

Carbetocin versus Oxytocin for Prevention of Postpartum Hemorrhage in Twin Pregnancies Delivered by Cesarean Section: A Randomized Controlled Trial

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ABSTRACT

Background: Research from the literature indicates that the likelihood of postpartum hemorrhage (PPH) is one of the most harmful aspects to take into account when preparing for a twin delivery.

Objective: Our foremost objective was to compare the effectiveness and adverse effects of carbetocin with oxytocin in preventing postpartum hemorrhage (PPH) in twin pregnant women following elective cesarean section (CS).

Study design: In this randomized controlled study, 118 pregnant women with twin pregnancies who were admitted for an elective cesarean section in two equal groups, were given intravenous slow IV boluses of carbetocin (**group A**) and slow intravenous oxytocin boluses (10 IU) (**group B**). Following the delivery of the second fetus, all patients were given the study medications.

Results: The need for additional uterotonics was statistically higher in group B than in group A; 5 (24.3%) versus 15 (13.1%) with P-value 0.025. While the estimated blood loss was statistically insignificant between both groups (928.5 ± 146.4 ml in (group A) versus 941.2 ± 277.2 ml in (group B), with P-value 0.311. As such, incidence of PPH was statistically insignificantly different between study groups (p value 0.239).

Conclusion: The use of carbetocin at elective cesarean section for twin pregnancy is not superior to slow IV oxytocin bolus in reducing the operative blood loss or prevention of PPH but it may reduce the postoperative need for additional uterotonics, especially in IVF twin gestation.

Keywords: Twin pregnancy, Carbetocin, Oxytocin, Postpartum Hemorrhage, Cesarean Section.

INTRODUCTION

About 1-2 percent of pregnancies result in twin pregnancies. Due to the increasing age of mothers during their first pregnancies and the ongoing advancement of assisted reproductive technology (ART) techniques, its occurrence has been steadily increasing over the past few decades ⁽¹⁾.

Multiple maternal and fetal variables contribute to the poor outcome of twin pregnancies, making obstetric care up until birth extremely difficult. Research from the literature indicates that the likelihood of postpartum hemorrhage (PPH) is one of the most harmful aspects to take into account when preparing for a twin delivery⁽²⁾. One of the most crucial steps in preventing postpartum hemorrhage is the administration of a uterotonic medication as soon as the fetus is born ⁽³⁾.

The most widely used uterotonic medication for controlling, preventing, and treating postpartum bleeding is oxytocin. Regular oxytocin administration has been shown to be beneficial during the third stage of vaginal delivery and is presumed to be equally beneficial during cesarean delivery ⁽⁴⁾.

In lieu of a continuous oxytocin infusion, patients undergoing choice chemotherapy can receive a single intravenous bolus of carbetocin (Pabal), a long-acting synthetic analogue of oxytocin with agonist effect, to prevent PPH and reduce the need for additional uterotonic medications. Furthermore, the adverse impact profiles of carbetocin and oxytocin are similar; nevertheless, carbetocin is easier to administer and is therefore preferred over conventional oxytocin regimens for cesarean deliveries ⁽⁵⁾.

The purpose of this study was to evaluate the efficacy and adverse effects of carbetocin against oxytocin in the prevention of PPH in twin pregnant patients undergoing elective cesarean sections.

PATIENTS AND METHODS

The present study is a prospective randomized controlled study that was carried out on 118 healthy pregnant women with twin gestation, admitted at Kasr Alainy Obstetrics and Gynecology Hospital for elective cesarean section, in the period of time from February 2023 to August 2023.

Inclusion criteria

Healthy pregnant females with twin gestation, aging between 18-40 years, parity ≤ 3 (whether the previous deliveries were vaginal or CS), gestational age from 35 to 40 weeks, BMI ≤ 35 kg/m², indicated for elective cesarean section under effect of spinal anesthesia, participated in the research.

