ABSTRACT

Background: Untreated retained placenta is the second most common cause of postpartum hemorrhage. Nowadays pharmacological management of retained placenta seems to be a good alternative to surgical intervention. Carbetocin which is an analogue of oxytocin is a drug indicated for controlling postpartum hemorrhage.

Aim: To compare carbetocin and oxytocin in terms of efficacy in the management of retained placenta.

Methods: We conducted our search in the different online databases for eligible clinical trials excluding observational studies. We used the Cochrane risk of bias tool to perform the quality assessment of the included trials. The assessed outcomes include total blood loss, duration of the third stage of labour, pre-delivery hemoglobin, post-delivery hemoglobin, manual removal of placenta, blood transfusion, additional uterotonic agents, placenta expelled spontaneously, adherent placenta, and successful expulsions.

Results: We included four trials in our meta-analysis. Our results yielded an overall favoring of the carbetocin group over the oxytocin group in terms of total blood loss (MD = -119.12, 95% CI [-130.76, -107.48], p<0.001), duration of the third stage of labor (MD = -4.44 [-7.11, -1.78], p=0.001), blood transfusion (RR = 0.46 [0.21, 1.02], p=0.05), the need for additional uterotonic drugs (RR= 0.30 [0.20, 0.44], p<0.001), placenta expelled spontaneously (RR= 1.14 [1.02, 1.26], p=0.02), and the manual removal of placenta (RR= 0.70 [0.50, 0.98], p=0.04). However, both drugs showed similar results regarding adherent placenta (RR= 0.46 [0.14, 1.44], p=0.18), successful expulsion (RR= 1.09 [0.94, 1.26], p=0.27), pre, and post-delivery hemoglobin.

Conclusion: To conclude, we found that carbetocin is associated with positive and promising results than oxytocin in the management of retained placenta and it is ass

INTRODUCTION

It is well-established that postpartum hemorrhage is the primary leading cause of maternal mortality, representing about 25% of the worldwide mortality rate. Additionally, postpartum hemor-
rhage leads to long-term disability and severe maternal morbidities such as blood transfusion, emergency surgery, and admission to the intensive care unit (Say et al., 2014; Hogan et al., 2010). A woman is said to have postpartum hemorrhage if she loses at least 500mL of blood after vaginal delivery or more than one liter after cesarean section. Uterine atony, which is the inability of the uterine muscles to contract properly, accounts for most cases of postpartum hemorrhage (Heneghan et al., 2012). The second most common cause of postpartum hemorrhage is untreated retained placenta (RP) (Bateman et al., 2010; Endler et al., 2012).

RP is a condition in which all or part of the placenta remains in the uterus during the late stage of delivery. It is one of the common causes of both primary and secondary postpartum hemorrhage (Perlman et al., 2019). Incidence of retained placenta is highly variable around the world affecting between 1 to 3% of vaginal deliveries (Nikolajsen et al., 2013). It is diagnosed if the placenta has not been delivered within an hour (Endler et al., 2014). Risk factors include the positive history of previous retained placenta, delivery of a premature fetus, previous history of uterine surgical interference, history of recurrent pregnancy loss, abortion, curettage, abortion, the delivery of more than five children, and unrecognized congenital anomalies of the female genital tract, especially uterine abnormalities (Grillo-Ardila et al., 2018).

The standard management of retained placenta is manual removal of placenta; however, this management is associated with hemorrhage, endometritis or perforation of the uterine wall. Nowadays pharmacological management of retained placenta seems to be a good alternative to surgical intervention. There is routine administration of oxytocin used as a prophylaxis against postpartum hemorrhage and its dose is frequently increased so surgeons consider it high risk (Shabana et al., 2012).

