

Carbetocin Versus Oxytocin And Ergometrine for Prevention of Postpartum Hemorrhage in Women With Twin Pregnancy Undergoing Elective Cesarean Delivery: A Randomized Controlled Trial

Original
Article

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ABSTRACT

Objective: To evaluate the effectiveness and safety of carbetocin compared with an intravenous infusion of oxytocin 10 IU plus an intramuscular injection of ergometrine 0.2 mg in decreasing blood loss during and after cesarean delivery for twin pregnancies.

Materials and Methods: This was a single-blind, randomized controlled study (NCT03578263). We randomly assigned 170 women who had twin pregnancies and were scheduled for elective or emergency cesarean birth under spinal anesthesia to receive a combination of a continuous intravenous infusion of 10 IU oxytocin in 500 mL 0.9 percent NaCl solution (125 mL/h) for 24 hours and I.M. Ergometrine 0.2mg, or an intravenous infusion of 100 micrograms carbetocin. The Blood loss at and 6 hours after cesarean birth was the primary outcome. We also shared if any more oxytocic medications were required, as well as any drug-related adverse effects.

Results: The total mean blood loss in the carbetocin group was not substantially different from the oxytocin plus ergometrine group (667.65 119.987 vs. 674.16 130.240 mL; $p = 0.741$). After using carbetocin and oxytocin with ergometrine, 8.2 percent and 10.6 percent of patients required further oxytocic treatment, respectively ($p = 0.599$). Side symptoms such as headache, nausea, and vomiting were substantially more common in the oxytocin plus ergometrine group than in the carbetocin group ($p = 0.004, 0.007, 0.009$).

Conclusion: Carbetocin is as effective as oxytocin with ergometrine in decreasing total blood loss during and after cesarean birth in women pregnant with twins, but it has fewer adverse effects.

Key Words: Carbetocin, ergometrine, oxytocin, postpartum hemorrhage, twins.

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INTRODUCTION

Despite advances in obstetrics treatment, postpartum hemorrhage (PPH) remains the leading explanation for maternal mortality, particularly in underdeveloped nations. Because uterine atony causes three-quarters of PPH, efforts are conducted within the last 20 years to seek out effective uterotonic medicines to regulate the third stage of labor.^[1]

PPH was considered to be unpredictable, thus the most objective was to supply prophylaxis for all parturient women who had a risk factor for PPH, also on have specialized patients have a cesarean birth (CB) for twin gestation.^[2]

CB is becoming more common, and as a result, the quantity of blood lost during CB (1000 mL) is quite twice that lost after childbirth (500 mL). In many parts of the planet, the CB rate is as high as 25-30%.^[3]

Obesity, anemia, white ethnicity, preeclampsia, anemia, polyhydramnios, and chorioamnionitis, also as a twin pregnancy, are all risk factors for uterine atony. Twin gestation has grown in recent decades as assisted reproduction technologies and ovarian stimulation techniques became more widely used for infertility treatment.^[4]

CB for twin pregnancy at 37 weeks or more has been linked to an increased risk of transfusion in several studies.^[5]

PPH is the most prevalent complication, accounting for around one-fifth of all cases and one-quarter of all maternal fatalities globally, increasing maternal morbidity and mortality despite the variety of methods available to reduce excessive hemorrhage after CB. It is estimated that 2% to 6 of all babies worldwide have primary PPH.^[6]

Interventions to stop post-partum hemorrhage, particularly in high-risk groups, must now be addressed on this research agenda.

In the third stage of labor, oxytocin is the preferred method for preventing uterine atony and bleeding after delivery. Nevertheless, due to temperature and weight, clean syringes and needles are needed, and direct intravenous infusion may result in nausea, vomiting, seizures, fluid overload, hypotension, pulmonary edema, and dysrhythmia.^[8]

Carbetocin, a man-made analog with a half-life 4–10 times that of oxytocin, is given as a slow single intravenous or intramuscular dosage of 100 g.^[9] In comparison to oxytocin, it's been linked to a big decrease within the incidence of PPH following cesarean birth, also as a lower requirement for further uterotonic medications after CD.^[10]

There is a scarcity of worldwide agreement on what the perfect uterotonic regime is. Furthermore, the shortage of consistency across worldwide standards for the first line uterotonic within the prevention of PPH adds to the uncertainty. However, there are presently no data to assess the efficiency of carbetocin in avoiding PPH in twin pregnancy, which may be a risk factor for uterine atony.