Exclusion criteria

While patients with placenta previa/accreta or placental abruption, patients with medical disorders (e.g., anemia, bleeding tendency, HTN, etc.), patients refusing participation, hypersensitivity to carbetocin or oxytocin, were taken out of the study.

Methodology in details:

This study is a randomized controlled study including healthy pregnant females with twin gestation, presenting for an elective CS at Kasr Alainy Obstetrics and Gynecology Hospital.

Sampling Method "randomization":

Systematic random sampling and women fulfilled the inclusion criteria were randomly assigned to either group. A computer-generated randomization worksheet (MedCalc © version) was used for the randomization process.

Sample size:

Using PASS program, setting alpha error at 5% and power at 80%, the result from previous studies that showed the prevalence of post partum hemorrhage following CS after use of carbetocin VS. oxytocin in twin gestation was 3.33 vs. 11.76%, respectively ⁽⁶⁾, sensitivity ranged from 70% to 90%, the needed sample size was determined to be including 118 healthy pregnant females that were equally divided in to two groups:

Group (A): Women with twin gestation undergoing elective cesarean section received carbetocin.

Group (B): Women with twin gestation undergoing elective cesarean section received oxytocin slow IV bolus injection.

INTERVENTIONS

All participants underwent the following:

Detailed history:

Full personal, present, past, family, surgical, medical, menstrual, obstetric history regarding LMP, number of previous cesarean section, previous pregnancy outcome and complications.

- **General examination:** Vital signs and BMI.
- **Abdominal examination:** including Leopold's maneuvers, fundal level, previous abdominal scars, fetal heart sounds and CTG if indicated.
- **Pelvic examination:** dilatation, effacement, presentation, status of fetal membranes, station and presence of cervical cerclage.
- **Ultrasound:** to determine fetal number, viability, presentation, placental location, liquor, gestational age and estimated fetal weight (EFW).
- **Routine Preoperative investigation:** RH, complete blood count (CBC), Coagulation profile, Kidney Function Tests (KFTs), Liver Function Tests (LFTs).
- **Anesthesia:** Spinal anesthesia was administered using a standardized approach. Prior to spinal anesthesia, patients underwent an intravenous 500 mL crystalloid bolus.

Intraoperative: A standardized surgical method was used to perform cesarean sections. Skin prep and urinary catheterization were carried out. Using a Pfannenstiel incision, the abdomen was opened in layers. The peritoneum covering the uterine isthmus and cervix was dissected downward, while the peritoneum covering the vesico-uterine pouch was already being cut horizontally. The procedure involved a lower uterine incision, fetal extraction, and delivery of the placenta.

-Group (A) (n= 59): received a bolus, slowly over 1 min, intravenous injection of 100-µg (1 ml) dose carbetocin (Pabal Ferring, West Drayton, UK).

-Group (B) (N=59): received a slow intravenous bolus of 10 IU oxytocin (Syntocinon; Novartis, Basel, Switzerland).

After the delivery of the second twin, every woman received their medication right away. Hemostasis was properly performed and the uterine incision was closed. The abdomen was layer-closed. The amount of blood in the suction set and the weight of the soaked towels (weight of wet towel - weight of dry towel) were used to quantify the intraoperative blood loss. The diagnosis of major intraoperative bleeding was blood loss of in excess of 1000 milliliters or the need for blood transfusion ⁽⁷⁾. From the moment of skin incision to the moment of skin closure, the operating time was computed.

Postoperative:

Following delivery, participants were monitored in the operating room and recovery area with the purpose of detecting uterine atony, postpartum bleeding, the need for further uterotonic medications, vital signs, repeated clinical examinations, and UOP measures. Each medication's side effects, including headache, shivers, nausea, and vomiting, were noted. Blood loss of $\geq 1,000$ ml after delivery is referred to as PPH ⁽⁸⁾.

-Additional uterotonics in the form of misoprostol and ergometrine were used with or without tranexemic acid as appropriate, based on the clinical circumstances.
-A full blood count (FBC) and measurements of hemoglobin and hematocrit were made 24 hours following delivery.

