Carbetocin versus Oxytocin for the Prevention of Postpartum Hemorrhage in Cesarean Deliveries: A Retrospective Study of Two Consecutive Periods

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Abstract

Objective The aim of the study is to investigate whether carbetocin prevents postpartum hemorrhage (PPH) more effectively than oxytocin

Methods   This historical retrospective single-center cohort study compares women who underwent cesarean deliveries during two periods. During period A, oxytocin was used as a 10-unit bolus immediately after delivery, with 20 units thereafter infused for 24 hours. During period B, carbetocin in a single 100-μg injection replaced this protocol. The main outcome was PPH, defined as a decline in hemoglobin of more than 2 g/dL after the cesarean. The analysis was performed on the overall population and then stratified by the timing of the cesareans (before or during labor). A logistic regression analysis was performed.

Results   This study included 1,796 women, 52% of whom had a cesarean before labor; 15% had a PPH. The crude PPH rate was lower in period B than in period A (13 vs. 17%, respectively, odds ratio 0.75, 95% confidence interval [CI]: 0.58–0.98). The difference was no longer significant in the multivariate analysis (adjusted odds ratio: 0.81, 95% CI 0.61–1.06). Results were similar when stratified by the timing of the cesareans (before or during labor).

Conclusion   Carbetocin is not superior to oxytocin in preventing PPH. However, it does provide the advantage of requiring a single injection.

Keywords
► oxytocin
► carbetocin
► postpartum hemorrhage
► cesarean delivery

Postpartum hemorrhage (PPH) accounts for 125,000 deaths per year worldwide and is the leading cause of maternal death.[1] Despite significant progress, it accounts for 18% of maternal deaths and 80% of preventable causes in France.[2] Uterine atony is its principal cause, responsible for nearly 70% of the cases.[3] Active management of delivery with uterotonic agents is thus recommended by all national guidelines and is reported to halve the PPH rate.[4] According to a 2013 Cochrane review, prophylactic oxytocin can prevent PPH, and an intravenous (IV) bolus dose of 10 IU is recommended as part of active management of the third stage of labor.[5] The World Health Organization recommendations for PPH treatment and prevention also advise the use of 10 units of oxytocin (intramuscularly or intravenously) for the prevention of PPH in all births.[6,7] This injection is often followed by a maintenance dose of 10 IU over several hours because the half-life of oxytocin is 4 to 10 minutes. Carbetocin, a synthetic oxytocin analog with a half-life of 40 minutes, has been available for 20 years and is hoped to provide better efficacy and a greater ease of use.

The main indication for which carbetocin has been proposed is cesarean delivery, because this mode of delivery is associated with a higher prevalence of severe PPH and requires invasive second-line therapies three times more often than vaginal deliveries do.[8] It has been evaluated in women with cesareans in small randomized trials and by subjective or post hoc judgment criteria (use of other uterotonics or fundal height in the immediate postpartum period). A 2018 Cochrane meta-analysis concluded that prophylactic carbetocin does not result in a lower incidence of PPH > 500 mL in cesarean deliveries, with a risk ratio of 0.71 (0.47–1.07).[9] This result was nonetheless limited by the number of studies available for this outcome (only six trials and 678 women with cesareans) and the moderate quality of the studies. On the other hand, blood loss and the need for additional uterotonic agents fell significantly, and other recent meta-analyses appear to show that carbetocin is superior to oxytocin.[10,11]

In 2012, our tertiary referral center replaced oxytocin by carbetocin for use in preventing PPH in cases of cesareans before or during labor. The objective of this study was to investigate whether the use of a single injection of carbetocin was more effective than an oxytocin bolus and 24-hour infusion for preventing PPH in a large sample of women with a cesarean delivery before or during labor.

Materials and Methods

This is a historical retrospective cohort study of patients who underwent cesarean deliveries in a single tertiary referral center in Paris region, France. Two periods were compared according to whether PPH prophylaxis used oxytocin (period A from January 1, 2011 to December 31, 2012) or carbetocin (period B from May 1, 2013 to December 31, 2014).