Carbetocin which is an analogue of oxytocin is a drug indicated for controlling postpartum hemorrhage. Recent studies showed that carbetocin could reduce postpartum hemorrhage after a caesarian section when compared to a placebo (Chen et al., 2016). A single intravenous dose of carbetocin equals a 16-hour intravenous infusion of oxytocin to increase the uterine wall to stop bleeding (Leung et al., 2006). Carbetocin is better than oxytocin in the management of retained placenta as it shows a better effect and longer duration of action. Some studies showed that long-term use of carbetocin is a modifiable risk factor for the retained placenta (Elfayomy et al., 2015).

We aim in this systematic review and meta-analysis to know the effect of using carbetocin in the management of retained placenta and the expected side effects of the drug.

METHODS

This meta-analysis was prepared based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) (Liberati et al., 2009).

Search strategy:

We searched several electronic databases including PubMed, and Cochrane CENTRAL through May 2020, using
keywords ("retained placenta") AND ("1-deamino-1-monocarba-2-(Tyr(OMe))-oxytocin" OR carbetocin OR dcomot OR Depotocin).

**Inclusion criteria:**
- **Population:** women with retained placenta
- **Intervention:** carbetocin
- **Comparator:** oxytocin
- **Outcomes:** the main outcome measures were total blood loss, duration of the third stage of labor, pre-delivery hemoglobin, post-delivery hemoglobin, manual removal of placenta, blood transfusion, additional uterotonic agents, placenta expelled spontaneously, adherent placenta, and successful expulsions.
- **Study design:** randomized controlled trials (RCTs)

**Study selection:**

The screening process was performed in two steps: the first one was both titles and abstracts screening of all articles that resulted from the search process according to our eligibility criteria. The second step was the full-text screening of the articles included in the previous step.

**Data extraction and analysis:**

The extracted data included: baseline characteristics of the study population, risk of bias assessment and study outcomes. Data were presented as the means and standard deviations (±SD) for numerical variables and as numbers and percentages for categorical variables. Retrieved data were entered into RevMan software (Review Manager, version 5.4) for meta-analysis. The mean difference (MD), relative risk (RR), and 95% confidence interval (CI) were calculated for different outcomes.

Statistical heterogeneity between studies was evaluated using forest plots and statistically using I-squared (I²) test. Values identified ≥50% were considered as significantly heterogeneous. When heterogeneity was significant, a random-effect model was used for data analysis. Fixed effect meta-analysis was used when there was no significant heterogeneity. Pooled analyses of data from all studies were performed for outcomes.

**Risk of bias assessment:**

We utilized the Cochrane risk of bias (ROB) assessment tool which is described in chapter 8.5 of the Cochrane handbook of systematic reviews of interventions 5.1.0 (Higgins et al., 2011). Risk of bias assessment assesses various domains: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, selective outcome reporting and other potential sources of bias. Each study is classified in each domain as low, high, or unclear risk of bias.

**RESULTS**

A total of 600 patients were included in this study, 298 patients received carbetocin to manage retained placenta, and 302 patients received oxytocin as a control group. Table 1 shows a summary of the included studies and baseline characteristics of different reported scores used by different trials. The mean age of patients was 27.37 years old for the carbetocin group, and 28.39 years old for the oxytocin group. Elfayomy et al (2015) showed that the success rate of the carbetocin group was 86.84% compared to 77.5% in the intra-umbilical
Elsafty et al. (2016) assessed the time of the third stage of labor and found that it was 33.4±20.4 minutes in the oxytocin group & 23.1±16.8 minutes in the carbetocin group (p=0.002). Maher et al (Maher et al., 2017) showed that the overall success rate of the carbetocin group was 71.3% compared to 66.7% in the oxytocin group (p<0.05). Salem et al (Salem et al., 2019) shows that Total blood loss (ml) and duration of the third stage of labor (minutes) were significantly lower in the carbetocin group when compared to the oxytocin group (p=0.04).

Results of the literature search

The literature search of databases yielded 309 studies. After the removal of duplicates, 199 unique citations remained. Title and abstract screening were conducted and 169 studies were excluded. The remaining 30 studies were eligible for full-text screening. Finally, four randomized clinical trials were included in this systematic review and meta-analysis (Figure 1).

