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Original Article

Carbetocin Versus Oxytocin For Prevention Of Atonic Post-Partum Hemorrhage In High-Risk Patients In A Tertiary Care Center: A Pilot Study

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Abstract:

Background: Primary postpartum hemorrhage (PPH) is a leading cause of maternal mortality, with a global prevalence of approximately 6%. Uterine atony is the commonest cause of PPH which may occur even without identifiable risk factors. Therefore, WHO recommends universal use of ecbolic drugs in the third stage of labor. Carbetocin, a synthetic heat-stable analog to the standard drug Oxytocin can be used. Whether Carbetocin is more effective is still controversial. In this pilot study, we compared the effectiveness and safety of Carbetocin to Oxytocin in preventing PPH in high-risk women during Cesarean section (CS).

Methodology: 80 participants were randomized to receive an intravenous injection of either 10 IU of Oxytocin or 100 mcg of Carbetocin in the third stage of labor.

Results: Both groups were comparable as regards age, gestational age, pre-operative Hb level, Body Mass Index, parity, number of CS, the presence of risk factors for PPH, and whether in labor or not. There were no differences in the amount of blood loss, the need for extra ecbolic dose, the need for surgical intervention, the need for blood transfusion, or intensive care unit admission. However, Oxytocin arm showed significantly less cost.

Conclusion: Oxytocin is significantly cheaper, which makes it preferable to use in a low-middle-income society, yet this must be tied to availability of optimum storage conditions that guarantee its effectiveness. Further randomized trials with bigger sample sizes and meta-analyses are recommended to test the applicability of our findings in other sites in the country.

Keywords: Post-partum hemorrhage; Carbetocin; Oxytocin; Atony

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Introduction:

Postpartum hemorrhage (PPH) is one of the obstetric emergencies that affects 1-10% of all deliveries globally and is considered one of the primary causes of maternal morbidity and mortality.(1) PPH can be defined as blood loss of more than 500 cc after vaginal delivery or more than 1000 cc after cesarean section (CS). Alternatively, it can be defined as any amount of blood loss that can lead to clinical and/or laboratory signs of shock or tissue hypoperfusion within 24 hours of birth in case of primary postpartum hemorrhage, or until six weeks after delivery in case of secondary postpartum hemorrhage.(2)

Uterine atony is the most common cause of PPH and is responsible for about 75% of cases.(3) Various risk factors have been linked to uterine atony.(4) Uterine overdistension due to multiple pregnancy, polyhydramnios, or fetal macrosomia; labor-related factors such as induction or Oxytocin augmentation of labor, prolonged labor, manual removal of placenta, and chorioamnionitis; and the use of uterine relaxants such as magnesium sulfate or halogenated anesthetic agents are some of these factors. Intrinsic variables such as past PPH, antepartum hemorrhage, uterine fibroids, obesity, diabetes mellitus, and age greater than 35 years are also considered. Despite the above-mentioned risk factors, still, no parturient is immune to PPH.(4) Therefore, The World Health Organization (WHO) currently recommends a specific approach to managing the third stage of labor in order to prevent PPH. The most important part of this approach is the universal use of prophylactic uterotonic medicines, which have been shown to reduce the risk of PPH by about 50%. (5)

The standard medication for preventing PPH is Oxytocin, but its effectiveness may be compromised in many low- and middle-income countries due to issues with transportation, storage, and quality control.(5) Other common uterotonics used in this setting include intramuscular ergometrine, and vaginal misoprostol.(6) In recent years, Carbetocin – an Oxytocin receptor agonist- has increasingly been used for the prevention of PPH with demonstrated prompt onset of action (within 1-2 minutes) and a prolonged duration of action. Its safety characteristics resemble those of Oxytocin,(7,8) Furthermore, it demonstrates superior thermal stability compared to Oxytocin.(9)

Previous studies have shown that there is a controversy between the effectiveness of carbetocin and Oxytocin in reducing the need for additional uterotonic drugs and blood transfusions. However, there is limited evidence comparing the two drugs specifically in high-risk women undergoing Cesarean sections. Therefore, this pilot study aimed to provide more insight into the effectiveness and safety of carbetocin compared to Oxytocin in preventing PPH in high-risk women delivered by CS with identifiable risk factors for uterine atony.

Methods:

I. Study setting:

The study was conducted at the Obstetrics and Gynecology Department, Sohag University Hospital, a tertiary health care center in Sohag City.

II. Study Design:

This is a pilot study that followed a two-arm parallel, double-blinded design with random allocation of participants into each arm (study or control). We recruited women delivering at Sohag University Hospital which is considered a tertiary care center in Sohag city, Eligible participants were pregnant women with identifiable one or more risk factor for PPH.