The purpose of this research is to assess the efficacy and safety of carbetocin vs an I.V. infusion of oxytocin 10 IU plus an I.M. Ergometrine 0.2mg in decreasing blood loss during and after twin cesarean birth.

PATIENTS AND METHODS

It was a single-blind, randomized clinical trial done at a tertiary university hospital (ClinicalTrials.gov: NCT03578263). The study was given the grant number (Aswu/273/7/18) by the ethical review board. Women who attended the outpatient obstetric clinic for prenatal care and who were pregnant with twins and planned for CB between August 1, 2018, and June 30, 2022, were included in the research. After giving informed permission, women who fulfilled the study's selection criteria were asked to participate.

This experiment was carried out and published in accordance with the CONSORT updated criteria for reporting parallel group randomized studies^[11], as well as ClinicalTrials.gov's amended recommendations for increasing the quality of randomized clinical trial reporting.

Eligible Participants

Women who were planned for elective or emergency cesarean section CB and had a twin pregnancy, with no known extra risk factors for postpartum hemorrhage, were included in the study. Exclusion criteria included

obesity, defined as a BMI >30 before pregnancy, as well as conditions that may predispose to uterine atony and postpartum hemorrhage, such as placenta previa, severe preeclampsia, polyhydramnios, uterine fibroids, prior history of uterine atony resulting in PPH, or bleeding diathesis. renal, vascular, and liver disorders. The necessity of using general anesthesia was also disregarded in the investigation.

A total of 220 patients were invited to participate; 50 were declined, 43 did not fulfil the inclusion requirements, and 7 refused. As a result, the research covered the remaining 170 patients. All participants had a thorough history, general, and obstetric checkup, their body weight and height were determined, and preoperative hemoglobin was collected for all of them, followed by an abdominal ultrasound examination. The study was described to all participants who met the qualifying requirements, including the benefits and probable side effects of the research medications. After receiving informed consent, individuals were randomly assigned to one of two groups: oxytocin with ergometrine (group1), or carbetocin (group 2).

Randomization

Patients were randomized to one of two groups, each with 170 patients, using a two-blocked randomization list that was coded (I or II) at a 1:1 ratio. The two parallel groups were made using a computer-generated randomization method. The designated groups will be kept secret within serially numbered, opaque envelopes that won't be opened until the hiring process is through. An impartial individual who will not be participating in this study will undertake patient allocation prior to the onset of spinal anesthesia. The experiment will be conducted in a single blinded environment; The drug kind will be kept a secret from the participants.

Intervention

Following the onset of spinal anesthesia and the birth of the baby, eligible individuals were randomly assigned to one of two groups.

The oxytocin + ergometrine group (group 1) received a 24-hour continuous intravenous infusion of 10 IU oxytocin in 500 mL 0.9 percent NaCl solution (125 mL/h) and 0.2 mg intramuscular ergometrine.

After the infant was born, the carbetocin (group 2) was given 100 g of carbetocin diluted in 10 ml normal saline and delivered slowly (over 30-60 seconds) intravenously by an anesthetist.

After the placenta was delivered, the attending obstetrician assessed the uterine tone on a 5-point Likert

scale (0 floppy, 4 rock hard), and then every 5 minutes until abdominal closure started.

If the uterine tone was insufficient or the caesarean section became hemorrhagic, further oxytocic treatment was administered.

If the uterine tone was low, further oxytocic treatment was administered.

Blood loss estimation

Intraoperative blood loss was calculated using the volume of the suction bottle's contents following the delivery of the infant and placenta, as well as the weight (in grammes) difference between the dry and damp operation sheets and towels (1 gramme = 1 ml). The difference in weight (in grammes) between the dry and soaked vaginal pads (1 gramme = 1 ml) was used to calculate post-operative blood loss by vaginal blood loss during the first 24 hours after surgery. The overall blood loss estimate was then determined by adding intraoperative and postoperative blood loss.

