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ORIGINAL ARTICLE

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Efficacy of oxytocin versus carbetocin in prevention of postpartum hemorrhage after cesarean section under general anesthesia: a prospective randomized clinical trial

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ABSTRACT

Objective: To compare the use of carbetocin and oxytocin in the prevention of postpartum hemorrhage after cesarean section.

Methods: The present study was a prospective double-blind randomized controlled clinical trial performed in two university-based hospitals in Tehran, Iran. Two hundred and twenty women with the gestational age of more than 37 weeks, who needed cesarean operation, participated in the study. Patients were assigned to receive either a single 100 μg IV dose of carbetocin or a standard 30-international unit IV infusion of oxytocin during 2 h after delivery of placenta. The primary outcome measures were postpartum hemorrhage requiring additional uterotonic drugs, bleeding volume, and the hemoglobin drops.

Results: There were meaningful differences in carbetocin versus oxytocin group regarding the hemoglobin drops (1.01 versus 2.05, $p = .01$), bleeding volume (430.68 CC versus 552.6 CC, $p < .001$), uterine massages frequency (3.7 versus 4.26, $p < .001$), and uterine height at 2, 4, and 24 h ($p < .001$). Oxytocin side effects were significantly higher in comparison with the carbetocin except pruritus which was observed in 27% of patients in the carbetocin versus no cases in the oxytocin group.

Conclusions: It may be concluded that carbetocin is a good alternative modality to conventional uterotonic agents such as oxytocin for the prevention of postpartum hemorrhage after cesarean sections.

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Introduction

Postpartum hemorrhage (PPH) is a common public health problem of childbearing and a leading cause of maternal morbidity and mortality worldwide. The maternal mortality rate in Iran was 2.5 in 100,000 live births in 2012 [1], and the major cause of mortality was postpartum hemorrhage (27%). Although obstetricians should identify the risk factors before and during delivery to improve the surgical conditions among high-risk women, significant life-threatening bleeding can occur even in the absence of other risk factors and without warning [2,3]. Some causes of PPH are the exhausted uterus or emergency cesarean section due to cephalopelvic disproportion or preeclampsia.

Active management of the third stage of labor with prophylactic use of uterotonic agents can reduce the rate of PPH [4–7,8], and prevent the irreversible functional consequences. The optimal agent is a product that can promote uterine contraction without significant side effects. Different prophylactic strategies have been described for the prevention of PPH. The most feasible therapeutic option is the use of oxytocin which is a nano-peptide with uterotonic properties [2,3]. Previous studies have demonstrated its useful effects and, at the present, it is the primary standard therapy to treat PPH. However, in some cases, there is a need for more potent therapeutics.

Methylergonovine is another uterotonic agent with similar effects to oxytocin and a longer half life [8,9].

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Some side effects of ergotamine consist of coronary artery spam and muscle contraction, so its use is contra-indicated in asthmatic patients [10], and also in preeclamptic women due to adverse effects on blood pressure [11,12].

Therefore, another drug with higher potency is needed for the prevention of PPH. Carbetocin is an eight amino long-acting oxytocin analogue introduced in 1987. The benefit of carbetocin is the longer half-life of about 60 min and 80% bioavailability compared with only 5 min of half-life for oxytocin [4–6]. Carbetocin may be used via intravenous or intramuscular routes and its effects start in the first 2 min and continue for 60 min. The previous studies have indicated no effect on blood pressure [6,13] after the administration of carbetocin. Several studies have compared oxytocin with carbetocin. Most of these studies have established that carbetocin is more effective than oxytocin in the prevention of postpartum hemorrhage and two studies have reported similar efficacy [14,15].

Although the carbetocin seems to be an ideal agent compared with oxytocin and methylergonovine, but it causes some adverse effects such as nausea, tremor, vomiting, and headache [16]. Previous studies have reported controversies about the side effects of carbetocin. The majority of these studies have been performed on patients undergoing vaginal delivery or cesarean section under local anesthesia. Local anesthesia may be associated with hypotension during the induction of anesthesia and it may worsen the side effects of drugs.