- The following formula was used for assessment in order to provide a more objective estimation of blood loss ⁽⁹⁾:

$$\text{EBL} = (\text{EBV} \times \text{Pre-op Hct} - \text{Post-op Hct}) / \text{Pre-op Hct}$$

Where: EBL (Estimated blood loss), EBV (estimated blood volume), Pre-op Hct (preoperative hematocrit), Post-op Hct (postoperative hematocrit),
Estimated blood volume = booking weight (Kg) $\times 85$

Ethical consideration:

The Ethics Committee of Cairo University's Faculty of Medicine gave its approval to the project. Following a straightforward description of the study's goals and potential benefits, along with an assurance that there would be no costs to the participants' health, all participants gave their informed consent. Subjects were allowed to leave the study at any stage and were not required to engage. The Helsinki Declaration was adhered to throughout the entire research project.

Statistical analysis

IBM SPSS (Statistical Package for the Social Sciences) v 23 for Windows (Chicago, USA) was used to code, calculate, and analyze the data. Numbers and percentages were used to display the qualitative data. Quantitative variables were shown as mean ± standard deviation (SD). To examine the relationship between categorical variables, the chi-square test was employed. In four-cell tables, if the expected cell count was less than five, the Fisher Exact Test was used in its place. The Mann-Whitney U test (z) was used to contrast two independent non-normally distributed continuous variables. The independent sample t-test was used to test the association between normally distributed continuous variables in two independent groups. Significant P-values were those less than 0.05.

RESULTS

This randomized controlled trial included 118 women with twin pregnancy undergoing elective cesarean delivery. These females were divided in two groups: **Group (A):** received carbetocin slow IV, while **Group (B):** received an intravenous slow bolus oxytocin 10 IU. **Table (1)** shows that there was significant difference between the 2 studied groups regarding gestational age and number of cesarian sections.

Table (1): Comparison between study groups based on base line characteristics (n=118)

	Carbetocin group (N=59)	Oxytocin group (N=59)	P-value
Age (years)	27.25±5.6	28.08±5.9	0.388
Parity	1.27±1.2	1.12±1.16	0.487
BMI (kg/m²)	31.72±5.4	31.42±4.1	0.624
Gestational age (weeks)	36.7±1.14	36.05±1.21	0.003
IVF pregnancy	15(25.4%)	18(30.5%)	0.538
Primary CS	34(57.6%)	47(79.7%)	0.037
Previous 1 CS	16(27.1%)	10(16.9%)	
Previous 2 CS	8(13.6%)	2(3.4%)	
Previous 3 CS	1(1.7%)	0(0%)	
Preoperative Hemoglobin (gm%)	10.43±0.92	10.5±0.76	0.351
Preoperative Hematocrite (%)	36.25±1.06	36.14±1.01	0.534

Table (2) shows that the **major intraoperative hemorrhage (≥ 1000 ml)** was slightly higher in oxytocin group than carbetocin group with no statistically significant difference between the two groups, while there were no significant differences between studied groups regarding **either the EBL** or the operative time.

Table (2): Comparison between groups based on operative data

	Carbetocin group (N=59)	Oxytocin group (N=59)	P value
Operative time (min.)	41.12±6.67	41.37±5.24	0.966
Estimated Blood Loss (EBL) (ml.)	928.563±146.4	941.2±277.2	0.146
EBL ≥ 1000 ml.	11(18.6%)	13(22%)	0.647

Table (3) shows that the use of **additional uterotonics** was statistically significantly higher in oxytocin than carbetocin group, on the other hand there were no significant differences between studied groups regarding **PPH, conservative management of PPH, BL, Transfusion, ICU admission, side effects and the mean hospital Stay time.**

There were no cases in the studied groups subjected to **hysterectomy, DIC or maternal mortality.**