Study Outcome

The primary result was the estimate of blood loss during and after caesarean delivery when TA plus buccal misoprostol or intravenous oxytocin was administered.

The requirement for any further oxytocic medications, postoperative Hemoglobin concentration, the incidence of postpartum hemorrhage, operational time, and the incidence of side effects were all secondary outcome measures (fever, headache, nausea, vomiting, and diarrhea).

Sample size

Based on the primary outcome (blood loss in women following caesarean birth), the sample size was estimated, using the oxytocin-assisted mean blood loss value of 974 mL with a standard deviation of 285 mL^[10]. 100 people in each group will have > 85% power at 5% significance to detect such a difference, assuming that TA with buccal misoprostol is superior to oxytocin in lowering blood loss by 125mL (Epi-info: Centres for Disease Control and Prevention, Atlanta, GA, USA).

Statistical Analysis

Data was statistically described when appropriate using the mean, SD, or frequencies (number of occurrences) and percentages. Numerical differences across research groups were compared using independent two-tailed t tests. Data that were categorical were compared using the Chi square (X²) test. The exact test was used in its place when the expected frequency was less than 5. A *P value* of less

than 0.05 was used to determine statistical significance. All statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 22 for Microsoft Windows.

RESULTS

Our research began with 220 twin-pregnant women who visited our hospitals and clinics. 50 patients were ruled out, 43 patients failed to satisfy the inclusion criteria, and 7 patients refused to take part. As a result, the remaining 170 patients were divided into two groups, each with 85 patients. Group I: (after birth of the infant, got 10-unit oxytocin in 500 mL normal saline IV + 0.2 mL ergometrine IM) and Group II: (after delivery of the baby, received 100 g carbetocin IV).

There was no statistically significant difference between the two groups in terms of age, weight, height, body mass index (BMI), parity, gestational age, prior CS scar, kind of CS (elective or emergent), and whether or not they were pregnant using assisted reproductive technology (ART). (See Table 1)

There were no statistical difference between the two groups with respect to their operative time, intraoperative blood loss, preoperative hemoglobin, postoperative hemoglobin, preoperative systolic and diastolic blood pressure, no of postpartum hemorrhage, no of blood transfusion, need to additional uterotonics, and extra surgical intervention. $p = (0.638, 0.741, 0.758, 0.064, 0.691, 0.765, 0.773, 0.599, 0.501, \text{ and } 0.773)$ respectively. however, both postoperative systolic and diastolic blood pressure was significant increase in group I compared to group II. $p = (0.0001 \text{ and } 0.0001)$ as the mean postoperative systolic blood pressure for group I was (130.28 ± 6.29) versus (113.24 ± 7.41) for group II and the mean postoperative diastolic blood pressure was (87.47 ± 6.20) for group I versus (73.04 ± 6.20) for group II. (Table 2)

In addition, the incidence of headache was 21.2 percent (18 patients) in group I vs 5.9 percent (5 patients) in group II, indicating a substantial increase in complication in the form of headache, nausea, and vomiting. $p = (0.004)$, the incidence of nausea in group I was 17.6% (15 patients) vs 4.7 percent (4 patients) in group II, $p = (0.007)$, and the incidence of vomiting in group I was 12.9 percent (11 patients) versus 2.4 percent (2 patients). However, there was no significant difference between the two groups in terms of fever and diarrhoea ($p = 0.009$) (0.682 and 0.371). (Table3)

Table 1: base line characteristics of pregnant women in the two groups: -

Parameters	Group I (n = 85)	Group II (n = 85)	Significance
Age (year)	30.74 ± 3.46	30.85 ± 3.72	0.848
Weight (kg)	76.54 ± 5.991	76.84 ± 6.697	0.763
Height (cm)	163.15 ± 4.05	163.06 ± 4.04	0.880
BMI	28.76 ± 2.12	28.87 ± 2.29	0.753
Parity (median) (Minimum – maximum)	0 (0 – 4)	0 (0 – 4)	0.422
Gestational age (weeks)	37.12 ± 1.73	37.33 ± 1.69	0.420
Previous CS scar (%)	17 (20)	19 (22.4)	0.707
Type of CS (%)			
Elective cs	40 (47.1)	39 (45.9)	0.878
Emergent cs	45 (52.9)	46 (54.1)	
ART (%)			
Yes	47 (55.3)	43 (50.6)	0.539
No	38 (44.7)	42 (49.4)	

BMI (body mass index), CS (Cesarean Section), ART (assisted reproductive technique).