Results of risk of bias assessment

Assessment of risk of bias among included studies revealed a low risk of bias. All studies reported adequate randomization of patients. Allocation concealment was properly met in addition to the blinding of both patients and personnel. Regarding outcome assessment, one study (Salem et al., 2019) did not report any data about the blinding of the outcome assessors. Two studies (Maher et al., 2017; Salem et al., 2019) reported a low risk of attrition bias, and all studies were put to low risk of reporting bias. No other bias was found.

Results of outcome analysis

1. Total blood loss:

Three studies reported total blood loss. The overall mean difference favored carbetocin over oxytocin group (MD = -119.12, 95% CI [-130.76, -107.48], p<0.001). We did not observe heterogeneity (p = 0.72, I^2 = 0%) (Figure 3).

2. Duration of the third stage of labour (minutes):

Two studies reported the duration of the third stage of labour (minutes). The mean difference preferred carbetocin over oxytocin group (MD = -4.44 [-7.11, -1.78], p=0.001). pooled studies were heterogeneous (p = 0.05, I^2 = 75%) (Figure 4).

3. Pre-delivery hemoglobin:

Two studies reported Pre-delivery hemoglobin. The overall mean difference showed no variation between carbetocin and oxytocin (MD = 0.07 [-0.03, 0.16], p=0.19). studies were homogeneous (p = 0.17, I^2=47%) (Figure 5).

4. Post-delivery hemoglobin:

Two studies reported Post-delivery hemoglobin. The overall mean difference showed similar hemoglobin levels in carbetocin and oxytocin (MD = 0.17 [-0.07, 0.41], p=0.16). we observed heterogeneity (p = 0.07, I^2 = 70%) (Figure 6).

5. Blood transfusion:

Three studies reported blood transfusion. The overall risk ratio favored carbetocin over oxytocin (RR = 0.46 [0.21, 1.02], p=0.05). We did not ob-
serve heterogeneity \( (p = 0.36; I^2 = 3\%) \) (Figure 7).

6. Additional uterotonic agents:

Three studies reported additional uterotonic agents. The combined risk ratio showed that carbetocin is better than oxytocin \( (RR = 0.30 [0.20, 0.44], p < 0.001) \). Data were homogenous \( (p = 0.30, I^2 = 17\%) \) (Figure 8).

7. Placenta expelled spontaneously:

Two studies reported the placenta expelled spontaneously outcome. The analysis showed that the rate of spontaneous expelled placenta is lower in the oxytocin group \( (RR = 1.14 [1.02, 1.26], p = 0.02) \). there was no heterogeneity \( (p = 0.88, I^2 = 0\%) \) (Figure 9).

8. Manual removal of placenta:

Manual removal of placenta was reported by three studies. The combined analysis demonstrated that the need for manual removal of placenta is lower in patients in the carbetocin group than those in the oxytocin group \( (RR = 0.70 [0.50, 0.98], p = 0.04) \). Data were homogenous \( (P = 0.36, I^2 = 1\%) \) (Figure 10).

9. Adherent placenta:

Two studies reported adherent placenta outcome. The overall analysis did not show a difference between both groups on adherent placenta \( (RR = 0.46 [0.14, 1.44], p = 0.18) \). pooled risk ratio was homogenous \( (p = 0.82, I^2 = 0\%) \) (Figure 11).

10. Successful expulsion:

Two studies reported successful expulsion. The overall risk ratio showed similar effect on placental expulsion \( (RR = 1.09 [0.94, 1.26], p = 0.27) \). we did not observe heterogeneity \( (p = 0.74, I^2 = 0\%) \) (Figure 12).

DISCUSSION

After our analysis, we found that carbetocin was superior to oxytocin for the management of the retained placenta regarding the total blood loss, the duration of the third stage of labor, the amount of blood transfusion, and the utilization of additional uterotonic agents. While oxytocin was superior to carbetocin regarding the expulsion of the placenta spontaneously. On the other hand, there was some sort of similarity between both agents regarding pre and post-delivery hemoglobin levels, the rate of removal of the placenta manually, the risk of the presence of adherent placenta, and the rate of successful expulsion of the placenta.