PPH prevention is used according to a strict protocol in our obstetrics department, in accordance with international recommendations. The administration protocol during period A was 10 IU by IV infusion for 1 minute then 20 IU as an IV

drip infusion for 24 hours; during period B, it called for carbetocin, 100 μg, as a single IV injection.

This study included all women with a cesarean delivery before or during labor after 24-weeks of gestation (WG) during both periods. The Ethics Committee with jurisdiction over our institution has provided a written approval statement confirming that our study complies with all international and French ethical rules and laws.

Our purpose was to study the prevention of PPH due to atony. Therefore, we excluded pregnancies with significant risk factors for other causes of PPH, including placenta previa, coagulation disorders, thrombocytopenia < 150,000 platelets/mm^3, uterine artery lesions, myoma previa, placental abruption, or uterine rupture. Women who had a transfusion for severe anemia without PPH were also excluded.

Quantification of blood loss in cases of cesarean deliveries is always difficult, due to the incomplete collection of losses, the mixing of amniotic fluid with maternal blood, etc. To identify women who had PPH after a cesarean delivery, we recorded for each of her last hemoglobin (Hb) concentration measured before this delivery (always performed during the preceding month) and the Hb concentration between postoperative day 1 and 3. PPH was then defined as a decline in the Hb concentration of more than 2 g/dL, and severe PPH by a reduction in Hb > 4 g/dL.[12]

To take intraoperative transfusions into account, we estimated that a packed red blood cell unit increased the Hb concentration by 0.5 g/dL. One unit of packed red cells is expected to increase the Hb concentration by 1 g/dL in a patient of average height and weight.[13] We halved this figure to take into account the impact of hemodilution in pregnancy. Accordingly, we approximated the postoperative Hb of women with transfusions according to the following formula: "postoperative Hb−0.5 × number of blood cells transfused."

The factors studied included the main risk factors for PPH recognized in the literature and were extracted from the unit's computerized database: maternal age, geographical origin, BMI (body mass index), parity, previous cesarean or other uterine scar, singleton or multiple pregnancy, neonatal weight, prematurity, vascular disease (preeclampsia, hypertension [HTA], proteinuria), duration of labor, and use of oxytocin (for women who had labor). We reviewed the complete records of all women who had had PPH for additional data.

The clinical protocol for PPH, defined as persistent bleeding due to uterine atony, was to use uterotonics agent sulprostone (500-μg IV injection in 1 hour and another 500-μg IV injection in 5 hours). French guidelines do not include methylergometrine. The second-line therapies used were intrauterine tamponade with a Bakri balloon, vascular ligatures (either uterine or hypogastric), uterine artery embolization, compressive sutures, or hysterectomy.

Statistical Analysis

Student's t-tests or Chi-square tests were used as appropriate (according to the type of variable to be compared between the two groups). Fisher's exact test was used for qualitative variables when the conditions for applying the Chi-square test were

not met. The analysis was performed for the overall population and then stratified for women who had a cesarean before labor and those with one during labor. A logistic regression analysis was performed to adjust for confounding factors. Factors included in the logistic regression for the overall population and the population of women with a prelabor cesarean to study the risk of PPH were maternal age ($>$ or ≤ 35 years), BMI ($>$ or ≤ 30), country of birth, previous cesarean or uterine surgery, macrosomia, multiple pregnancy, preterm birth < 37 WG, multiparity, preeclampsia/gestational hypertension. Factors included in the logistic regression for the subgroup of women who had a cesarean during labor also included labor duration and the use of oxytocin in the model. A p-value < 0.05 was considered to be significant.

The statistical analysis was performed with Stata 13.0 software, TX.

Results

During the study period, 1,867 women had cesarean deliveries. After the exclusion of 71, the study included 1,796 women: 987 in period A and 809 in period B (►**Fig. 1**).

The populations of the two study periods were comparable for socioeconomic and obstetric characteristics, except that women in period A were 2 years older at this cesarean delivery and had a higher prevalence of previous cesareans and other uterine scars (43 vs. 38%, $p = 0.04$) (►**Table 1**).