Variables are presented as mean and standard deviation, median (minimum – maximum) and number (percentage).

Table 2: preoperative, operative and postoperative outcome in the two groups:-

Variables	Group I (n = 85)	Group II (n = 85)	Significance
Operative time	64.16 ± 16.31	63.0 ± 15.93	0.638
Intraoperative blood loss	674.16 ± 130.240	667.65 ± 119.987	0.741
preoperative hemoglobin	10.53 ± 0.74	10.57 ± 0.75	0.758
Postoperative hemoglobin	9.56 ± 0.54	9.73 ± 0.63	0.064
Preoperative (SBP)	116.07 ± 6.44	116.47 ± 6.64	0.691
Postoperative (SBP)	130.28 ± 6.29	113.24 ± 7.41	0.0001*
Preoperative (DBP)	74.42 ± 6.46	74.72 ± 6.34	0.765
Postoperative (DBP)	87.47 ± 6.20	73.04 ± 7.74	0.0001*
Post-partum hemorrhage (%)	7 (8.2)	6 (7.1)	0.773
Need Blood Transfusion (%)	9 (10.6)	7 (8.2)	0.599
Additional uterotonics (%)	13 (15.3)	10 (11.8)	0.501
Extra surgical intervention (%)	7 (8.2)	6 (7.1)	0.773

SBP (systolic blood pressure), DBP (diastolic blood pressure), *Statistically Significant Difference

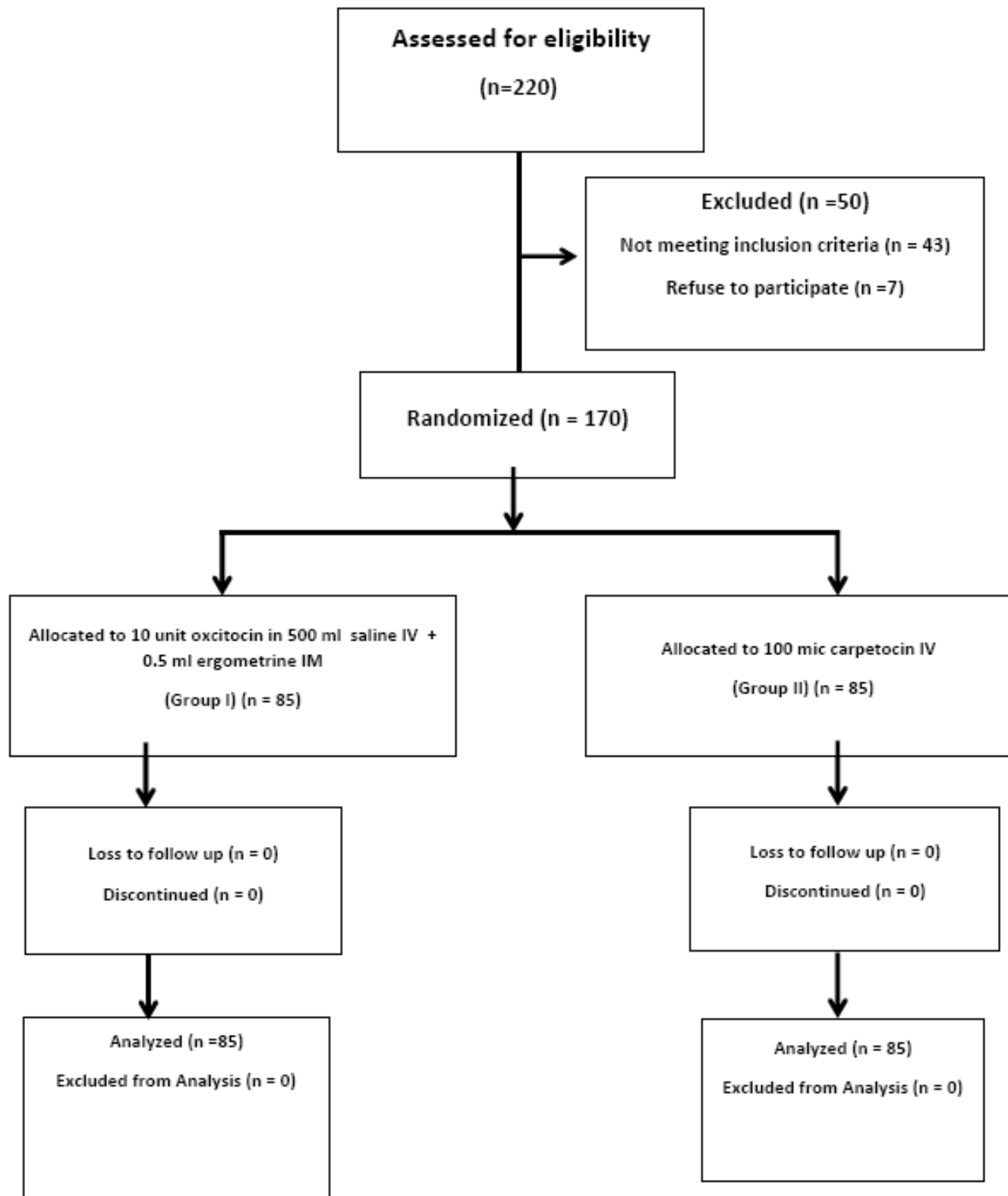
Variables are presented as mean and standard deviation and number (percentage).