A large meta-analysis was performed by Mitra et al (Mitra et al., 2020) in 2020 and involved 15 RCTs. Mitra et al aimed to investigate different pharmacological agents for the treatment of the retained placenta. They included 2204 patients treated with oxytocin, prostaglandin, nitroglycerin, ergometrine, or carbetocin. They measured only four outcomes; the need for manual extraction, estimated blood loss, the need for blood transfusion, and maternal fever. Their results were similar to ours. As they found that prostaglandin and carbetocin agents were better than oxytocin regarding the spontaneous delivery of the placenta. Additionally, they demonstrated that carbetocin is a better choice than oxytocin for postpartum hemorrhage prevention either after vaginal or cesarean delivery as reported in the studies that evaluate both agents for the pre-
Table (1): shows a summary of the included studies and baseline characteristics of different reported scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Age, y mean (SD)</th>
<th>BMI, mean (SD)</th>
<th>Parity, mean (SD)</th>
<th>Birth weight mean (SD)</th>
<th>Gestational Age, y mean (SD)</th>
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<tbody>
<tr>
<td></td>
<td>Car-betocin</td>
<td>Oxytocin</td>
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<td>2015</td>
<td>38</td>
<td>40</td>
<td>31(5.0)</td>
<td>32.7(5.1)</td>
<td>2.5 (1.8)</td>
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<td>Car-betocin</td>
<td>Oxytocin</td>
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<td>1.21 (1.31)</td>
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<td>Maher</td>
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<td>2016</td>
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<td>96</td>
<td>27.42(5.26)</td>
<td>27.78(5.22)</td>
<td>25.02 (2.80)</td>
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<td>2.20 (1.27)</td>
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<td>Salem</td>
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<td>2019</td>
<td>100</td>
<td>100</td>
<td>25.4(4.7)</td>
<td>26.6(4.6)</td>
<td>27.2 (2.6)</td>
<td>3765 (330)</td>
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<td>2.5(1.8)</td>
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Y=year, SD= standard deviation, BMI= body mass index, NR= not reported
Figure (1): shows a PRISMA flow diagram of our literature search.
Figure (2): Risk of bias summary

Figure (3): Total blood loss
Figure (4): Duration of the third stage of labor (minutes)

Figure (5): Pre-delivery hemoglobin

Figure (6): Post-delivery hemoglobin

Figure (7): Blood transfusion

Carbetocin vs. Oxytocin in Retained Placenta

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Figure (8): Additional uterotonic agents

Figure (9): Placenta expelled spontaneously

Figure (10): Manual removal of placenta

Figure (11): Adherent placenta
vention of hemorrhage (Voon et al., 2018; Jin et al., 2019). The half-life of oxytocin is shorter than carbetocin which may explain the superiority of carbetocin. Having heat-safe storage in low-resource environments and heat stability for transport is another advantage of carbetocin (Malm et al., 2018).

For the treatment of retained placenta, sixteen studies with a pharmacologic intervention compared to a placebo were included in a prior review that was published in 2015. The authors came to the conclusion that there was no evidence that interventions involving oxytocin, nitroglycerin, or prostaglandin agents were any better than a placebo in preventing the need for manual placenta removal compared with the placebo. But only one study examined a prostaglandin administered intra-umbilically, and no studies using carbetocin as the study agent were involved due to their eligibility requirements (Duffy et al., 2015).

In 2019, Abdelhamid et al conducted a RCT that included 100 subjects involved in the analysis. They aimed to make a comparison between oxytocin and carbetocin regarding the uterotonic effect. They found that oxytocin was inferior to carbetocin in the decrease of the need for additional contraction of the uterus either for vaginal delivery or for cesarean delivery as we found in our analysis (Abdelhamid et al., 2019).