Overall, 52% of the cesareans were performed before labor. Among them, 15% of the women had a PPH and 0.8% a severe PPH. Blood cell transfusion was required in 0.7% of the cases.

►**Table 2** reports the maternal and neonatal outcomes overall and according to timing of the cesarean. The PPH rate was lower in period B than in period A (13 vs. 17%,

Table 1 Maternal demographic and obstetrical characteristics

	Period A N = 987 (%)	Period B N = 809 (%)	p-Value
Age (mean ± SD)	34 ± 5.5	32 ± 5.5	< 0.01
BMI > 30	244 (25%)	219 (27%)	0.25
Country of birth			
France	284 (29%)	210 (26%)	0.50
North Africa	350 (35%)	308 (38%)	
Sub-Saharan Africa	229 (23%)	182 (22%)	
Others	118 (12%)	102 (13%)	
Previous cesarean or uterine surgery	422 (43%)	308 (38%)	0.04
Multiple pregnancy	71 (7%)	58 (7%)	0.95
Nulliparous	736 (75%)	596 (74%)	0.66
Preeclampsia or gestational hypertension	101 (10%)	80 (10%)	0.81
Preterm birth < 37 w of gestation	211 (21%)	158 (20%)	0.33
Birth weight (g) ± SD	3,018 ± 866	3,033 ± 928	0.72
Birth weight >4,000 g	80 (8.1%)	79 (9.8%)	0.22
Cesarean before labor	481 (49%)	454 (56%)	
Cesarean during labor	506 (51%)	355 (44%)	
Oxytocin during labor[a]	347/506 (69%)	247/355 (70%)	0.75
Length of labor (h)[a] ± SD	7.3 ± 4.3	8.3 ± 4.6	0.001

Abbreviations: BMI, body mass index; SD, standard deviation.
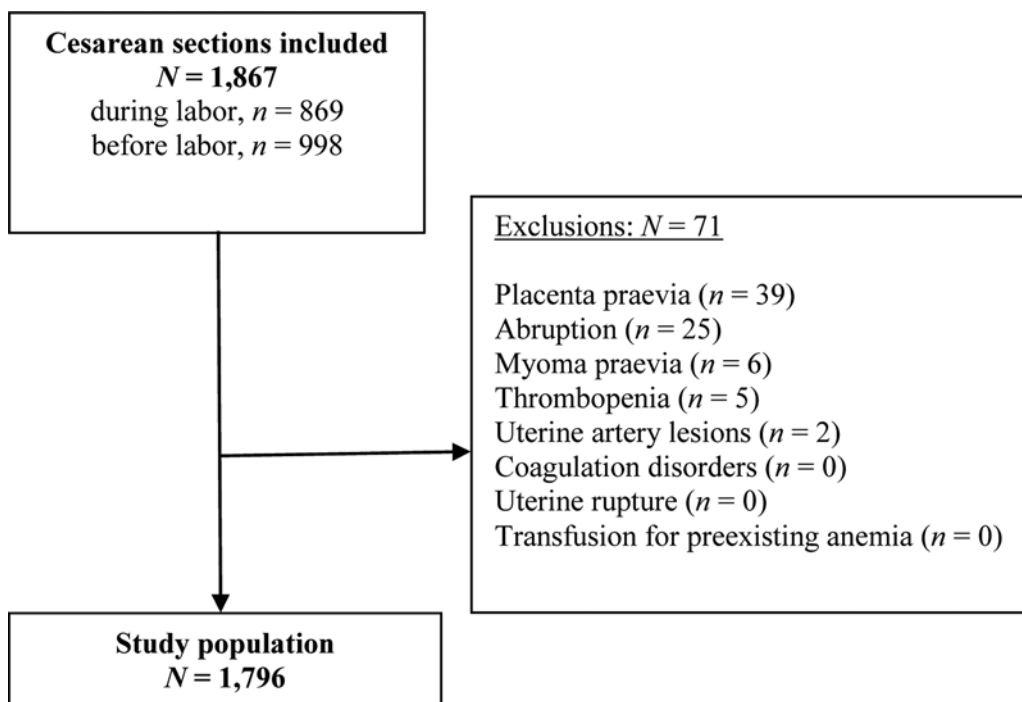[a]506 patients went into labor during period A and 355 during period B.