A total of 80 eligible parturient participants with a gestational age of ≥ 34 weeks, and who were candidates for cesarean delivery, at the Obstetrics and Gynecology Department, Sohag University Hospital were recruited. The study was conducted in the interval between July 1st 2022- July 31st 2023.

III. Inclusion Criteria for the Study group:

Patients at risk for PPH who were undergoing CS either elective or during labor at a gestational age of ≥ 34 weeks. Risk factors included one or more of the following: History of PPH, delivery of a macrocosmic baby (> 4000 g), multiple gestation, Polyhydramnios, grand multiparity, interstitial or submucous uterine fibroid (Single larger than 4 cm or Multiple myomata with collective diameter > 4 cm), chorioamnionitis.

IV. Exclusion Criteria:
Patients without a high risk for post-partum hemorrhage, patients with coagulation defects, and patients with premature pregnancies <34 weeks were excluded from the study.

V. Patient recruitment and randomization:
All patients fulfilling eligibility criteria were approached by the treating physician who explained the nature of the study and were counseled about potential risks and benefits, the risk of intraoperative hemorrhage and PPH, the need for blood product transfusion and the possibility of cesarean hysterectomy if needed to control severe bleeding. After proper counseling, written informed consent was signed by each patient. Patients were allocated randomly through a computer-generated random list into two groups: A and B.
Patients in (Group A) received the standard dose of 10 IU Oxytocin in one-milliliter ampoule (Syntocinon: MARCYRL Pharma, Egypt) by iv infusion drip after delivery of the fetus, while patients in (Group B) received carbetocin 100 mcg in one-milliliter ampoule (Bleedaceas, IBSA Egypt) by direct IV injection after delivery of the fetus.
The identifiable markings of the two studied drug ampules were masked by white adhesive tape. All ampules were marked by a letter of A or B before the start of the study. Both the patient and the attending physicians were blinded to the drug being used.

VI. Trial procedures:
A) Patient assessment:
Patients were subjected to complete history taking including personal history including age, obstetric history including parity and mode of previous deliveries, history of chronic diseases, and medication. Patients underwent standard general examination including measurement of weight and height which were used to calculate the body mass index (BMI) for each patient. Abdominal and local clinical examination were performed.

B) Blood loss estimation:
Estimation of postpartum hemorrhage was done using the towel weighing method. The circulating nurse weighed the surgical towels and swabs before surgery and weighed them again after surgery when soaked with blood. The difference between preoperative and postoperative weight was estimated to almost equal the volume of lost blood based on 1 gm of blood equaling 1 ml of blood [10], The scrubbed nurse was tasked with soaking up all blood in the surgical area using the same surgical sponges and swabs, with no suction being used unless necessary, in which case, the blood accumulated in the suction container was added to the blood in the absorbent material. Attention was given to collecting all or almost all the amniotic fluid with a different suction device. In addition, the placenta was not included in the calculations of blood loss. The circulating nurse weighed the material and recorded the relevant data.

C) Medical and/or surgical intervention:
During CS following the delivery of the fetus, after the initial dose of studied drugs was given as described above, the operational surgeon assessed the patient regarding uterine tone and soaking of the bedding and towels. If the uterus was lax or significant bleeding was observed, patients were given extra doses of Oxytocin, 10 IU each up to 30 IU. If there was no response, surgical intervention was done as needed, e.g. compression sutures as B-lynch sutures or uterine artery ligation.
Patients were observed for 24 hours for assessment of any bleeding and there was no incidence of primary PPH after the end of CS.

VII. Study Outcomes:
A) The primary outcome was to determine the amount of blood loss in ml intraoperative and during the first 24 hours postpartum.
B) Secondary outcomes included 1-whether the patient needed extra ecbolic dose or not, 2- the number of extra doses if any, 3-surgical intervention done if any (compression sutures as B-lynch sutures, uterine artery ligation), 3- the need for blood transfusion, 4- number of blood transfusion units given to the patient, and 5- whether the patient was admitted to ICU postoperatively.

VIII. Statistical analysis:
Statistical analysis was performed using Statistical Package for Social Science (IBM SPSS) version 24 (SPPS Version 24). The data were tested by the Shapiro-Wilk test for normality of distribution.

Student-t test or Mann-Whitney test were used for comparing continuous variables between the two groups according to whether the variable results were normally or abnormally distributed respectively. The Chi-square test was used for comparing categorical variables.