Salem et al performed a study that investigate the efficacy of intra-umbilical vein injection of oxytocin versus carbetocin in the treatment of retained placenta. 200 females were analyzed in this study. Like our results, they found that the duration of the third stage of labor and the total loss of blood were markedly lower in the carbetocin cohort than in the oxytocin cohort. Also, the carbetocin cohort was associated with lower rates of the additional uterotonic agents needed, the incidence of postpartum hemorrhage, and the blood transfusion needed than the oxytocin cohort (Salem et al., 2019).

The safest and most efficient management approach for retained placenta after cesarean or vaginal delivery requires more randomized controlled trials. According to the findings of this meta-analysis, these will probably require large, multicenter trials with arms for both study agents and placebo.

**Limitations**

The utilization of clinical assessment to identify the retained placenta has some limitations as it would be hard to make sure whether the placenta was pathologically attached (accrete), nor-
mally adherent, or trapped in the lower segment of the uterus at the time of randomization. One of these subtypes may benefit more than the others from the interventions. The small number of involved trials and the small sample size are other limitations of our meta-analysis.

CONCLUSION

For the management of the retained placenta, carbetocin is more sufficient than oxytocin as it decreases the amount of blood loss, the duration of the third stage of the delivery, the need for other uterotonic agents, and the amount of blood transfusion.

REFERENCES


مقارنة بين الكربيتوصين والأوكسيتوصين من حيث الفعالية في علاج المشيمة المحتشبة بها؛ مراجعة منهجية وتحليل بعدي
علي البنداري - إبراهيم سويدان
قسم أمراض النساء والتوليد جامعة بنها - بنها - مصر

الخلفية: عدم علاج المشيمة المحتشبة ثاني أكثر أسباب النزيف شيوعا بعد الولادة. في الوقت الحاضر، يبدو أن العلاج الدوائي للمشيمة المحتشبة هو بدائل جيدة للتدخل الجراحي، الكاربيتوصين يظهر للأوكسيتوصين هو دواء يشار إليه للتحكم في نزيف ما بعد الولادة.

الهدف: مقارنة الكربيتوصين والأوكسيتوصين من حيث الفعالية في علاج المشيدة المحتشبة.

الطريقة: أجرينا بحثًا وفقًا لقواعد البيانات المختلفة عبر الإنترنت للتجارب السريرية المتعلقة بأستثناء الدراسات القائمة على الملاحظة. استخدمنا أدلة كوكرين المعدلة لخطر التحيز للتجارب العشوائية لإجراء تقييم جودة التجارب المضمنة. تشمل النتائج التي تم تقييمها فقدان الدم الكلي، ومرة المرحله الثالثة من المخاض، والهيموجلوبين قبل الولادة، والهيموجلوبين بعد الولادة، والإرادة اليدوية للمشيمة، ونفل الدم، وعوامل توتر الرحم الإضافية، والمشيمة المطرودة تلقائيًا، والمشيمة الملتصقة، وعمليات الطرد الناجحة.

النتائج: قمنا بتسجيل أربع تجارب في تحليلنا البدعي. أسفرت نتائجنا عن تفضيل شامل لمجموعة الكاربيتوصين على مجموعة الأوكسيتوصين من حيث إجمالى فقدان الدم (MD = 119.12 - 119.44, p = 0.048, MD = 0.13, RR = 0.76, 0.50 < p < 0.98, RR = 0.10, RR = 0.26, p = 0.049, RR = 0.10, 0.001 < p < 0.05, RR = 0.26, 0.001 < p < 0.05).

ومع ذلك، أظهرت النتائج ملائمة فيما يتعلق بالمشيمة المستضيفة (p = 0.18, RR = 0.94, 0.77 < p < 0.94, RR = 0.82).

الاستنتاج: في الختام، وجدنا أن الكاربيتوصين مرتبط بنتائج إيجابية وواعدة من الأوكسيتوصين في علاج المشيمة المحتشبة.

10. المصرية للعلوم الطبية (1) يونيو 2020: 105-118

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