Some other studies have compared oxytocin and carbetocin in vaginal delivery or cesarean section under spinal or epidural anesthesia. The regional anesthesia is also associated with hypotension and headache which interfere with the side effects of uterotonic agents.

There is limited comparative evidence on efficacy and adverse effects of carbetocin in deliveries with general anesthesia. So, the present study was conducted to evaluate the efficacy and adverse effects of carbetocin versus oxytocin in preventing the postpartum hemorrhage among women undergoing cesarean section with general anesthesia in Iran.

Materials and methods

This study was approved by the Ethics Committee of Infertility and Reproductive Health Research Center (IRHRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran (SBMU.RAM.REC.1390.15). The present study was performed as a parallel double-blind randomized controlled clinical trial with a 1:1 allocation ratio. This study was performed in the delivery suite of two university-based obstetrics units: Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, and Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences – Yazd, Iran. Using Altman's Nomogram for two equal sized groups and based on a power of 80% and standardized difference of 0.4, the calculated sample size was at least 200 participants in both groups; therefore, 230 consecutive pregnant women who were candidates for cesarean section were recruited from April 2012 to September 2013 and an written informed consent was obtained from all patients. Finally, 220 women met our inclusion criteria and participated in the study. The flowchart of patient participation is presented in Figure 1. The women were randomly assigned to receive either a single dose of 100 μg IV carbetocin or a standard 30 international units (IU) IV infusion of oxytocin during 2 h immediately after placental delivery using block randomization. In each hospital, 55 women received oxytocin and 55 received carbetocin. The women and practitioners were not aware of the type of intervention. Selection and randomization of the patients were performed by a coordinating nurse, using a series of sequentially numbered sealed envelopes; therefore, the sequence of allocation was hidden. Then the outcomes, including the need for additional uterotonic agents, were compared between two groups.

The inclusion criteria were the presence of at least one risk factor for postpartum hemorrhage among patients who could not give birth and then underwent emergency cesarean delivery (prolonged third stage of labor, mediolateral episiotomy, previous postpartum hemorrhage, arrest of descent, soft-tissue lacerations, augmented labor, forceps or vacuum delivery, Asian or Hispanic ethnicity, midline episiotomy, and nulliparity), and lack of hypersensitivity to oxytocin and carbetocin. The excluding criteria were patient's refusal to cooperate, major therapeutic side effects, history of cardiac and renal diseases, preeclampsia, and twin pregnancy.

Demographic data such as maternal age, fetal sex, gravid, parity, abortion and pregnancy outcomes, as well as the cause of cesarean section were recorded. The outcome variables included the need for additional uterotonic drugs, drug side effects (headache, dizziness, tremor, nausea, vomiting, and urinary retention), the need for blood transfusion, hemoglobin change (compared between baseline and 24 h after labor), bleeding volume (total amount of gauze count (CC), aspirator volume (ml), used pads count (CC)), times of uterine massages, uterine height, as well as

