



Original Article

Carbetocin versus oxytocin for prevention of postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery

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ARTICLE INFO

Article history:

Accepted 22 August 2016

Keywords:

Twin pregnancy
Uterine atony
Carbetocin
Oxytocin

ABSTRACT

Objective: To compare the efficacy and safety of carbetocin with those of oxytocin infusion in women with twin pregnancy undergoing elective cesarean delivery.**Material and methods:** The present observational study conducted from January to December 2014 at a single center in Taiwan enrolled 64 women with twin pregnancy induced using in vitro fertilization—embryo transfer. The women were divided into a carbetocin group who received a single injection of 100 µg carbetocin (n = 25) and a control group who received a continuous intravenous infusion of 10 IU oxytocin in 500 mL 0.9% NaCl solution (125 mL/h) for 24 h (n = 39). Operative outcomes were compared between the groups.**Results:** The mean estimated blood loss during surgery was lower in the carbetocin group compared with the control group (871 ± 305 and 922.8 ± 430 mL, respectively), but the difference was not significant (P = 0.06). There was also no significant difference in the drop in hemoglobin level between two groups. The mean operative time was significantly shorter in the carbetocin group compared with the control group (P = 0.001).**Conclusion:** Carbetocin is as effective as oxytocin in preventing primary postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery.© 2017 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Uterine atony is the major cause of postpartum hemorrhage (PPH), accounting for up to 80% of PPH cases [1]. PPH is the leading cause of maternal morbidity and mortality worldwide, resulting in up to 28% of maternal deaths [2]. Therefore, inducing a rapid and effective uterine contraction following delivery is an important

issue. Risk factors of uterine atony include obesity, White or Hispanic race/ethnicity, polyhydramnios, preeclampsia, anemia, and chorioamnionitis as well as twin pregnancy [1]. With the increasingly common use of ovulation induction and assisted reproduction techniques, the incidence of multiple gestation pregnancies has progressively increased [3]. Suzuki et al. [4] reported that elective cesarean delivery of twin pregnancy at a gestational age of 37 weeks or greater may increase the risk of blood transfusion.

Several uterotonic agents are used to prevent PPH because of uterine atony, including oxytocin [5,6], ergot alkaloid [7,8], and prostaglandin [9–11]. Oxytocin is the most commonly used uterotonic agent for the prevention of PPH [6]. The advantage of oxytocin over other uterotonic agents is its lower cost and rapid onset

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of action. However, the disadvantage is its short duration of action [5].

Carbetocin (Duratocin), a long-acting synthetic analog of oxytocin with agonist action, was found more effective in reducing the incidence of PPH because of its ability to induce strong uterine contractions. Its half-life is 40 min, and uterine contractions occur in less than 2 min after intramuscular or intravenous (IV) administration [12]. A single bolus of 100 µg carbetocin has been shown to be as effective as a continuous 16-h infusion of oxytocin in reducing the intraoperative blood loss in women undergoing elective cesarean delivery [13]. Carbetocin also resulted in a significantly lower incidence of additional oxytocin intervention in the carbetocin group compared with the oxytocin group in women undergoing elective cesarean delivery [14]. However, another study demonstrated a different result that carbetocin have similar requirements for additional uterotonics at non-elective cesarean section [15,16]. A recent study by El Behery et al. [17] also demonstrated that a single 100-µg IV bolus of carbetocin is more effective than IV oxytocin infusion for maintaining adequate uterine tone and preventing postpartum bleeding in obese nulliparous women undergoing emergency cesarean delivery. These data suggest that a single bolus of carbetocin may be a good alternative to the IV oxytocin infusion commonly used to prevent PPH after cesarean delivery [18]. However, there are currently no data to evaluate the efficacy of carbetocin in twin pregnancy, a risk factor of uterine atony, for preventing PPH.

The aim of this pilot study was to compare the efficacy and safety of carbetocin with those of IV oxytocin infusion in women with twin pregnancy undergoing elective cesarean delivery.

Materials and methods

This was an observational study conducted from January to December 2014 in the delivery suite of a tertiary hospital in Taipei, Taiwan. Women with twin pregnancy induced using in vitro fertilization-embryo transfer (IVF-ET) were eligible for the study. All women were undergoing cesarean delivery. This study was reviewed and approved by our institution's Institutional Review Board.

