 (0.37–1.07)	.09	83%
Blood transfusion	Amornpetchakul (2018), Kabir (2015), Maged (2016), Widmer (2018)	230/15094	203/15089	1.13 (0.94–1.37)	.19	17%
Uterine massage	Boucher (2004), Kabir (2015)	36/130	53/124	0.40 (0.06–2.58)	.34	53%
Flushing	Amornpetchakul (2018), Maged (2016), Widmer (2018)	10/15030	5/15017	1.90 (0.68–5.33)	.22	0%
Vomiting	Boucher (2004), Maged (2016), Widmer (2018)	35/14937	33/14920	0.85 (0.13–5.45)	.86	58%
Abdominal pain	Amornpetchakul (2018), Boucher (2004), Widmer (2018)	69/15013	57/14994	1.20 (0.85–1.71)	.30	12%
Nausea	Boucher (2004), Maged (2016)	8/183	8/177	0.95 (0.37–2.44)	.91	29%
Dizziness	Amornpetchakul (2018), Boucher (2004), Maged (2016)	15/359	9/351	1.56 (0.71–3.42)	.27	0%
Headache	Amornpetchakul (2018), Boucher (2004), Maged (2016)	11/359	15/351	0.76 (0.22–2.63)	.66	43%
Palpitation	Amornpetchakul (2018), Maged (2016)	5/276	2/274	2.48 (0.49–12.70)	.27	0%
Itching	Boucher (2004), Maged (2016)	1/183	4/177	0.52 (0.02–14.52)	.70	58%
Shivering	Boucher (2004), Maged (2016)	10/183	7/177	1.31 (0.54–3.22)	.55	0%

Risk factors of postpartum hemorrhage include history of postpartum hemorrhage, retained placenta, polyhydramnios, multiple pregnancies, prolonged labor, etc.[18] It is not clear which women benefit most from carbetocin for prevention of postpartum hemorrhage. Further trial might focus on certain subpopulations such as women with polyhydramnios, multiple pregnancies, or prolonged labor. Future trials also need to identify the optimal dose, timing, and administration route of carbetocin for these women.

In conclusion, this meta-analysis showed that carbetocin was as effective and safe as oxytocin for prevention of postpartum hemorrhage in women undergoing vaginal delivery, and the choice of carbetocin for routine prophylaxis will depend on cost-effectiveness.

Author contributions

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Supervision: Xin-Hang Jin, Dan Li.
Validation: Xin-Hang Jin, Dan Li, Xia Li.
Writing – original draft: Xin-Hang Jin, Dan Li.
Writing – review & editing: Xin-Hang Jin.

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