Cesarean sections included
N = 1,867
during labor, $n = 869$
before labor, $n = 998$

Exclusions: $N = 71$

Placenta praevia ($n = 39$)
Abruption ($n = 25$)
Myoma praevia ($n = 6$)
Thrombopenia ($n = 5$)
Uterine artery lesions ($n = 2$)
Coagulation disorders ($n = 0$)
Uterine rupture ($n = 0$)
Transfusion for preexisting anemia ($n = 0$)

Study population
N = 1,796

Fig. 1 Flowchart.

Table 2 Maternal and neonatal outcomes according to timing of cesarean

	Period A	Period B	OR	aOR (95% CI)
Overall population	*n = 987 (%)*	*n = 809 (%)*		
Postpartum hemorrhage	163 (17)	105 (13)	0.75 (0.58–0.98)	0.81 (0.61–1.06)[a]
Severe postpartum hemorrhage	11 (1)	4 (0.5)	0.44 (0.14–1.40)	0.47 (0.14–1.53)[a]
Use of additional uterotonics (sulprostone)	26 (3)	12 (1)	0.56 (0.28–1.11)	0.58 (0.28–1.17)[a]
Red blood cell transfusion	7 (0.7)	6 (0.7)	1.04 (0.35–3.13)	0.98 (0.31–3.06)[a]
Conservative surgery	6 (0.6)	1 (0.1)	0.21 (0.02–1.72)	–
Intrauterine tamponade	5 (0.5)	1 (0.1)	0.25 (0.03–2.12)	–
Embolization/Hysterectomy	0	0	–	–
Women who had a cesarean during labor	*n = 506 (%)*	*n = 355 (%)*		
Postpartum hemorrhage	107 (21)	64 (18)	0.82 (0.58–1.15)	0.77 (0.54–1.11)[b]
Severe postpartum hemorrhage	6 (1)	3 (0.8)	0.71 (0.18–2.86)	0.87 (0.18–4.12)[b]
Use of additional uterotonics (sulprostone)	15 (3)	8 (2)	0.75 (0.32–1.80)	0.79 (0.31–2.0)[b]
Red blood cell transfusion	4 (0.8)	2 (0.6)	0.71 (0.13–3.90)	–
Conservative surgery	3 (0.6)	1 (0.3)	0.47 (0.05–4.57)	–
Intrauterine tamponade	3 (0.6)	1 (0.3)	0.47 (0.05–4.57)	–
Embolization/Hysterectomy	0	0	–	–
Women who had a cesarean before labor	*n = 481 (%)*	*n = 454 (%)*		
Postpartum hemorrhage	56 (12)	41 (9)	0.75 (0.49–1.15)	0.79 (0.51–1.23)[a]
Severe postpartum hemorrhage	5 (1)	1 (0.2)	0.21 (0.02–2.81)	0.20 (0.02–1.81)[a]
Use of additional uterotonics (sulprostone)	11 (2)	4 (0.9)	0.38 (0.12–1.20)	0.35 (0.15–1.15)[a]
Red blood cell transfusion	3 (0.6)	4 (0.9)	1.42 (0.32–6.36)	–
Conservative surgery	3 (0.6)	0	–	–
Intrauterine tamponade	2 (0.4)	0	–	–
Embolization/Hysterectomy	0	0	–	–

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a]Model 1: Factors included were maternal age (> or ≤ 35 y), BMI (> or ≤ 30), country of birth, previous cesarean section or uterine surgery, macrosomia, multiple pregnancy, preterm birth < 37 wk of gestation, multiparity, preeclampsia/gestational hypertension.