Table 3: complication in the two groups: -

variables	Group I (n = 85)	Group II (n = 85)	Significance
Fever (%)	4 (4.7)	2 (2.4)	0.682
Headache (%)	18 (21.2)	5 (5.9)	0.004*
Nausea (%)	15 (17.6)	4 (4.7)	0.007*
Vomiting (%)	11 (12.9)	2 (2.4)	0.009*
Diarrhea (%)	3 (3.5)	1 (1.2)	0.371

* Statistically Significant Difference

Variables are presented as number (percentage).



DISCUSSION

This study is that the first single blind randomized controlled trial comparing the effectiveness of intravenous carbetocin versus intravenous oxytocin plus IM. Ergometrine for diminishing blood loss for pregnant ladies with twins who are experiencing CB. The outcomes demonstrated that the intravenous carbetocin was like intravenous oxytocin plus IM. Ergometrine for decrease the intraoperative and total blood loss, transfusion after CB, incidence of postpartum hemorrhage and therefore the got to extra additional uterotonics. Also, the side effect like headache, increase systolic and diastolic BP postoperative, and nausea and vomiting are significantly more in intravenous oxytocin plus IM. Ergometrine group.

In the better of our knowledge for the use of carbetocin in reducing blood loss during CD, no studies were recognized.

In the previous three decades, high-income nations have boosted their twin pregnancies by up to 75 percent^[12]. Approximately half of these twin pregnancies were getting to end during a cesarean delivery, which is 2.5 times the danger of singleton pregnancy^[13].

As a result, patients with a minimum of two risk factors for PPH, twin pregnancy and cesarean delivery, are getting more prevalent in our everyday clinical practice.^[14,15]

In our study, The difference in operational time between the carbetocin and oxytocin plus ergometrine wasn't statistically significant

Seow *et al.*^[16] found that when carbetocin was used rather than oxytocin, the surgical time for cesarean sections in twin pregnancies was 9 minutes shorter within the carbetocin group.

In comparison to the oxytocin + ergometrine group, there have been no significant differences in estimated blood loss within the carbetocin group. The findings were almost like those of Boucher *et al.*^[17] Attilakos *et al.*^[18] and Bonis^[19] who showed no significant differences between carbetocin and oxytocin in blood loss after cesarean sections, despite a bent toward reduced blood loss with carbetocin.

Our study was also following findings from Attilakos *et al.*^[20] Chong *et al.*^[21] Higgins *et al.*^[22] and Eftekhari *et al.*^[23] who found that no significant differences in the rate of transfusion between oxytocin and carbetocin.