IX. Ethical Consideration:

The Trial protocol was approved by the Medical Research Ethics Committee, Faculty of Medicine-Sohag University (Soh-Med-22-07-02) and was registered with Clinical Trials.gov Identifiers: (NCT05479357).

Results:

I. Demographic Data of the Studied Population, This study was conducted on 80 women divided into two groups; A and B which were comparable to each other as regards: age, gestational age in Days, pre-operative Hb level, Body Mass Index, parity, number of CS, and whether the participants were in labor or not as shown in Table 1.

Table 1: Comparison between demographic characteristics of the 2 studied groups.

Variable	Group A (N=40)	Group B (N=40)	P value
Age (Years) [Mean±SD]	30.78±5.664	30.53±6.247	0.852*
GA (days) [Mean±SD]‡ Approximate GA (weeks+days)	249.17±16.65 35w+4d ± 2w+2d	250.67±18.33 35w+6d ± 2w+4d	0.703*
Pre-operative Hb (gm/dl) [Mean±SD]	11.43±1.27	11.46±1.30	0.919*
BMI Median (IQR)	33.25 (28.6 - 37.8)	32.4 (27.30 - 38.25)	0.912**
Previous CS N (%)	28 (70.0%)	32 (80%)	0.302†
Number of previous CS Median (IQR)	1 (0.0-4.0)	2.0 (1.0-3.0)	0.961†
In labor N (%)	32 (80%)	31 (77.5%)	0.785†

Group A: The drug used was Oxytocin,
Group B: Drug used was Carbetocin,
N: number of cases were included,
IQR: interquartile range,
CS: Cesarean section, **BMI:** body mass index,
Hb: Hemoglobin level, **GA:** Gestational age.
*Student-t test, **Mann-Whitney test, †Chi-square test, ‡ The analysis was done using GA in days

II. Risk factors for PPH of the studied population:
As illustrated in Table 2, the most frequent risk factor was multi-fetal pregnancy affecting 15 cases in Group A and 17 cases in Group B. Multi-fetal gestation and other risk factors such as grand Multiparity, polyhydramnios, chorio-amnionitis, macrosomia and history of PPH also were comparable in the two groups. A combination of more than one risk factor was present in only one case in each group.

Table 2: Comparison between risk factors for PPH of the 2 studied groups.

Variable	Group A (N=40) N (%)	Group B (N=40) N (%)	P value
Multi-fetal pregnancy	15 (37.5%)	17 (42.5%)	0.333*
Grand Multiparity	10 (25%)	12 (30%)	
Polyhydramnios	8 (20%)	3 (7.5%)	
Chorioamnionitis	5 (12.5%)	2 (5%)	
Macrosomia	1 (2.5%)	3 (7.5%)	
History of PPH	0 (0%)	2 (5%)	
Multi-factorial	1 (2.5%)	1 (2.5%)	

Group A: The drug used was Oxytocin,
Group B: The drug used was Carbetocin,
N: number of cases were included, PPH: post-partum hemorrhage.
*Chi-square test.

III. Comparison of the outcomes between the two groups:

There was no significant difference in the amount of estimated blood loss between the two groups. Median blood loss (interquartile range (IQR)) was 348.5 ml (285 - 474.5) versus 368. ml (298.5 – 594), *P*=0.222 in Group A versus Group B respectively. Secondary outcomes such as the need for blood transfusion, surgical intervention, need for ICU admission, and need for extra-ecbolics were all comparable among the 2 groups. However, the total cost of ecbolic drugs given to each patient including additional ecbolic doses calculated in Egyptian pounds was significantly higher in Group B compared to Group A (Table 3).

Table 3: comparison of the study outcomes between study groups

Variable	Group A	Group B	P Value
Blood Loss volume Median (IQR)	348.5 ml (285 - 474.5)	368. ml (298.5 – 594)	0.222*
Need for Blood transfusion N (%)	1 (2.5%)	1 (2.5%)	1**
Surgical intervention N (%)	2 (5%)	1 (2.5%)	0.556**
ICU admission N (%)	0 (0%)	1 (2.5%)	0.314**
Needed extra ecbolic N (%)	10 (25%)	8 (20%)	0.592**
Extra Oxytocin units Median (IQR)	10.0 (10-30 IU)	27.5 (10-30IU)	0.326*
Total cost in EGP Median (IQR)	6.2 (6.2-10.7)	75 (75.0 -75.0)	<0.0001*

Group A: The drug used was Oxytocin,
Group B: The drug used was Carbetocin,
N: number of cases were included,
IQR: interquartile range, **EGP:** Egyptian pounds.
-Surgical intervention: compression sutures as B-lynch sutures.
-Extra-ecbolic: Oxytocin up to 30 IU.
*Mann-Whitney test, **Chi-square test.