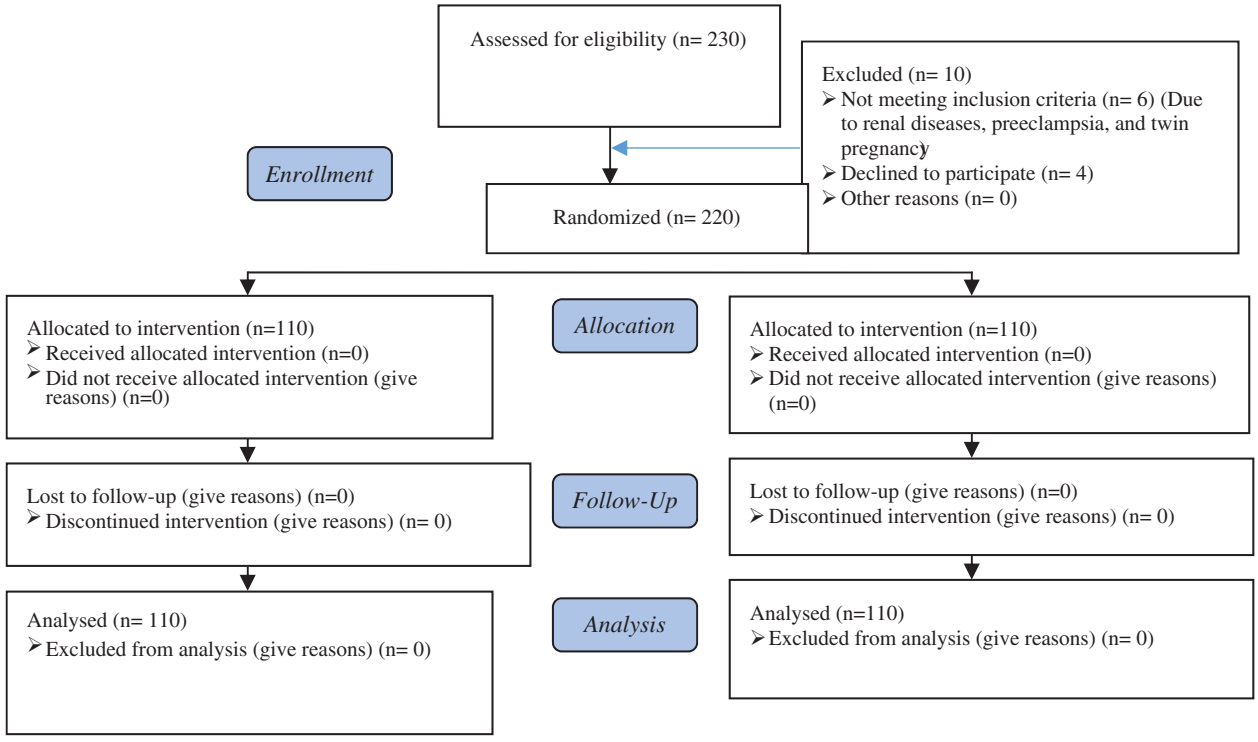

Figure 1. Flowchart of eligible patients.

hemodynamic indices such as blood pressure, pulse rate, and respiratory rate. All patients were checked for any complaints or side effects of Carbetocin and oxytocin. Drugs side effects were recorded in a questionnaire during 3 h after injection.

This study was approved by the Ethics Committee of Infertility and Reproductive Health Research Center (IRHRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran (SBMU.RAM.REC.1390.15).

SPSS software version 21 (SPSS Inc, Chicago, IL) was employed to analyze data. Descriptive statistics, Chi-square, and independent-sample *T* test were used to compare two groups. *p* values less than .05 were considered statistically significant.

Results

Of 230 eligible women, 220 participated in the study. There were no losses after randomization since the intervention and follow up was done during the admission period. The demographic data of the patients including age, previous obstetrics history and current pregnancy information are shown in Table 1.

The mean age, gravid, parity, live child count, abortion count, dead child count, gestational age, and birth weight were similar between the two groups ($p > .05$). Also there were no differences with regard to the frequency of premature rupture of membranes (PROM), meconium, oxytocin induction, placenta previa, leiomyoma, and fetal distress among the two groups of patients ($p > .05$).

Table 1. Demographic data of both the groups of patients.

	Oxytocin ($n = 110$)	Carbatocin ($n = 110$)	p^a value
Age (years)	27.69 ± 5.7	26.93 ± 5.4	.643
Gravid	1.9 ± 1.2	1.7 ± 0.9	.980
Parity	1.6 ± 0.8	1.4 ± 0.7	.870
Abortion	1.5 ± 1.1	1.06 ± 0.7	.786
Gestational age (weeks)	38.43 ± 2.09	38.85 ± 1.09	.621
Birth weight (g)	3245.18 ± 582	3297.73 ± 452	.708
Patients with myoma	1.99 ± 0.095	1.99 ± 0.095	.744
Patients with PROM	1.98 ± 0.134	1.96 ± 0.18	.780
Patients with meconium	1.91 ± 0.28	1.95 ± 0.22	.864
Patients with placenta previa	1.99 + 0.095	2.0 ± 0.0	.857
Patients with fetal distress	1.92 + 0.27	1.97 ± 0.16	.866

Data are presented as mean ± SD.
[a]Independent *T*-test
Abbreviations: PROM: premature rupture of membranes.