In terms of the usage of additional uterotonics, while there's a trend within the carbetocin group to use them less, (11.8 vrsus 15.3%), this difference doesn't approach statistical significance in our study.

166 twin pregnancies at term having elective or emergency cesarean delivery were enrolled by L Sotillo *et al.* They evaluated the consequences of one 100 mg carbetocin dosage to a regimen of oxytocin (20 IU in Ringer lactate 500 ml in 10–15 min). Intraoperative hemorrhage, surgical time, hemoglobin drop, hematocrit decline, further uterotonic usage, the requirement for transfusion, and/or IV iron treatment were the first factors investigated. Carbetocin appears to be more beneficial than oxytocin in preventing PPH, they find.^[10]

Erkan Kalafat *et al.* completed a comprehensive review to evaluate the usage of carbetocin during CB and identified Carbetocin is efficient in lowering the need for further uterotonic usage and postpartum transfusion in women having caesarean deliveries who are more susceptible to PPH.^[24]

The efficacy of carbetocin was compared thereto of other uterotonics during a recent Cochrane network meta-analysis. 57 the utilization of carbetocin was associated with a decreased incidence of PPH (>500mL), (RR:0.72, 95 percent CI:0.52-1.00).^[25]

The incidence of side effects like headache and nausea and vomiting in women receiving oxytocin plus ergometrine was significantly above that within the carbetocin group. These findings are almost like the results of other studies^[26,27].

Carbetocin is an analog of oxytocin that features a longer half-life than oxytocin. Carbetocin also possesses a heat-stable state, unlike oxytocin. this is often an important characteristic since oxytocin's heat-lability has been found to be a severe restriction, especially in resource-constrained environments.^[16]

Our study's single-center design and use of a gravimetric method to quantify blood loss instead of the alkaline hematin method, which may be a proven technique for precise measurement of blood loss, were also limitations. But Marcel H. *et al.* (2004) compare gravimetric and colorimetric techniques of measuring surgical blood loss in veterinary surgery and conclude that estimation of blood loss using a gravimetric approach is an accurate and impartial instrument to measure intraoperative blood loss.^[28]

One of the strengths of our investigation was that a single-blind randomized examination was adequately powered to match the effect of intravenous carbetocin versus intravenous oxytocin Plus IM ergometrine on the quantity of perioperative blood loss. Another quality of the investigation lies in its simplicity of use of carbitocin can bring about a clinically significant decrease in intraoperative blood loss.

