Comparison between oxytocin intravenous bolus, oxytocin intravenous bolus and infusion, rectal misoprostol and carbetocin infusion for the control of blood loss at elective cesarean section

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Comparison Between Oxytocin Intravenous Bolus, Oxytocin Intravenous Bolus and Infusion, Rectal Misoprostol, and Carbetocin Infusion for the Control of Blood Loss at Elective Cesarean Section

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Abstract

Background: Uterine atony is the greatest typical etiology of primary postpartum hemorrhage (PPH). The atonic PPH rates of developed nations are rising despite regular active control of the third stage of work. Primary PPH continues to be the greatest cause of maternal mortality in less developed nations.

Aim and objectives: To assess the effectiveness of rectal misoprostol, oxytocin infusion, and oxytocin intravenous bolus and infusion in reducing blood loss during and after elective caesarean delivery.

Patients and methods: This prospective research included 200 pregnant patients who were hospitalized to the labor ward at the Department of Obstetrics and Gynecology of Al-Hussein University Hospital.

Result: There was a significant difference among included groups regarding additional uterotonic use intraoperatively, as it was used in 17, 12, 13, and 5 in groups 1, 2, 3, and 4, respectively.

Conclusion: Compared with the oxytocin and misoprostol groups, carbetocin is only effective in reducing postpartum bleeding and is related with a reduced requirement for further uterotonic medicines or surgical hemostatic treatments.

Keywords: Carbetocin, Cesarean section, Control blood loss, Misoprostol, Oxytocin

1. Introduction

One of the more common major procedures among women across the globe is a cesarean section. Over the last four decades, these procedures have increased to between 20 and 30% in the majority of affluent nations, up to 40% in China, and as high as 70% in certain Latin American nations.1

One of the leading causes of maternal mortality globally is postpartum hemorrhage (PPH), which is responsible for up to 30% of maternal fatalities. Every effort should be taken to minimize the blood loss during cesarean birth as it is much more than during natural birth.2

Uterine atony is the most typical cause of primary PPH. The atonic PPH rates of developed nations are rising despite regular active control of the third stage of work. Primary PPH continues to be the greatest cause of maternal mortality in less developed nations. Over time, many uterotonic techniques have been used. Studies on oxytocin, ergometrine, misoprostol, and PGF2-alpha are substantial. However, more research is needed to determine the best way to take these medications and how much to take.3

The preferred medication is oxytocin 10 IU i.m./intravenous (i.v.), which the WHO advises for use during the third stage of labor in all deliveries to avoid PPH. The guidelines are more commonly...
accepted for vaginal birth, and studies have demonstrated that there are no safety issues with either i.v. infusion or i.v. bolus following vaginal delivery.\(^4\)

To prevent postpartum blood loss from the point of placental attachment, oxytocin encourages uterine smooth muscle contraction. In comparison with other uterine stimulants, oxytocin has the benefit of being less expensive and acting more quickly. Its brief duration of effect, however, when administered as a quick i.v. bolus, results in hypotension and tachycardia.\(^5\)

It is advised in the USA to provide an oxytocin infusion rather than a bolus dosage. This strategy can be motivated by worries about bolus oxytocin’s physiological effects. The potential benefit of an i.v. oxytocin infusion during a cesarean delivery is to sustain uterine contractility during the surgical operation and the first few hours after delivery, when primary bleeding is most common. i.v. oxytocin has a short half-life (4–10 min). The usage of carbetocin (a long-acting synthetic oxytocin) in place of oxytocin after cesarean surgery and the most current Canadian recommendations all advocate these newer uterotonic drugs. However, carbetocin is costly and unavailable in limited-resource environments.\(^6\)

Prostaglandins, like misoprostol and carboprost, have been investigated as alternative therapies during the last 20 years. A more recent uterotonic drug with oxytocin receptor agonist characteristics is carbetocin, which is a long-acting synthetic octapeptide analogue of oxytocin. Due to its 4–10 times longer elimination half-life than oxytocin, carbetocin has the advantage of a longer period of oxytocic activity without the need for extra postdelivery treatment.\(^7\)