The exclusion criteria included twin pregnancy not induced by IVF-ET, gestational hypertension, preeclampsia, and cardiac or renal disease. Sixty-four women were enrolled in this study and divided into 2 groups. The women in group 1 ($n = 25$) received a bolus IV injection of 100 µg carbetocin as soon as the baby was delivered but before the placenta was delivered. The women in group 2 (control group; $n = 39$) received a continuous IV infusion of 10 IU oxytocin in 500 mL 0.9% NaCl solution (125 mL/h) as soon as the baby was delivered and for 24 h afterward to prevent PPH. All procedures were performed by the first author, with assistance from a senior resident.

The primary outcome variable of this study was the drop in hemoglobin level documented by comparing the maternal hemoglobin concentration on admission before cesarean delivery with that measured 24 h after delivery. Other secondary outcome variables assessed included estimated blood loss during surgery, and lochia within 2 h after delivery, the duration of the operation, the incidence of primary PPH (defined as blood loss more than 1000 mL), and blood transfusion. The blood loss was estimated after excluded amniotic fluid volume in each case. Maternal pulse rate and fetal body weight were also recorded. The need for additional uterotonic agents (oxytocin, methylergometrine, misoprostol) was measured.

Statistical analysis

For a power analysis of 90%, the study needed of 25 patients in each group.

Data were expressed as means \pm SD, as appropriated. Normality of continuous variables was assessed with the Kolmogorov–Smirnov test. An unpaired *t*-test was used for the statistical analysis of continuous variables with normal distributions. Between-group differences of non-continuous variables were assessed with the chi-squared method and Yate's correction, if needed. *P*-values < 0.05 were considered to be significant. Analysis was performed using the PASW Statistics 18 (SPSS, Chicago, IL, USA).

Results

The mean ages of the carbetocin and control group were 34.5 ± 4.2 and 33.7 ± 3 years, respectively ($P > 0.05$). There were no significant differences in the duration of infertility and gestational age of delivery between the groups (Table 1).

The maternal clinical variables of the study and control groups are shown in Table 2. The mean amount of estimated blood loss during surgery was lower in the carbetocin group compared with the control group (871 ± 305 and 922.8 ± 430 mL, respectively), but the difference was not significant ($P = 0.06$). Thirty-six (92.3%) and 22 (88%) women in the control and study group, respectively to have a blood loss more than 500 cc in this study. However, only 59% (23/39) in control group and 48% (12/25) in the study have a blood loss of equal to or more than 1000 cc. In addition, lochia 2 h after delivery and the mean drop in the hemoglobin level 24 h after delivery was also not statistically different between the groups ($P = 0.06$).

The mean operative time was significantly shorter in the carbetocin group compared with the control group ($P = 0.001$), and the carbetocin group had a significantly higher mean heart rate compared with the control group ($P = 0.002$). The control group had a higher incidence of blood transfusion (10.3%) compared with the carbetocin group (0%), but the difference was not significant. The incidence of needed additional uterotonic agents was not significantly difference between two groups.

Discussion

In the present study, we found that using carbetocin as a routine uterotonic drug is as effective as oxytocin in infertile women with twin pregnancy following cesarean delivery. This study suggests that carbetocin could be an alternative to oxytocin for women with twins pregnancy undergoing cesarean delivery.

In this study, we found that the incidence of primary PPH is high if PPH is defined as blood loss more than 500 cc (92.3% vs. 88% in group 1 and 2, respectively). However, if PPH is defined as blood loss ≥ 1000 cc, the incidence of PPH is 59% and 48% in group 1 and 2, respectively. The incidence of PPH is still high even though PPH is defined as blood loss of more than 1000 cc. Therefore, a more accurate criterion for defining of PPH should be performed in the future.

The lower blood loss we observed in the carbetocin group may have been due to the strong uterine contraction induced by the

Table 1
Characteristics and clinical features of the control and study groups.

	Control group	Study group	<i>P</i>
Age	33.7 ± 3	34.5 ± 4.2	0.45
Duration of infertility (years)	3.4 ± 2.1	3.5 ± 2.3	0.90
BW (kg)	69.8 ± 11.1	71.6 ± 10.1	0.52
Height	160.5 ± 5.1	160.4 ± 5.0	0.94
Parity	0.23 ± 0.5	0.16 ± 0.4	0.57
Gestational age of delivery (weeks)	35.2 ± 2.6	35.2 ± 2.7	0.92

Values are mean \pm SD, unless otherwise stated.

Table 2
Maternal outcome of the control and study groups.

	Control group	Study group	P
Fetal body weight 1 (gm)	2157 ± 484	2190 ± 477	0.79
Fetal body weight 2 (gm)	2272 ± 486	2284 ± 490	0.93
Operative time (min)	49.9 ± 13.8	40.8 ± 7.1	0.001
Blood loss (cc) during operation	922.8 ± 430	871 ± 305	0.06
Lochia (cc) 2 h after operation	150 ± 50	125 ± 25	0.12
Hemoglobin (Hb) before operation (gm/dl)	11.7 ± 1.7	11.5 ± 1.5	0.61
Hb 24 h after operation	10.0 ± 1.7	9.9 ± 1.5	0.71
Drops of Hb	1.7 ± 1.5	1.6 ± 1.4	0.89
Incidence of blood transfusion	10.3% (4/39)	0%	0.098
Heart rate (beats/min)	75 ± 25	112 ± 35	0.002
Need for additional uterotonic agents	23.1% (9/39)	8% (2/25)	0.12

Values are mean ± SD, unless otherwise stated.

Bold values indicate $P < 0.05$ considered significant, unpaired *t*-test, carbetocin versus control.

carbetocin injection, which may mean that the blood loss decreased during the operation, even though there was no statistically significant ($P = 0.06$). However, the difficulty of estimating blood loss during surgery because the blood is mixed with amniotic fluid, making the blood loss cannot be accurately measured. In addition, there was no difference in the drop of haemoglobin concentration within the first 24 h between the two groups. This result is similar to other studies that carbetocin is associated with less blood loss compared to syntometrine in the prevention of PPH [17,19]. However, several more recent studies demonstrated there was no difference in the amount of estimated blood loss between carbetocin and oxytocin [15,16,20]. A larger study should be performed in the future.

The statistically shorter operating time in the carbetocin group was an interesting finding that may also be explained by the strong contraction induced by carbetocin, meaning that less massage of the uterus is needed during the operation, thus allowing the surgeon to concentrate more on the surgery itself and therefore save operating time. Although surgical skill of the surgeon can also affect operation time, all procedures in this study were performed by the same surgeon. This finding has never being reported in the literature.

Twin pregnancy is one of the most important risk factors of PPH because of overextension of the uterus [1]. Therefore, the high incidence of blood transfusion noted in twin pregnancy may be owing to PPH. In the present study, the oxytocin group showed a trend of a higher incidence of blood transfusion and need for additional uterotonic agents compared with the carbetocin group. However, because of the small sample size, the difference was not statistically significant. A larger sample is needed in the future to investigate these issues.

There were no major side effects or complications in either group in the present study. Abdominal pain, dizziness and nausea are the most common side effects of carbetocin owing to the severe contraction of the uterus [21,22]. Although the women in the carbetocin group had a higher incidence of tachycardia compared with the oxytocin group, the tachycardia subsided within 60 min of the injection without any treatment [22]. Nevertheless, it may confound monitoring of women with bleeding and miss diagnosis of PPH because of hemodynamic unstable due to increase of heart rate.

In conclusion, carbetocin is as effective and as safe as oxytocin for preventing primary PPH in infertile women with twin pregnancy undergoing elective cesarean delivery. Women treated with carbetocin also may be less likely to need a blood transfusion. Therefore, carbetocin should be considered as a good alternative to oxytocin for managing delivery of the placenta for prevention of

postpartum hemorrhage in twin pregnancy receiving elective cesarean section.

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgement

This study was supported by the Shin-Kong Wu-Ho-Su Memorial Hospital (Grant No. SKH-8302-103-DR-23).

References

- [1] Wetta LA, Szychowski JM, Seals S, Mancuso MS, Biggio JR, Tita AT. Risk factors for uterine atony/postpartum hemorrhage requiring treatment after vaginal delivery. *Am J Obstet Gynecol* 2013;209(51):e51–6.
- [2] Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. Who analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066–74.
- [3] Russell RB, Petrini JR, Damus K, Mattison DR, Schwarz RH. The changing epidemiology of multiple births in the united states. *Obstet Gynecol* 2003;101:129–35.
- [4] Suzuki S, Inde Y, Igarashi M, Miyake H. Elective cesarean as a risk factor for transfusion after delivery of twins. *J Nippon Med Sch* 2008;75:247–9.
- [5] Roach MK, Abramovici A, Tita AT. Dose and duration of oxytocin to prevent postpartum hemorrhage: a review. *Am J Perinatol* 2013;30:523–8.
- [6] Grotegut CA, Paglia MJ, Johnson LN, Thames B, James AH. Oxytocin exposure during labor among women with postpartum hemorrhage secondary to uterine atony. *Am J Obstet Gynecol* 2011;204(56):e51–56.
- [7] Fujimoto M, Takeuchi K, Sugimoto M, Maruo T. Prevention of postpartum hemorrhage by uterotonic agents: comparison of oxytocin and methyl-ergometrine in the management of the third stage of labor. *Acta Obstet Gynecol Scand* 2006;85:1310–4.
- [8] Saito K, Haruki A, Ishikawa H, Takahashi T, Nagase H, Koyama M, et al. Prospective study of intramuscular ergometrine compared with intramuscular oxytocin for prevention of postpartum hemorrhage. *J Obstet Gynaecol Res* 2007;33:254–8.
- [9] Chaudhuri P, Biswas J, Mandal A. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women. *Int J Gynaecol Obstet* 2012;116:138–42.
- [10] Chaudhuri P, Majumdar A. Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage. *Int J Gynaecol Obstet* 2015;128:48–52.
- [11] Nasr A, Shahin AY, Elsamman AM, Zakherah MS, Shaaban OM. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. *Int J Gynaecol Obstet* 2009;105:244–7.
- [12] Sweeney G, Holbrook AM, Levine M, Yip M, Alfredson K, Cappi S, et al. Pharmacokinetics of carbetocin, a long-acting oxytocin analogue, in nonpregnant women. *Curr Ther Res* 1990;47:528–40.
- [13] Boucher M, Horbay GL, Griffin P, Deschamps Y, Desjardins C, Schulz M, 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;18:202–7.
- [14] Dansereau J, Joshi AK, Helewa ME, Doran TA, Lange IR, Luther ER, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Am J Obstet Gynecol* 1999;180:670–6.
- [15] Whigham CA, Gorelik A, Loughnan TE, Trivedi A. Carbetocin versus oxytocin to reduce additional uterotonic use at non-elective caesarean section: a double-blind, randomised trial. *J Matern Fetal Neonatal Med* 2016;1–4.
- [16] Razali N, Md Latar IL, Chan YK, Omar SZ, Tan PC. Carbetocin compared to oxytocin in emergency cesarean section: a randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2016;198:35–9.
- [17] El Behery MM, El Sayed GA, El Hameed AA, Soliman BS, Abdelsalam WA, Bahaa A. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in obese nulliparous women undergoing emergency cesarean delivery. *J Matern Fetal Neonatal Med* 2016;29:1257–60.
- [18] Maged AM, Hassan AM, Shehata NA. Carbetocin versus oxytocin in the management of atonic post partum haemorrhage (PPH) after vaginal delivery: a randomised controlled trial. *Arch Gynecol Obstet* 2016;293:993–9.
- [19] Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. *Cochrane Database Syst Rev* 2012;4:CD005457.
- [20] Jin B, Du Y, Zhang F, Zhang K, Wang L, Cui L. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *J Matern Fetal Neonatal Med* 2016;29:400–7.
- [21] Moertl MG, Friedrich S, Kraschl J, Wadsack C, Lang U, Schlembach D. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. *BJOG* 2011;118:1349–56.
- [22] Leung SW, Ng PS, Wong WY, Cheung TH. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *BJOG* 2006;113:1459–64.