Discussion:

Postpartum hemorrhage (PPH) is a major cause of maternal deaths, particularly in developing nations, with uterine atony being the most prevalent underlying cause.[11] The preventive use of uterotonics, such as Oxytocin, has proven to be effective in reducing PPH. Oxytocin, the preferred drug for preventing PPH, has a short half-life and necessitates continuous infusion or repeated injections. Carbetocin, a newer version of Oxytocin, has a longer half-life and is more resistant to heat. [12]

The current study compares the effectiveness of carbetocin versus Oxytocin in managing blood loss and preventing PPH in high-risk cases undergoing CS. We assessed parameters like the amount of intraoperative blood loss, uterine tone, the need for additional uterotonic agents, the need for blood transfusion, the need for surgical intervention, and the cost-effectiveness of using both drugs.

We found no significant difference in the primary outcome of blood loss between the two groups. Additionally, there were no significant differences in most of the secondary outcomes such as the need for blood transfusion, surgical intervention, the need for extra ecbolic, and the need for ICU admission.

Our study goes in line with the work done by Ghosh and colleagues, [13] who found no difference in the efficacy of both carbetocin and Oxytocin in preventing PPH with the analysis taking into account both biological risk factors for PPH (such as macrosomia, parity 3 or more, and history of PPH) and pharmacological risk factors (such as induction or augmentation). That was a secondary analysis of a multi-center randomized clinical trial, the CHAMPION which included 29,538 patients. However, their study included only patients undergoing vaginal delivery.

Similar findings were also reported by Sudjai and colleagues[14] in a population of 120 pregnant women at high risk for PPH undergoing CS. However, they could detect significantly less usage of additional uterotonic drugs in the carbetocin group compared to the Oxytocin group which is contrary to our results. Although statistically insignificant, more units of extra Oxytocin were used in the carbetocin group compared to the Oxytocin group.

On the other hand, a meta-analysis that included a total of 46 trials studying the efficacy of various drugs in preventing postpartum hemorrhage during cesarean delivery concluded that carbetocin was potentially better than other ecbolics including Oxytocin in minimizing blood loss.[15] However, although statistically significant, the estimated difference in blood loss (54.83 mL; 95% confidence interval, 26.48–143.78) between the two drug study groups was considered of low clinical importance.

Additionally, in a retrospective study of 1,796 women, the rate of PPH was lower with carbetocin compared to Oxytocin, but this difference was not statistically significant according to the multivariate analysis, and there was no difference in the need for usage of extra ecbolics.[16]

Altogether, available studies show no marked superiority of carbetocin over Oxytocin that can be translated into clinically meaningful differences in PPH occurrence.

In low and middle income countries, the effectiveness of Oxytocin may be compromised due to issues with transportation, storage, and quality control.[5] However, this should be balanced with the high cost of carbetocin compared to Oxytocin. In the current study, we show that using Oxytocin was more cost-effective with no compromise in the reduction of the amount of blood loss. In situations where good storage conditions can be adequately secured, Oxytocin might be a better and cheaper choice to produce effective prevention of PPH.

Our study was strengthened by using a randomized double-blinded design which limits biases of the interpreter and the patient. Also, all drugs were of the same patch to ensure that there were no interpatch differences and kept in the same conditions. We also provided a cost-effectiveness analysis suitable for our conditions and can be applied by other Egyptian centers.

This pilot study had a relatively limited sample size of eighty participants, which may limit the generalizability of the findings. Also, the study was carried out exclusively at a single maternity hospital, potentially confining the external validity of the outcomes to distinct environments or populations. The work exclusively concentrated on cesarean section, omitting other modes of delivery, like

vaginal deliveries, thereby potentially restricting the relevance of our findings to a broader population. Long-term follow-up data on outcomes, such as maternal morbidity or mortality were not provided, thus preventing a more comprehensive evaluation of carbetocin effectiveness in preventing PPH. The study did not compare carbetocin with other commonly used interventions for PPH prevention, such as misoprostol or tranexamic acid, thus limiting a more comprehensive understanding of the relative effectiveness of different interventions.

In conclusion, there was no difference between Oxytocin and Carbetocin in terms of patients' outcomes. Oxytocin is more cost-effective, which makes it a much preferable option for the prevention of PPH in a low middle income society, yet this has to be tied to availability of optimum storage conditions that guarantees the effectiveness of the drug. Our findings are limited by the pilot nature of the study and the limited sample size and bigger sample size randomized trials in similar settings and meta-analyses are recommended to test the applicability of our findings in other sites in the country.

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