As shown in Table 2, the mean hemoglobin change, bleeding volume, and massage times were significantly higher in the oxytocin group compared with the carbetocin group ($p < .05$). Also the mean uterine height (in different measurements) and the pulse rate were significantly higher in the oxytocin group compared with the carbetocin group ($p < .05$); but the blood pressure and the respiratory rate were comparable between the two groups ($p > .05$) (Table 2). The frequency of additional uterotonic drugs use was 36.4% in the oxytocin group versus 10% in the carbetocin group, which indicated a significantly higher usage in the oxytocin group. There was not any need for blood

Table 2. Comparison of the hemodynamic changes and additional uterotonic agents between the two groups of patients after the cesarean section.

	Oxytocin ($n = 110$)	Carbetocin ($n = 110$)	p[a] value[b]
Hgb drop changes (mg/dl)	2.05 ± 1.2	1.1 ± 1.01	.010
Bleeding volume (mg/dl)	552.64 ± 156	430.68 ± 118	.003
Additional uterotonic drug (mg)	2.36 ± 0.4	1.1 ± 0.3	.033
Uterine height in 2 h (cm)	19.18 ± 1.6	18.42 ± 1.3	.000
Uterine height in 4 h (cm)	18.28 ± 1.2	17.4 ± 1.1	.000
Uterine height 24 h (cm)	17.14 ± 1.1	16.4 ± 1.08	.00
Massage times (seconds)	4.26 ± 0.8	3.7 ± 0.6	.003
Pulse rate (no.)	90.16 ± 6.6	87.38 ± 5.2	.031
Respiratory rate (no./min)	17.34 ± 1.3	17.82 ± 1.8	.033
Systolic blood pressure (mmHg)	108.77 ± 7.9	108.82 ± 8.8	.450

[a]*T* test was used.
[b]A probability value of less than .05 was considered significant.

Table 3. Comparison of the side effects between the two groups of patients after cesarean section.

	Oxytocin ($n = 110$)	Carbetocin ($n = 110$)	p[b] value
Vomiting (%)[a]	7.2	6.3	.550
Headache (%)[a]	11.9	1.8	.003
Nausea (%)[a]	17.2	15.4	.710
Tremor (%)[a]	12.7	2.7	.005
Dizziness (%)[a]	7.3	0.9	.007
Pruritus (%)[a]	0	27	.000

[a]Data are presented as %.
[b]*T* test was used.

transfusion in both groups. The side effects of oxytocin and carbetocin are presented in Table 3. Headache (11.9 versus 1.8%), dizziness (7.3 versus 0.9%), and tremor (12.7 versus 2.7%) were more common among patients in the oxytocin group ($p < .05$); but nausea and vomiting were not different across groups ($p > .05$). No cases of urinary retention were observed in both groups. Twenty-seven percent in the carbetocin group and none of patients in the oxytocin group had pruritus ($p < .05$).

Discussion

Although the maternal mortality has decreased in recent years, but PPH is still considered as a major contributor to maternal mortality and morbidity worldwide. Significantly, active management of the third stage plays an important role in the prevention of PPH and only uterotonic agents can reduce the risk by 60% [17]. Although the oxytocin is the first line of treatment, but there has not been any gold standard and professional agreement for selecting one drug [18]. Intrauterine pressure including the frequency, amplitude, and duration of contractions is significantly higher with low-dose carbetocin in comparison with high-dose oxytocin and the uterotonic effects of carbetocin last for 3 h [19]. Carbetocin, a long-acting oxytocin agonist, appears to be a promising agent for the prevention of PPH and can be useful instead of other medications [6]. In the present study, we found that the need for uterotonic drugs was significantly higher in the oxytocin group (p value $<.05$).