CONCLUSION

Carbetocin is as effective as oxytocin with ergometrine in decreasing total blood loss during and after caesarean birth in women pregnant with twins, but it has less adverse effects.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Guasch E, Gilsanz F. Massive obstetric hemorrhage: Current approach to management. *Med Intensiva*. 2016;40:298-310.
2. Say L, Chou D, Gemmill A, *et al.* Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2:e323-e333..
3. TIMOR-TRITSCH, Ilan E.; MONTEAGUDO, Ana. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. *American journal of obstetrics and gynecology*, 2012, 207.1: 14-29..
4. BRILEY, A., *et al.* Reporting errors, incidence and risk factors for postpartum haemorrhage and progression to severe PPH: a prospective observational study. *BJOG: An International Journal of Obstetrics & Gynaecology*, 2014, 121.7: 876-888.
5. World Health Organization. WHO Guidelines for the management of postpartum haemorrhage and Retained Placenta; 2009 [cited 2018 Mar 15]. Available from: http://whqlibdoc.who.int/publications/2009/9789241598514_eng
6. Gallos ID, Papadopoulou A, Man R, *et al.* Uterotonic agents for preventing postpartum hemorrhage: a network meta-analysis. *Cochrane Database Syst Rev*. 2018;12:CD011689.
7. WORLD HEALTH ORGANIZATION, *et al.* WHO recommendations Uterotonics for the prevention of postpartum haemorrhage: Web annex 7: Choice of uterotonic agents. World Health Organization, 2018.
8. Zein El Abdeen, E., & Shehata, N. (2018). Carbetocin versus oxytocin and ergometrine for prevention of postpartum hemorrhage following caesarean section. *Evidence Based Women's Health Journal*, 0(0), 138–143. <https://doi.org/10.21608/ebwhj.2018.6218>
9. Nirmala K, Zainuddin AA, Ghani NA, Zulkifli S, Jamil MA. Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery. *J Obstet Gynaecol Res*. 2009; 35: 48-54.
10. SOTILLO, Laura, *et al.* Efficacy of carbetocin for preventing postpartum bleeding after cesarean section in twin pregnancy. *The Journal of Maternal-Fetal & Neonatal Medicine*, 2020, 33.2: 267-271.
11. Schulz KF, Altman DG, Moher D. Consort 2010 statement: updated guidelines for reporting parallel group randomized trials. *BMC Medicine* 2010; 8: 18.
12. Martin JA, Hamilton BE, Ventura SJ, *et al.* Births: final data for 2011. *Natal Vital Stat Rep*. 2013;62(1):1–69.
13. Conde-Agudelo A, Belizan JM, Lindmark G. Maternal morbidity and mortality associated with multiple gestations. *Obstet Gynecol*. 2000;95(6 Pt 1):899–904.
14. Demetz J, Clouqueur E, D'Haveloose A, *et al.* Systematic use of carbetocin during cesarean delivery of multiple pregnancies: a before-and-after study. *Arch Gynecol Obstet*. 2013;287(5):875–880.
15. Seow KM, Chen KH, Wang PH, *et al.* Carbetocin versus oxytocin for prevention of postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery. *Taiwan J Obstet Gynecol*. 2017;56(3):273–275.
16. Nirmala K, Zainuddin AA, Ghani NA, Zulkifli S, Jamil MA. Carbetocin versus syntometrine in prevention of post-partum hemorrhage following vaginal delivery. *J Obstet Gynaecol Res*. 2009; 35: 48-54.
17. Boucher M, Horbay GL, Griffin P, *et al.* Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. *J Perinatol*. 1998;18(3):202–207.
18. Attilakos G, Psaroudakis D, Ash J, *et al.* Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG*. 2010;117(8):929–936.
19. Bonis M, Torricelli M, Leoni L, *et al.* Carbetocin versus oxytocin after caesarean section: similar

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- efficacy but reduced pain perception in women with high risk of postpartum haemorrhage. *J Matern Fetal Neonatal Med.* 2012;25(6):732–735.
20. A. Conde-Agudelo, A. Nieto, A. Rosas-Bermudez, R. Romero Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and meta-analysis *Am J Obstet Gynecol*, 209 (2013), pp. 40.e1-40.e17
 21. Attilakos G, Psaroudakis D, Ash J, *et al.* Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG.* 2010;117(8):929–936.
 22. LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. *Cochrane Database Syst Rev.* 2012;4:CD005457.
 23. Higgins L, Mechery J, Tomlinson AJ. Does carbetocin for prevention of postpartum haemorrhage at caesarean section provide clinical or financial benefit compared with oxytocin? *J Obstet Gynaecol.* 2011;31(8):732–739.
 24. Ortiz SR, Perez RA, Hernandez RS, *et al.* WITHDRAWN: Carbetocin versus oxytocin for prevention of postpartum hemorrhage: a randomised controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 2014
 25. Kalafat, Erkan, *et al.* "Efficacy of carbetocin in the prevention of postpartum hemorrhage: a systematic review and Bayesian meta-analysis of randomized trials." *The Journal of Maternal-Fetal & Neonatal Medicine* 34.14 (2021): 2303-2316.
 26. Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D *et al.* Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. *The Cochrane database of systematic reviews.* 2018; 4: Cd011689
 27. Attilakos, G., Psaroudakis, D., Ash, J., Buchanan, R., Winter, C., Donald, F., ... Draycott, T. (2010). Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG: An International Journal of Obstetrics & Gynaecology*, 117(8), 929–936. doi:10.1111/j.1471-0528.2010.02585.x
 28. Askar AA, Ismail MT, El-Ezz AA, Rabie NH. Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. *Arch Gynecol Obstet.* 2011; 284: 1359-65
 29. Larsson C, Saltvedt S, Wiklund I *et al.* Estimation of blood loss after cesarean section and vaginal delivery has low validity with a tendency to exaggerate. *Acta Obstet Gynecol Scand*2006; 85: 1448–1452
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