Carbetocin has a comparable safety profile to oxytocin and is well tolerated. To raise uterine tone and decrease intraoperative blood loss in women having planned cesarean sections, it has been shown that a single i.v. dosage of carbetocin is just as effective as a 16-h i.v. oxytocin infusion. In terms of cost-efficiency and extra dosage, carbetocin outperforms oxytocin.\(^8\)

Misoprostol is a prostaglandin E1 analog that may be administered orally, sublingually, rectally, or vaginally. Additionally, PPH is prevented and treated using misoprostol. When compared with alternative methods of misoprostol administration, it has been shown that the use of rectally delivered misoprostol in situations of bleeding is related with reduced incidence of adverse effects. It is less costly and thermally stable than oxytocin; therefore, it does not need to be refrigerated.\(^9\)

Misoprostol undergoes de-esterification in the liver after delivery (via mouth, sublingual, vaginal, or rectal route), turning it into misoprostol acid. The physical-chemical structure of the collagen in the cervix changes as a result of this active metabolite’s direct action on prostaglandin receptors, softening and maturing the cervix and promoting its dilatation. Additionally, it encourages elevated intracellular calcium, which is essential for myometrial muscle contraction. The most often reported adverse effects of misoprostol include nausea, vomiting, diarrhea, stomach discomfort, fever, and chills. Rare but severe responses might include uterine rupture, hypercontractility, and tachysystole. These effects are all dose dependent and tend to be milder in the early hours after usage.\(^10\)

The goal of the current research was to determine how well the use of i.v. oxytocin bolus, infusion, rectal misoprostol, and carbetocin infusion reduced loss of blood during and after an optional cesarean surgery.

2. Patients and methods

The emergency department of Al-Azhar University Hospitals served as the site of this prospective research. It began from August 2021 to February 2022. A total of 200 pregnant women who had been admitted to the labor ward participated in this research.

Inclusion criteria were all willing patients who were between the ages of 20 and 35 years, had a full-term pregnancy that was over 37 weeks along with cephalic presentation, and having an elective cesarean delivery.

Exclusion criteria were previous history of PPH; multiple pregnancies; hypertension; preeclampsia; eclampsia; heart, renal, or liver disorders; diabetes mellitus; patients with gestational diabetes; low-lying placenta; placenta previa, accreta, percreta, and accidental hemorrhage; antepartum hemorrhage; and coagulation disorders. When they anticipated substantial hemorrhage, clinicians made their own decision to remove more patients, following the advice of the study ethical committee.

The cases that fulfilled the criteria were simple randomly distributed into four groups: first group included 50 women who received oxytocin i.v. bolus (10 IU), second group included 50 women who received oxytocin i.v. bolus (10 IU)+infusion 10 IU dissolved in 500 ml saline, third group included 50 women who received misoprostol rectally 800 μg (four tablet each table 200 μg), and fourth group included 50 women who received an ampule of carbetocin infusion (100 μg/ml) dissolved in 500-ml saline.
All eligible research participants underwent the following: informed consent was obtained. Data on demographics, pregnancies, and postpartum were kept. Every patient received drug according to the allocated group. Cesarean delivery was performed. The operating obstetrician evaluated the uterine tone on a five-point Likert scale (0 floppy and 4 rock hard) immediately after placenta delivery and then every 5 min until abdominal closure started. The operation’s data were documented. The surgeon assessed the amount of blood lost.

3. Results

Regarding demographic data and basal characteristic, there was no significant difference among the research groups (Table 1).

Regarding amount of blood lost, mean postpartum hemoglobin, mean postoperative hematocrit value, and fall hematocrit, there was a significant difference between the research groups (Table 2).

Regarding operative and postoperative stay duration, there was no significant difference among the study groups (Table 3).

Regarding additional uterotonic use, there was a significant difference between included patients in additional intraoperative uterotonic use (Table 4).

Regarding need for blood transfusion and adverse effects, there was no statistically significant difference (P > 0.05).

In addition, the randomized study by Elgazayerli14 compared the safety and efficacy of carbetocin, misoprostol, and syntocinon to determine which drug helps to minimize blood loss after cesarean delivery. They enrolled 180 women who attended for delivery. The age, BMI, gestational age, gravidity, and parity in the three studied groups showed insignificant differences between them.