[b]Model 2: Factors included were maternal age (> or ≤ 35 y), BMI (> or ≤ 30), country of birth, previous cesarean or uterine surgery, macrosomia, multiple pregnancy, preterm birth < 37 wk of gestation, multiparity, preeclampsia/gestational hypertension, as well as labor duration and the use of oxytocin.

respectively, odds ratio 0.75, 95% confidence interval [CI] 0.58–0.98). Nonetheless, the difference was no longer significant in the multivariate analysis (adjusted odds ratio: 0.81, 95% CI 0.61–1.06). Results were similar in the two subgroups —women with a cesarean before labor and those with cesarean during labor. Similar trends were shown for the rates of use of additional uterotonics, red blood cell transfusion, conservative surgery, and uterine tamponade. There was no arterial embolization or hysterectomy in any group.

Discussion

This study shows that a single injection of carbetocin is not superior to a standard protocol of an injection of oxytocin followed by 20 units in 24 hours for preventing PPH after a cesarean before or during labor.

The main strength of our study is the large number of women included. This is, by far, the largest study to date comparing oxytocin and carbetocin.[14–24] They were powered to detect a difference of 40 to 50% reduction of PPH (defined by 500 mL) in a population in which 17 to 18% of the women were treated by oxytocin. It seems unlikely to us that carbetocin could provide so much greater a benefit than oxytocin. Our study was designed to detect a 25% difference for the outcome, which seems much more realistic.

Another important strength of our study was the use of an objective method to quantify PPH. The quantification of blood loss is difficult, especially during a cesarean when blood loss is necessarily mixed with amniotic fluid. Moreover, during surgery, blood is also collected through compresses making the blood loss quantification even more difficult. Therefore, blood loss is frequently underestimated.[25,26] The difference between pre- and postoperative Hb concentration is the most objective approach for accurately evaluating blood loss after cesarean deliveries, and this method has frequently been used to evaluate blood loss after PPH.[27,28] In previous studies, the primary outcome used has often been subjective, such as uterine atony or the need for other uterotonics.[15,17–20,22,23]

In nonblinded trials, this might well have led to observation bias.

Another strength of the study was that all data were collected prospectively. Moreover, we had data on the management of labor in each case. We were thus able to adjust our results for intrapartum cesareans for labor duration and early use of oxytocin, both major risk factors for PPH.[29,30]

The main weakness of our study is that it was not a randomized double-blinded study, which would provide the highest level of proof for comparing the efficacy of carbetocin and oxytocin in preventing PPH. Another is that other factors might have changed between the two consecutive periods, in particular, changes in some members of the medical team in this university center. However, written medical protocols and a daily meeting reviewing all women who gave birth during the past 24 hours guarantee the continuity of medical care. There was no other change in protocols/type and dose of drugs for PPH management over the period of the study. Another weakness is the absence of a strict protocol for the timing of blood samples to calculate the difference between pre- and post-cesarean Hb. It is unlikely, however, that this could influence the results since nearly all maternal blood samples were taken the day after the cesarean.

This study is consistent with the most recent Cochrane analysis.[9] Similarly, other studies also using the change in Hb as an outcome found no significant difference between carbetocin and oxytocin.[18,22] One trial with protocols similar to ours (1 bolus of oxytocin of 5 IU followed by a maintenance dose of 20 IU for 8 hours vs. 100 µg carbetocin) and including 635 women also found similar PPH rates in the two arms.[20]

Some studies using the need for additional uterotonics as the main outcome have reported carbetocin to be superior.[18,20,31] This outcome, however, is highly subjective and not a direct maternal health end point. The use of other uterotonics varies quite substantially between obstetrics professionals, because it relies on the subjective evaluation of bleeding and the expected risk of failure of the prophylactic injection used. Similarly, some studies have chosen uterine atony or the need for uterine massage as end points, but they have the same drawbacks.[19,20]

Although not superior to oxytocin in preventing PPH, carbetocin allows the early removal of IV lines, which is a component of current protocols for enhanced recovery after cesarean deliveries.[32] Some cost-benefit analyses have shown that reductions in retreatment, staffing requirements, transfusions, and potential medication errors mitigate carbetocin's higher initial cost.[33,34] Therefore, from a pharmacoeconomic perspective, carbetocin may be cost-effective as prophylaxis against PPH in cesarean deliveries.

In conclusion, even in this large sample, carbetocin is not superior to oxytocin in preventing PPH. It does provide the advantage of requiring a single injection.

Conflict of Interest
None.

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