Table (3): Comparison groups based on treatment outcomes

	Carbetocin group (N=59)	Oxytocin group (N=59)	P value
PPH	4(6.8%)	9(15.3%)	0.241
Postoperative HB	9.4±0.77	9.5±0.75	0.425
Postoperative HCT	35.1±1.1	35.1±1.12	0.931
Conservative treatment	1(1.7%)	4(6.8%)	0.364
Hysterectomy	0(0%)	0(0%)	1
DIC	0(0%)	0(0%)	1
Blood transfusion	4(6.8%)	6(10.2%)	0.743
Hospital stay	33.46±13.8	35.1±1.12	0.151
ICU admission	1(1.7%)	4(6.8%)	0.364
Maternal mortality	0(0%)	0(0%)	1
Side effects of drugs	2(3.4%)	4(6.8%)	0.679
Additional uterotonics	5(8.47%)	15(25.42%)	0.025

Table (4): Additional uterotonic use in oxytocin group was related to high parity, IVF twin pregnancy, higher gestational age, EBL ≥ 1000, blood transfusion, and PPH occurrence, while PPH was related to high parity, IVF twin pregnancy, EBL ≥ 1000 and blood transfusion.

Table (4): Correlation between PPH and additional uterotonic use in oxytocin group and patient characteristics

	Additional uterotonics (N=59)		PPH (N=59)	
	R *	P value	R *	P value
Age	- 0.042	0.754	- 0.046	0.754
Parity	- 0.297	0.022	- 0.371	0.022
BMI	0.11	0.405	-0.006	0.405
GA	0.267	0.041	0.218	0.041
Number of CS	- 0.04	0.743	- 0.202	0.743
IVF	0.628	0.001	0.640	0.001
Pre-HB	0.175	0.186	0.132	0.186
Pre-HCT	0.116	0.382	0.124	0.382
Operative time	0.115	0.384	0.206	0.384
EBL	0.624	0.001	0.648	0.001
EBL≥1000	0.910	0.001	0.798	0.001
Transfusion	0.447	0.001	0.637	0.001
Post-HB	-0.225	0.087	-0.242	0.087
Post-HCT	-0.211	0.109	-0.291	0.109
PPH	0.727	0.001	NA	NA

* R: Pearson correlation coefficient *NA: not applicable.

DISCUSSION

About 1-2 percent of pregnancies result in twin pregnancies. Due to the increasing age of mothers at their first pregnancies and the ongoing advancement of assisted reproductive technology (ART) treatments, its occurrence has been steadily increasing over the past few decades (10). The available research provides evidence that the potential of postpartum bleeding, also known as PPH, is one of the most harmful aspects to take into account when scheduling a twin delivery. Postpartum bleeding is thought to be the primary cause of maternal mortality globally, accounting for as much as 28% of cases, and it is more common in multiple pregnancies than in singletons (11).

Since intravenous oxytocin has a brief half- life (4–10 minutes), it may be advantageous for preserving the contractility of the uterus during the cesarean section operation and the first few hours after delivery, which is when the majority of primary bleeding happens (12).

According to recent research, a single carbetocin bolus could be a useful substitute for the IV oxytocin infusion that is frequently given to singleton CD patients to prevent PPH following cesarean delivery. Nevertheless, there are currently insufficient data to assess the effectiveness of carbetocin in avoiding PPH in twin pregnancies, which is a precursor for uterine atony (13).

FIGO reiterates its advice that oxytocin be used as the first line of defense against postpartum hemorrhage (PPH) in vaginal and cesarean births. Under circumstances where oxytocin is not accessible or its efficacy cannot be ensured, it is advised to utilize other

uterotonics such as carbetocin, ergometrine/methylergometrine, or misoprostol (14).

The administration of carbetocin as an initial-line uterotonic for prevention of cesarean birth or vaginal delivery with a single risk factor has been confirmed by the Society of Obstetricians and Gynecologists of Canada (SOGC) in an updated article (15).

Based on the limited available evidence, controversy, concerns regarding the cost-effectiveness and the limited availability of carbetocin in low resource settings, a standard recommendation may require further clinical trials.

This study compared the effects of intravenous slow bolus oxytocin against carbetocin in twin pregnancies treated with elective cesarean sections.