Our findings showed that there was no difference in vital signs across the included groups.

4. Discussion

The largest frequent kind of serious obstetric bleeding is called primary PPH. The loss of 500 ml or greater of blood from the vaginal tract within 24 h after childbirth is the definition of PPH.11

The Royal College of Obstetricians and Gynecologists recommends the ergot analog ergometrine as a second-line pharmacological therapy for uterine atony in instances of postpartum bleeding following first-line oxytocin dosing. Ergometrine is a second-line uterotonic agent owing to its adverse effects (hypertension, nausea, and vomiting).12

Regarding demographic data and basal characteristics of study group populations, we found that there was no difference among included groups regarding age, gestational age, BMI, hemoglobin, and hematocrit value of the study group populations.

Our research was consistent with Abd El-Gaber et al.,13 who aimed to compare the effectiveness of carbetocin, oxytocin, and misoprostol in preventing atonic PPH in 200 pregnant women having planned cesarean sections. Regarding the mother’s age, BMI, parity, and gestational age, there was no statistically significant difference (P > 0.05).

Table 1. Demographic data and basal characteristic of research group populations.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (50)</th>
<th>Group 2 (50)</th>
<th>Group 3 (50)</th>
<th>Group 4 (50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.22 ± 6.12</td>
<td>25.68 ± 5.13</td>
<td>28.82 ± 6.4</td>
<td>26.68 ± 8.11</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.84 ± 0.41</td>
<td>38.93 ± 1.92</td>
<td>38.14 ± 0.41</td>
<td>37.93 ± 0.92</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 3.7</td>
<td>32 ± 2.1</td>
<td>31 ± 2.6</td>
<td>32 ± 3.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.9 ± 1.28</td>
<td>11.1 ± 1.28</td>
<td>10.5 ± 1.38</td>
<td>10.2 ± 0.98</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hematocrit value (%)</td>
<td>33.08 ± 2.1</td>
<td>32.81 ± 2.13</td>
<td>31.90 ± 3.04</td>
<td>32.62 ± 3.25</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 2. Hematologic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (50)</th>
<th>Group 2 (50)</th>
<th>Group 3 (50)</th>
<th>Group 4 (50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total amount of blood lost (ml)</td>
<td>819 (236)</td>
<td>974 (243)</td>
<td>756 (252)</td>
<td>674 (385)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>0–499</td>
<td>15 (30)</td>
<td>19 (38)</td>
<td>17 (34)</td>
<td>10 (20)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>500–999</td>
<td>25 (50)</td>
<td>21 (42)</td>
<td>20 (40)</td>
<td>32 (64)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>10 (20)</td>
<td>10 (20)</td>
<td>13 (26)</td>
<td>8 (16)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mean postpartum hemoglobin (g/dl)</td>
<td>10.2</td>
<td>10.5</td>
<td>10.1</td>
<td>10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fall Hb (mean)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mean postoperative Hematocrit value (%)</td>
<td>28.3</td>
<td>27.5</td>
<td>28.3</td>
<td>30.32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fall hematocrit (%) (mean)</td>
<td>4.78</td>
<td>5.31</td>
<td>3.6</td>
<td>2.3</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
In agreement with our results, the study by Kansouh and El Naggar\textsuperscript{15} reported that vital indicators such as systolic blood pressure and diastolic blood pressure did not vary across the included groups. Moreover, in line with our results, Fahmy et al.\textsuperscript{16} revealed that there were no differences among included groups regarding vital signs including heart rate and baseline blood pressure.

Regarding estimated blood loss in each group, we found that there was a significant difference among included groups regarding estimated blood loss; however, the most blood loss in each group was between 500 and 999 ml.

Our results were supported by Abd El-Gaber et al.,\textsuperscript{13} who reported that regarding the frequency of PPH and its major degree, there were statistically significant differences among the three groups, although there was only a moderately statistically significant difference in its small degree ($P < 0.001$ and 0.05, respectively).

Moreover, in agreement with our results, Elgaayerli\textsuperscript{14} revealed that the intraoperative blood loss was higher in group A (syntocinon group) (660.0 ± 36.2 ml), whereas group C (carbetocin group) showed the least amount of blood loss, with statistically significant difference.