Blood pressure changes are an important factor in uterotonic administration after delivery. The previous studies have established that there is not a significant difference considering the hemodynamic changes between carbetocin and oxytocin and it is a safe medication [20].

In patients with severe preeclampsia, there is an increased risk of postpartum hemorrhage, but treatment of the PPH in preeclampsia and other chronic hypertension disorders is troublesome. This is due to hemodynamic changes and when there is a need for more uterotonic agents the administration of the second-line treatments such as methylergonovine is contraindicated [21]. The present study indicated that the blood pressure did not have significant changes after the carbetocin administration, so in these conditions, carbetocin might be considered as an appropriate alternative to oxytocin for the prevention of postpartum hemorrhage.

It has been reported that the administration of carbetocin in doses of 20–100 Mg in cesarean sections under spinal anesthesia is associated with high incidence of hypotension [22]. Since in our study, there were no significant differences of blood pressure between the two groups of patients, it seems that this hypotension is due to the anesthetic complications more than the side effects of carbetocin.

The mean hemoglobin change, bleeding volume, and massage times were significantly higher in the oxytocin group compared with the carbetocin group. These findings suggest the better efficacy of carbetocin in the management of postpartum hemorrhage compared with oxytocin.

Data from previous clinical randomized studies indicate that carbetocin as a uterotonic agent is a safe medication among patients with severe blood loss and hemorrhagic shocks after cesarean section under general anesthesia [22–24].

It has also been reported that carbetocin has fewer adverse effects versus other alternative uterotonic agents [25]. In the present study, the frequency of nausea and vomiting was not different between the two groups. Also no cases of urinary retention and blood transfusion were observed in both groups.

Attilakos et al. [6] showed that significantly higher number of women require additional oxytocics in the oxytocin group compared with the carbetocin group, which is in agreement with our results. The findings of the current study are also consistent with another

study which suggested that 100 μg of intravenous carbetocin is more effective than oxytocin in preventing the PPH among women undergoing caesarean deliveries [7].

A double-blind randomized controlled trial has found significant differences in the number of women requiring additional uterotonic medications [26]. Overall, uterotonic intervention was clinically observed in 44.6% who received carbetocin compared with 63.6% who were given an IV oxytocin infusion. In the present study, these amounts were 10% versus 36.4% in carbetocin and oxytocin groups, respectively. They also found no differences in hemodynamics and hemoglobin changes between the two groups [26]. In contrast to their findings, we found a significant difference in hemoglobin levels.

Higgins et al. [27] suggested that no clinically significant benefit is associated with the use of carbetocin instead of oxytocin. However, oxytocin imposes a higher cost for the treatment [26]. Peters [28] evaluated the therapeutic outcomes of carbetocin treatment and concluded that carbetocin is probably as effective as oxytocin in the prophylactic management of PPH with a similar safety profile to oxytocin. Our results indicate that carbetocin is not only as potent as oxytocin but even more rewarding. Similar to our findings, a randomized controlled clinical trial by Borruto et al. among 104 women demonstrated that carbetocin can be delivered through IV injection and results are equivalent to those of oxytocin on the maintenance of uterine tonicity and the limitation of blood losses, in the postoperative period after delivery by cesarean section [29].

Also similar to our findings, a review study has indicated that carbetocin significantly reduces the need for additional uterotonic agents or uterine massage to prevent excessive bleeding compared with placebo or oxytocin. As a point, they reported that the risk of headache and nausea were similar in women who received carbetocin or oxytocin [30], but in our study, the headache was more common in the oxytocin group.

Conclusion

According to our findings in current randomized clinical trial, it may be concluded that carbetocin is a good alternative modality to conventional uterotonic agents such as oxytocin, for the prevention of postpartum hemorrhage after cesarean sections performed under general anesthesia. Further studies are needed to analyze the cost-effectiveness of carbetocin as an uterotonic agent.

Disclosure statement

The authors have no conflict of interest with the subject matter of the present study.

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