In the interest of objectivity, we estimated total losses of blood at the time of the cesarean surgery and immediately afterward, but as a primary outcome, we opted for a calculation-based estimate based on preoperative and postoperative packed cell volume. In resource-poor environments where blood tests are not frequently conducted, the calculated blood loss would have greater significance.

Our intraoperative data revealed that **major intraoperative hemorrhage (≥ 1000 ml)** was slightly higher in oxytocin group than carbetocin group (13 (22%) versus 11 (18.6%)), with no statistically significant difference between the two groups (p-value 0.647), while there were no significant differences between studied groups regarding **either the estimated blood loss** or the operative time (P values 0.146 and 0.966, respectively).

This contradicts the findings of **Esseissah et al.**, who found that the approximate loss of blood varied significantly amongst groups administered carbetocin (16). They compared carbetocin versus oxytocin and ergometrine in all cases (including singleton pregnancies) delivered by caesarian section.

After extensive deliberation, we selected two primary outcomes, both of which represented uterine atony. Since major obstetrical bleeding is the main reason of maternal mortality globally, it is the most relevant clinical outcome. In cases of uterine atony, however, medical professionals may step in and give an extra uterotonic medication (7). This action would be a significant result in and of itself.

Additional uterotonics in the form of misoprostol and ergometrine were used with or without tranexemic acid as appropriate, based on the clinical circumstances. This additional use was statistically higher in oxytocin than carbetocin group (15 (25.42 %) versus 5 (8.47 %) with p-value 0.025), which is consistent with **Kang et al.**, who found that the carbetocin group similarly required less uterotonics (18.4% vs. 24.4%, p = 0.03) (17).

Hsu et al.'s study, however, found no differences in the usage of additional uterotonic medicines or the requirement for blood transfusions (13).

On the other hand, there were no significant differences between studied groups regarding **PPH** (4 (6.8%) versus 9(15.3%) with p-value 0.241), or **blood transfusion** (4 (6.8%) versus 6 (10.2%) with p-value 0.743), in carbetocin vs. oxytocin groups respectively. PPH in the study population was managed as per routine steps. Most cases were managed conservatively by applying uterine massage, bimanual compression and additional uterotonic. Only 4 cases required bilateral uterine artery ligation. No cases of **re-exploration, application of compression sutures, peripartum hysterectomy or maternal mortality** were encountered.

We extended our study to correlate our outcomes with patient specific factors for more precise analysis. Additional uterotonic use in the oxytocin group was related to high parity, IVF twin pregnancy, higher gestational age, EBL \geq 1000, blood transfusion and PPH occurrence, **while** PPH occurrence in oxytocin group was statistically higher in cases of high parity, IVF twin pregnancy, EBL \geq 1000 and blood transfusion. So, consideration should be paid to the choice of the proper prophylactic uterotonic agent.

Carbetocin was statistically as tolerable as oxytocin as regards side-effects (2 (3.4%) versus 4 (6.8%) with p-value 0.679). Side effects in either group were generally mild, such as shivering, mild nausea and vomiting.

Postoperative hematological indices are accurate indicator of patient general condition and may be a reflection to postoperative and puerperal anemia, which has an impact on wound healing, patient recovery and breast feeding⁽¹²⁾. They were found not to be statistically different between study groups (p values 0.425 and 0.931 for postoperative hemoglobin and hematocrit respectively). However, **Sotillo et al.** concluded that the oxytocin group had a greater fall in the hemoglobin level (1.7 versus 1.2, p 0.02) and greater need for blood transfusion (9.3 versus 1.3%, p 0.03)⁽¹⁸⁾. They included obese patients, emergency CS as well as more IVF twin pregnancies than our study

Multiple clinical trials studied the use of carbetocin versus oxytocin for prevention of PPH in singleton pregnancies delivered by either vaginally or by the use of caesarian section. **However, only few studies evaluated such clinical comparison in twin gestation undergoing elective CS.**

The impact of carbetocin and oxytocin on isoflurane-induced uterine hypotonia in twin pregnancy patients having cesarean section was assessed by **Fahmy et al.** It seems that carbetocin reduced postpartum bleeding more effectively than oxytocin, requiring less uterotonic in the process⁽¹⁹⁾. This study differs with ours only in the statistical difference in EBL. This can be explained by the smaller sample size and effect of general anesthesia, which may affect the EBL, uterine atony and subsequent need for additional ecobolics.