In contrast with our results, the study by Kansouh and El Naggar\textsuperscript{15} reported that blood loss in the oxytocin group of patients (782.8 ± 370 ml) was nonsubstantially greater than that in carbetocin group patients (685 ± 350 ml) ($P = 0.07$). The disagreement may be due to the variations in sample size and sample characteristics including age and comorbidities.

Regarding hemoglobin change after surgery, the present study showed that there was a significant difference among included groups regarding hematocrit change.

In agreement with our study, Abd El-Gaber et al.\textsuperscript{13} reported on the tested groups’ preoperative and postoperative hemoglobin and hematocrit value levels. Regarding the lowering of both parameters,
there was a statistically significant difference among the three groups \( (P < 0.04) \).

Moreover, in harmony with our results, Elgazayerli\(^1\) reported that the reduction in hemoglobin and hematocrit in the carbetocin group was more significant than the other two groups.

However, the study by Kansouh and El Naggar\(^1\) reported that between the two groups, there was no statistically significant difference in the amount of hemoglobin reduced 24 h after surgery or the hemoglobin change. This is because no significant difference regarding blood loss was reported.

Our results showed also that there was no significant difference among included groups regarding operative and postoperative stay duration. However, there was a significant difference among included groups regarding additional uterotonics use.

In agreement with our study, Abd El-Gaber et al.\(^1\) showed that there was a significant difference among included groups regarding additional uterotonics use.

Moreover, Kansouh and El Naggar,\(^1\) reported that there was a significant difference among included groups regarding need for other uterotonics agents.

Furthermore, our study results were supported by Sotillo et al.,\(^1\) who reported that both groups' surgical times were comparable (average durations for the oxytocin and carbetocin groups were 40.1 and 38.7 min, respectively). The carbetocin group required somewhat fewer extra uterotonic, but once again, the difference did not achieve statistical significance.

Regarding the need for blood transfusion and other adverse effects, we found that there was a significant difference among included groups regarding need for blood transfusion. However, other adverse effects (headache, vomiting, and chest pain) did not show any significant difference among included groups.

In agreement with our study, Abd El-Gaber et al.\(^1\) reported that there was a significant difference among included groups regarding need for blood transfusion.

In contrast with our results, the study by Elgazayerli\(^1\) reported that the need for blood transfusion in group A was four cases, whereas in the carbetocin group, no one needed blood transfusion, with statistically significant differences. There was a substantial enhancement in complications in groups 1 and 2 more than group 3.

Furthermore, Kansouh and El Naggar\(^1\) reported that blood transfusions occurred more often (9.41\%) in the oxytocin group than in the carbetocin group (2.22\%), and the variation was statistically substantial \( (P < 0.05) \). Regarding adverse effects of drugs, there was no significant difference between the two groups. The incidence of tachycardia and headache was substantially increased in the carbetocin groups \( (P < 0.05) \).

Regarding time lapse and uterine tone among the studied groups, we revealed that there was a significant difference among included groups regarding uterine tone. However, time lapse did not show any significant difference among the included groups.

Furthermore, Dell-Kuster et al.\(^1\) examined the maximal uterine tone of carbetocin administered intravenously as a bolus and as a short infusion for cesarean delivery; they found that the former was 89 and the latter was 88 (median difference 1.3, 95\% confidence interval: 5.7–3.1). Blood pressure, estimated blood loss, further usage of uterotonics, and adverse effects were equivalent.

### 4.1. Conclusion

In individuals undergoing elective cesarean birth who have high-risk characteristics, carbetocin is better to oxytocin and misoprostol in avoiding and decreasing the incidence of atonic PPH. In comparison with oxytocin and misoprostol groups, carbetocin is only effective in reducing postpartum bleeding and is linked with a reduced requirement for further uterotonics medicines or surgical hemostatic treatments. Compared with oxytocin and misoprostol, it causes extended uterine tetanic spasm during and after cesarean birth.

### Conflict of interest

There were no conflicts of interest.

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5. Torloni MR, Siaulys M, Riera R, et al. Route of oxytocin administration for preventing blood loss at caesarean section: