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Original Article

Carbetocin in prevention of postpartum hemorrhage: Experience in a tertiary medical center of Taiwan

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ABSTRACT

Objective: The aim of this retrospective observational study was to determine the efficacy of carbetocin in reducing blood loss and primary postpartum hemorrhage (PPH) in vaginal and cesarean deliveries in a tertiary hospital in Taiwan.

Materials and methods: Eligible gravid women (27–41 weeks) with available data were categorized into those treated prophylactically with and without carbetocin. The primary outcome was blood loss and incidence of primary PPH as measured by intrapartum/intraoperative and postpartum (recovery room) blood loss.

Results: A total of 1069 deliveries were evaluated. Maternal age (~31 years of age), body mass index (~27 kg/m^2) and parity (~1.4) were similar among those treated with and without carbetocin for both vaginal and cesarean deliveries. The majority [749/1069 (70.1%)] of deliveries were vaginal; a similar proportion of women undergoing vaginal [221/749 (29.5%)] and cesarean [110/320 (34.4%)] deliveries received prophylactic carbetocin for prevention of PPH. Among vaginal deliveries, there was no significant difference in intrapartum ($p = 0.083$) or postpartum ($p = 0.925$) blood loss, or incidence of PPH ($p = 0.092$) between women with versus without carbetocin prophylaxis. However, there was a significant reduction in the intraoperative and total blood loss among cesarean deliveries with versus without carbetocin prophylaxis ($p < 0.001$). The incidence of PPH was higher [84/320 (26.3%)] among cesarean than among vaginal deliveries [62/749 (8.3%)], but was significantly lower among cesarean deliveries with [18 (16.36%)] versus without [66 (30.45%); $p = 0.003$] carbetocin prophylaxis.

Conclusion: In Taiwan, prophylactic use of carbetocin resulted in significantly less blood loss and incidence of PPH in cesarean than in vaginal deliveries.

Introduction

Primary postpartum hemorrhage (PPH) is a major cause of maternal mortality, with a worldwide prevalence of ~6% [1]. PPH arises mainly from the failure of the uterus to contract after delivery, leading to blood loss of ≥ 500 mL in vaginal delivery, > 1000 mL in cesarean section (CS), or a substantial drop in hematocrit compared with the antepartum level; those conditions may occur in the first 24 hours after delivery (primary PPH) or between 24 hours and 6 weeks after delivery (secondary PPH) [2,3]. Risk factors include history of prior PPH, large baby, parity, prolonged or augmented labor, placental abnormalities, anemia, and CS, although PPH may also occur in women with no identifiable risk factors [4–10].

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First-line uterotonic agents promote uterine contractions and increase uterine tone, thereby reducing blood loss [4,11]. Women who do not respond to first-line therapy require further interventions, including the use of additional uterotonic agents [3]. Active management of third-stage labor (AMTSL) helps reduce the rate of severe primary PPH, the need for transfusion, and subsequent uterotonic therapy [2]. Oxytocin is a widely used and effective first choice uterotonic agent in the universal prevention of PPH [12,13]. However, due to its short half-life (10–15 minutes) [14], it is administered intramuscularly (IM) at a dose of 10 IU or as an intravenous (IV) infusion for the prevention of PPH as part of AMTSL. Although an IV bolus of oxytocin, (5–10 IU, given over 1–2 minutes), can be used after vaginal delivery, it is not recommended for use in elective CS [15,16].

Alternatively, carbetocin, a synthetic analog of oxytocin (100 μg), can be given in elective CS as an IV bolus over 1 minute, instead of a continuous oxytocin infusion, for the prevention of PPH and to decrease the need for therapeutic uterotonic agents (level of evidence: I–B). With a plasma half-life of 40 minutes, carbetocin has a longer duration of action than oxytocin [15,16]. It is indicated for the prevention of uterine atony and PPH following elective CS under epidural or spinal anesthesia [17]. Intravenous injection of carbetocin produces rhythmic uterine contractions lasting approximately 60 minutes while IM injection significantly prolongs its activity (~120 minutes; $p = 0.02$) [18].

Compared with oxytocin, carbetocin lowers the risk of PPH, significantly decreases the need for additional uterotonic agents [19], and achieves better uterine contractility in both cesarean [20,21] and vaginal deliveries [22,23]. Additionally, oxytocin and carbetocin have similar adverse-event profiles, but its ease of administration [20,24,25] favors the use of carbetocin over traditional oxytocin regimens in cesarean deliveries [19,26].

Considering that AMTSL is vital for PPH reduction worldwide [12], we conducted this study to determine the real-world efficacy of carbetocin in reducing blood loss and primary PPH in vaginal and cesarean deliveries in a tertiary hospital in Taiwan.

Materials and methods

Study design

This retrospective observational study evaluated the blood loss and incidence of primary PPH in women treated prophylactically with carbetocin (Duratocin, Ferring Pharmaceuticals, Inc., Saint-Prex, Switzerland) or any other uterotonic agent for AMTSL during vaginal or cesarean delivery. Data from a tertiary hospital in Taiwan were analyzed from January 2014 to September 2014. The hospital database was searched for eligible gravid women who delivered vaginally or underwent a CS. They were categorized into two groups: those who received carbetocin prophylactically for prevention of PPH and those who did not. The primary outcome was to determine the blood loss and incidence of primary PPH by measuring the intra- and postpartum blood loss during vaginal delivery or CS, either with or without carbetocin prophylaxis.

Participants

Women beyond 27 weeks of gestation (27–41 weeks) who underwent either vaginal delivery or CS were included in the analysis. They were to have complete data available pertaining to age, weeks of gestation, height, weight, intrapartum period, and postpartum period, including follow-up 4–6 weeks after delivery. Women with hypertension, preeclampsia, and heart disease were excluded.

Treatment and assessments

Carbetocin was administered IV [100 μg (1 mL) bolus, slowly over 1 minute] after vaginal delivery or complete delivery of the newborn by CS. Carbetocin could be administered either before or after delivery of the placenta. Women who were not treated with prophylactic carbetocin were provided appropriate standard of care based on hospital protocol with single dose of oxytocin (5 U). Thereafter, blood loss was estimated intrapartum and every half hour during the period of postpartum observation, including 2 hours in the recovery room by the attending nurses, and was assessed by weighing the gauze and pad soakage. PPH was characterized by blood loss of $\geq$ 500 mL for vaginal and $\geq$ 1000 mL for cesarean deliveries. Women diagnosed with PPH were treated with repeat carbetocin, oxytocin, or intramuscular ergonovine.

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA). Group comparisons were performed with Chi-square tests (with continuity corrections in the case of 2×2 tables) and Student t tests for categorical and continuous variables.

Results

Maternal disposition and characteristics of carbetocin

A total of 1627 deliveries were assessed, of which 1069 were included in the study, based on the eligibility criteria. The majority [749/1069 (70.1%)] of deliveries were vaginal, and carbetocin was used in a similar proportion of patients undergoing vaginal [221/749 (29.5%)] and cesarean [110/320 (34.4%)] deliveries (Figure 1).

In general, maternal characteristics such as mean age (~31 years), mean body mass index (~27 kg/m^2), and mean parity (~1.4) were similar between the groups treated with and without prophylactic carbetocin for both vaginal and cesarean deliveries, except that maternal age and parity were different in the certain situations (Table 1).

Postpartum blood loss during vaginal delivery

The mean [standard deviation (SD)] intrapartum blood loss during vaginal delivery was similar among women treated with [226.19 (156.31) mL] and without carbetocin [250.17 (178.45) mL; $p = 0.083$]. The blood loss in the recovery room was also similar among women treated with [101.31 (83.19) mL] and without [110.89 (83.98) mL] carbetocin ($p = 0.925$). The difference in the total amount of blood loss between the groups treated with and without carbetocin ($p = 0.149$) was not significant (Figure 2).

Postpartum blood loss during CS

As anticipated, the mean (SD) blood loss during CS was approximately three- to four-fold higher than in vaginal delivery. However, the mean (SD) blood loss during CS was significantly lower in women treated with [640.47 (331.58) mL] versus without [822.38 (371.96) mL; $p < 0.0001$] carbetocin prophylaxis. The blood loss in the postoperative recovery room was similar between the groups treated with versus without carbetocin prophylaxis. Overall, total blood loss was significantly lower in women treated with versus without carbetocin prophylaxis ($p < 0.001$) (Figure 3).

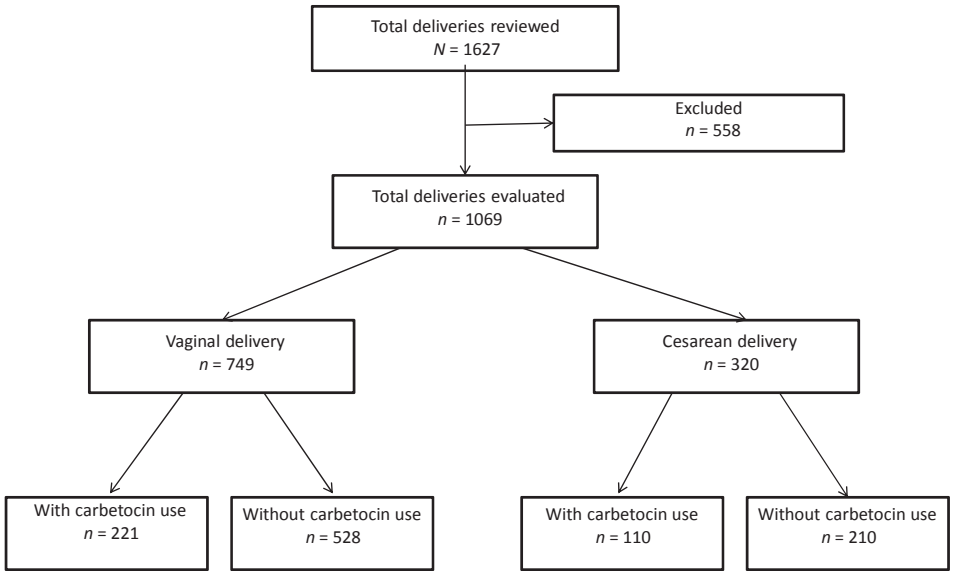

Figure 1. Algorithm of patient disposition. Women with hypertension, preeclampsia, heart disease, and lack of data pertaining to age, gestational weeks, height, weight, intrapartum period, and postpartum period, including 4-week to 6-week follow-up, were excluded.

Table 1
Characteristics of the study population.

Characteristic	Vaginal delivery			Cesarean delivery		
	With carbetocin $n = 221$	Without carbetocin $n = 528$	p	With carbetocin $n = 110$	Without carbetocin $n = 210$	p
Maternal age (y)	31.56 (3.02)	31.78 (2.38)	0.335	32.27 (2.94)	31.67 (1.63)	0.049
BMI (kg/m^2)	25.8 (3.36)	26.06 (4.04)	0.338	26.97 (3.9)	27.75 (4.5)	0.499
Parity	1.46 (0.59)	1.49 (0.66)	0.021	1.37 (0.56)	1.51 (0.70)	0.121

Data are presented as mean (standard deviation).
BMI = body mass index.

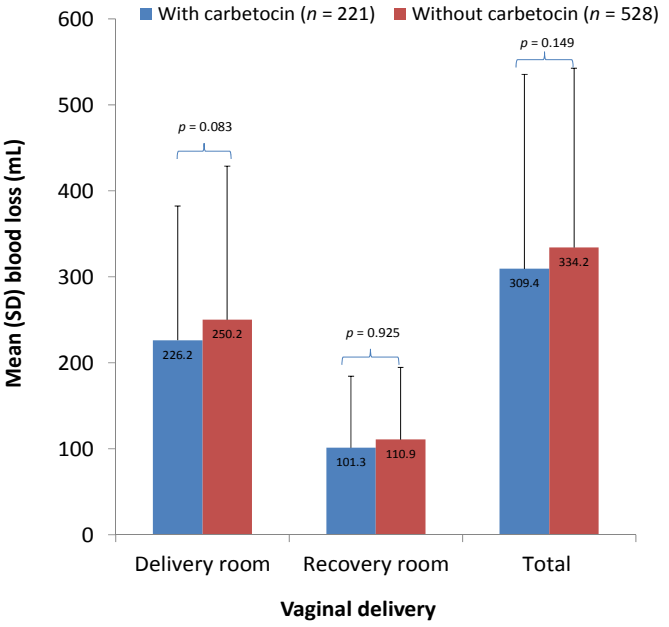

Figure 2. Postpartum blood loss with and without use of prophylactic carbetocin during vaginal delivery.

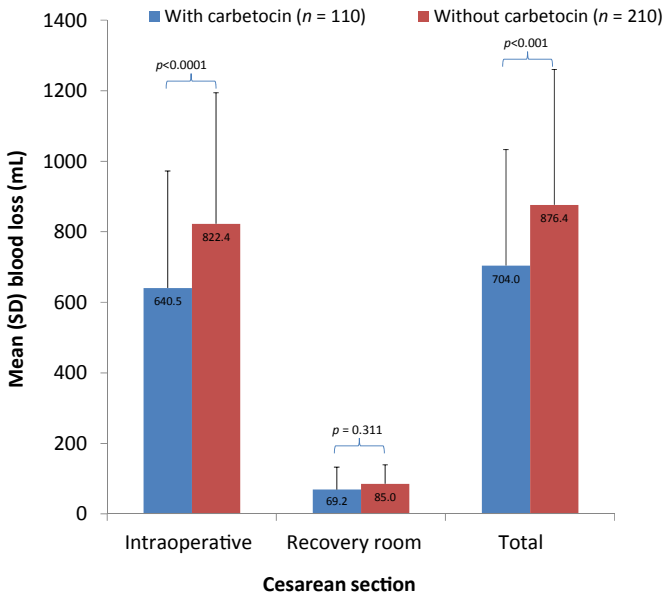

Figure 3. Postpartum blood loss with and without use of prophylactic carbetocin during cesarean delivery.

Primary PPH

The incidence of primary PPH in vaginal deliveries was 8.3% (62/749). There was no significant difference in the incidence of PPH among women treated with [12 (1.6%)] versus without [50 (6.7%)] carbetocin prophylaxis (Pearson Chi-square with continuity correction, $p = 0.092$). The incidence of PPH was higher [26.3% (84/320)] in women with cesarean than in vaginal deliveries. However, among cesarean deliveries, the use of carbetocin prophylaxis showed the significant benefits to decrease the risk of PPH, the data showed that the incidence of PPH was significantly lower for women treated with carbetocin prophylaxis compared with that in women without (18 [5.6%] vs. 66 [20.6%], Pearson Chi-square with continuity correction, p = 0.006) (Table 2)).

Discussion

This retrospective observational study evaluated the real-world efficacy of carbetocin in reducing blood loss and incidence of primary PPH among vaginal and cesarean deliveries in a tertiary hospital in Taiwan. The mean maternal age of the identified cohort was 31.76 years; no specific pattern of carbetocin use was identified in Taiwan, as it was used in ~30% of both cesarean and vaginal deliveries. Although carbetocin is indicated for prevention of uterine atony in CS (not in vaginal delivery) in 23 countries [19], its use was low in Taiwan. The results were consistent with the literature available for AMTSL with carbetocin for cesarean deliveries and not vaginal deliveries [19,21,25,27–29]. For vaginal deliveries, the use of prophylactic carbetocin did not significantly decrease intrapartum and early postpartum blood loss in the recovery room compared with other uterotonic agents. However, the use of prophylactic carbetocin significantly decreased the blood loss during CS, which was also reflected in the significant decrease in total blood loss. Since CS is an important risk factor for PPH, we noted a higher incidence of primary PPH among cesarean (26.3%) compared with vaginal deliveries (8.3%). The use of prophylactic carbetocin significantly decreased the incidence of PPH among cesarean than in vaginal deliveries.

Oxytocin is effective in reducing PPH in vaginal deliveries compared with placebo [8]. The availability of an active comparator such as oxytocin does not permit the use of placebo in clinical trials. Recent studies show that, for prevention and treatment of PPH, carbetocin is a better alternative to oxytocin for vaginal deliveries [22,23,29], including high-risk deliveries [23]. However, we observed no significant difference in blood loss or incidence of PPH among vaginal deliveries, with or without the use of carbetocin.

Of note, although AMTSL is a vital component of PPH-reduction strategies around the world [12], substantial variations are found in PPH prevention and management guidelines among four national organizations, [American College of Obstetrician and Gynecologists, the Royal Australian and New Zealand College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists, and the Society of Obstetricians and Gynecologists of Canada (SOGC)] [30]. The SOGC recommends carbetocin as a 100-μg IV bolus given over 1 minute instead of continuous oxytocin infusion in elective CS for the prevention of PPH [15]. Furthermore, based on a PPH and preeclampsia/eclampsia survey from 37 countries, despite the essential policies and programs, potential gaps impede efforts to implement the PPH and preeclampsia/eclampsia programs [31]. Based on a review of seven studies comparing the effectiveness of active versus expectant management of the third stage of labor, it is of critical importance to look at the individual components of third-stage management [2]. A large multicenter trial by the World Health Organization in 2012 highlighted the importance of an efficacious uterotonic agent; the study emphasized that uterotonics remain the primary intervention. Controlled cord traction and uterine massage may add a small benefit or no benefit, respectively, for the prevention of PPH among women who have received a uterotonic [32].

Although the amount of blood loss is a definitive indicator of efficacy, the requirement for additional uterotonic agents is also an important marker of uterine tone and blood loss. In a double-blind, randomized, single-center study in the United Kingdom, use of prophylactic carbetocin for cesarean deliveries was associated with a lower need for additional oxytocic agents than with prophylactic oxytocin (5 IU) [25]. Similarly, comparison of carbetocin with oxytocin infusion in a small, prospective, controlled trial of cesarean deliveries with at least one risk factor for PPH, carbetocin demonstrated equal safety and efficacy in maintaining uterine tone with an added benefit of reduction in postoperative pain perception [28]. In a prospective case–control study of cesarean deliveries, carbetocin was also shown to be more effective in terms of additional uterotonic requirements than a continuous infusion of oxytocin, with a similar hemodynamic profile and a minor antidiuretic effect [21]. In a double-blind, randomized study of cesarean deliveries, carbetocin was as effective as, and more reliable than, a continuous infusion of oxytocin in maintaining adequate uterine tone and preventing excessive intraoperative blood loss after delivery of the placenta [27].

Based on a meta-analysis including six trials comparing carbetocin with oxytocin, the use of carbetocin significantly decreased the need for uterotonic agents [risk ratio (RR), 0.62; 95% confidence interval (CI), 0.44–0.88; 4 trials, 1173 women] and lowered the risk of PPH (RR, 0.55; 95% CI, 0.31–0.95; 3 trials, 820 women) compared to oxytocin for cesarean deliveries only. However, the use of carbetocin was associated with a reduced need for uterine massage following both CS (RR, 0.54; 95% CI, 0.37–0.79; 2 trials, 739 women) and vaginal delivery (RR, 0.70; 95% CI, 0.51–0.94; 1 trial, 160 women). Similarly, meta-analysis of four trials comparing IM carbetocin and IM syntometrine for women undergoing vaginal deliveries showed that use of carbetocin decreased the mean blood loss (mean difference, 48.84 mL; 95% CI, from −94.82 to −2.85; 4 trials, 1030 women), the risk of adverse events such as nausea and vomiting (RR, 0.24; 95% CI, 0.15–0.40; 4 trials, 1030 women); vomiting (RR, 0.21; 95% CI, 0.11–0.39; 4 trials, 1030 women), and the incidence of postpartum hypertension at 30 minutes (RR 0.07; 95% CI 0.01–0.49; 2 trials, 570 women) and 60 minutes after delivery (RR 0.07; 95% CI 0.01–0.54; 2 trials, 540 women) [19].

Although the results of this observational study are in line with the published literature on cesarean deliveries, we report numerous potential limitations such as the retrospective study design and data from a single center in Taiwan. Furthermore, visual estimation of blood loss in vaginal delivery could have contributed to the lack of statistical significance in these deliveries. We

Table 2
Incidence of primary postpartum hemorrhage (PPH) with and without prophylactic carbetocin: cross-tabulation for vaginal and cesarean deliveries.

Vaginal delivery	No PPH	PPH	Total
Without carbetocin	478 (63.8)	50 (6.7)	528 (70.5)
With carbetocin	209 (27.9)	12 (1.6)	221 (29.5)
Total, *n* (%)	687 (91.7)	62 (8.3)	749 (100.0)
Pearson Chi-square, $p = 0.067$.			
Pearson Chi-square with continuity correction, $p = 0.092$.			
Cesarean delivery	**No PPH**	**PPH**	**Total**
Without carbetocin	144 (45.0)	66 (20.6)	210 (65.6)
With carbetocin	92 (28.8)	18 (5.6)	110 (34.4)
Total, *n* (%)	236 (73.8)	84 (26.3)	320 (100.0)
Pearson Chi-square, $p = 0.004$.			
Pearson Chi-square with continuity correction, $p = 0.006$.			

Data are presented as *n* (%).

acknowledge that visual assessment of blood loss is known to underestimate actual blood loss by up to 50% and is highly unreliable, making meaningful comparisons between studies difficult [33,34]. Nonetheless, visual estimation remains the method of choice in clinical practice due to its relative ease and convenience. Other quantitative methods to estimate blood loss, e.g., gravimetric and photometric assessment, are time consuming and not feasible in clinical practice [35]. Changes in hematocrit and hemoglobin levels before and after delivery offer a more reliable alternative, although the levels may not be available. Clinical signs and symptoms such as pallor, lightheadedness, weakness, palpitations, and fatigue, have been recommended rather than visual estimation. However, those clinical markers are surrogate measures for blood loss estimation and are therefore not accurate [15,35]. Further limitations include lack of stratification based on indication for CS, maternal risk factors, age, and use of assisted delivery (forceps or vacuum). Nevertheless, the results from this observational study are encouraging and point to the effectiveness of carbetocin in reducing blood loss and PPH in cesarean deliveries, which are both increasing worldwide and remain an important risk factor for PPH [36].

Conclusion

The use of prophylactic carbetocin did not significantly decrease the intrapartum or early postpartum blood loss in the recovery room for vaginal deliveries in Taiwan. However, a significant decrease in blood loss was noted with the prophylactic use of carbetocin in cesarean deliveries. The use of prophylactic carbetocin significantly decreased the incidence of PPH more in cesarean than in vaginal deliveries. In fact, CS-related PPH often results in catastrophic problems, and often needs a complicated method for preservation of the uterus [37,38]. Therefore, the finding of a significant reduction of incidence of PPH for CS patients who were treated with carbetocin prophylaxis might further suggest the risk of peripartum hysterectomy could also be decreased, although we did not have the latter data to support it.

Conflicts of interest

All authors declare no conflict of interest.

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