In a different study, the effects of carbetocin against methergine and oxytocin in combination were compared to prevent PPH in high-risk vaginal births instances. When it came to minimizing postpartum loss of blood, it was discovered that carbetocin worked better than IM oxytocin in combination with 1 ml and 0.2 mg of IM methylergonovine maleate⁽²⁰⁾. The authors evaluated high risk cases subjected to vaginal deliveries and used combined oxytocin – methylergonovine treatment as a comparator. Their study showed similar conclusion as our study but with a statistically significant difference in postpartum hematological indices.

In a third trial, the prevention of postpartum bleeding in late premature twin pregnancies after cesarean surgery was examined in relation to carbetocin versus oxytocin. Compared to oxytocin, carbetocin required fewer additional uterotonic drugs (23.33 vs. 35.29%, P < 0.05)⁽²¹⁾. They came to the general conclusion that carbetocin is preferable to oxytocin. However, in contrast to our study, the oxytocin group had a higher mean amount of blood lost during cesarean delivery (685 \pm 350 vs. 782.8 \pm 370 ml, P > 0.05) and the carbetocin group had a lower incidence of primary PPH (>1000 ml) during cesarean delivery (3.33 vs. 11.76%, P < 0.05).

According to research by **Seow et al.**, infertile women with twin pregnancies awaiting elective cesarean section can maintain appropriate uterine tone and prevent postpartum bleeding with a single 100 mg intravenous bolus of carbetocin, which is equally safe and efficacious as an intravenous oxytocin infusion. As opposed to our findings, the carbetocin group's mean operating time was considerably less than that of the control group (P 0.001)⁽²²⁾. They recruited a fewer sample size and excluded previous caesarian delivery.

Strength points with our study is that we have formulated similar base-line patient criteria (as age, BMI, spinal anesthesia, gestational age, preoperative severe anemia etc.), to eliminate most statistical bias and confounding variables. We recruited large number of candidate patients. As such, it was a double-blind randomization study. Correlation of study primary endpoints to different baseline characteristics and secondary outcome variables gave better formulation for our recommendations.

One of the study's limitations was that it was carried out by various obstetricians, so the intervention might not have had the best level of technique standardization. The usefulness of carbetocin during cesarean delivery in twin gestations requires larger investigations or prospective trials. To determine whether this relatively new medication is cost-effective, more research of this kind is required. Future studies focused at lowering significant obstetric bleeding and hemorrhagic issues in twin pregnancies are crucial, even as the rates of cesarean sections continue to rise. Research from the past has demonstrated that an emergency cesarean section carries a higher risk of

serious obstetrical bleeding than an elective one. Future research should focus on non-elective deliveries as this research was restricted to women enduring elective cesarean sections.

CONCLUSION

In conclusion, our randomized controlled study revealed that the use of carbetocin at elective cesarean section for twin pregnancy is not superior to 10 IU slow IV oxytocin bolus in reducing the operative blood loss or prevention of PPH but it may reduce the postoperative need for additional uterotonic. In patients with high parity, IVF twin pregnancy, higher gestational age, EBL \geq 1000, blood transfusion, and PPH incidence, the necessity for extra uterotonic was especially clear.

The manuscript's authors declare that:

- 1) the work is not being considered by anybody else;
- 2) none of the material has been previously published; and
- 3) the manuscript has been read and approved by all writers.

- **Conflict of Interest:** The authors claim they don't have any competing interests.
- **Acknowledgment:** None.
- **Funding Source:** This study was self-funded.

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