

Effects of Oxytocin and Carbetocin on Haemostatic Variables in Pregnant Women after Cesarean Section

Testa S¹, Paoletti O¹, Dellanoce C¹, Bassi L¹, Zimmermann A¹, Morandini R¹, Tala M¹, Catalano F¹, Mammoliti D² and Riccardi A²

¹Haemostasis and Thrombosis Center, Department of Laboratory Medicine, AO Istituti Ospitalieri, Cremona, Italy

²Obstetrics and Gynaecology Division, AO Istituti Ospitalieri, Cremona, Italy

*Corresponding author: Testa S, MD, Hemostasis and Thrombosis Center, AO Istituti Ospitalieri, Viale Concordia 1, 26100 Cremona, Italy, Fax: +390372405457, Tel: +390372405453, E-mail: s.testa@ospedale.cremona.it

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Abstract

Background: Uterine atony is the first cause of haemorrhage at delivery. To prevent post partum major bleeding uterotonic prophylactic drugs are commonly used after caesarean section. Few studies showed an haemostatic activation after oxytocin infusion while no data are available on carbetocin.

Aim: Our study aimed to evaluate if two uterotonic agents -carbetocin and oxytocin- provoke a different activation of the coagulation system in a clinical condition already known to be associated with significant changes of haemostasis. Moreover, the incidence of bleeding and thromboembolic events were evaluated.

Method: 50 consecutive women undergoing elective cesarean section, without previous bleeding or thrombotic events were enrolled. 25 women were treated with a standard 2 hours oxytocin IV infusion (10IU) and 25 women with carbetocin 100 µgr IV. Blood samples for coagulation profile (PT, aPTT, vWF:Ag, D-Dimer), blood cell count were collected before delivery (T0), 1 hour (T1) and 24 hours (T2) after drug infusion. We also studied thrombin generation, as expression of the balance between hyper- and hypo-coagulability, to obtain informations about the haemostatic assessment and its modifications in the two study groups.

Results: No major bleeding and thromboembolic events were observed in the two patient groups. Blood cell count, coagulation screening test didn't show significant differences between the two study treatments. An increase of thrombin generation was observed in carbetocin group, without, however, reaching a statistical significance.

Conclusion: This observational study shows a similar action of carbetocin compared to oxytocin on haemostatic system. Even if additional trials are necessary to confirm these preliminary data, this study suggests that carbetocin could be as safe as oxytocin in term of haemostatic action on patients already known to be at risk not only for bleeding but also for thromboembolic events in the post-partum and puerperium.

Keywords: Carbetocin; Oxytocin; Cesarean section; Uterotonic agents; Coagulation test; Thrombin generation test

Introduction

Postpartum haemorrhage (PPH) is the major cause of maternal morbidity and mortality [1]. Primary PPH is defined as a blood loss more than 500 ml after vaginal delivery and more than 1000 ml after caesarean section, occurring within the 24 hours following birth [1]. Even if multiple PPH predisposing factors are well known, such as a previous PPH, pre-eclampsia, coagulation defects, multiple gestation and caesarean section, in nearly one-third of cases no risk factors are identified [2]. However, uterine atony is the first cause of haemorrhage at delivery [3].

To prevent post partum major bleeding different strategies are adopted and many uterotonic prophylactic drugs are commonly used after caesarean section [4,5]. Oxytocin, a peptide hormone chemically synthesized in a biologically active form, is currently used as uterotonic agent of first choice, showing a good safety profile and decreasing PPH incidence of about 40% [6]. On the other hand a significant limitation for its clinical use is represented by its short half-life (4-10 min), that requires continuous intravenous infusion or multiple intramuscular injections. To improve drug management carbetocin, another uterotonic agent, has been introduced in clinical practice. Carbetocin is a longer acting uterotonic agent, with a half-life of 40 min, rapid onset of action, prolonged efficacy (about 1 hour) and similar safety profile [7].

Several studies have compared efficacy and safety of both uterotonic agents [7-13]. A recent Cochrane review of published randomized trial showed no significant clinical differences in term of PPH incidence but carbetocin demonstrated a reduction in the need for additional uterotonic requirements [14].

Oxytocin, as synthetic hormone, has multiple central and peripheral actions [15]. It acts on human reproductive system also inducing uterine myometrial contractions to favour labour and delivery and shows haemostatic changes on the fibrinolytic system, on platelet aggregation and on coagulation factor activity [16].

Haemostatic changes during pregnancy and puerperium have been well described [17], but very few observations, limited on oxytocin, are available about the effect on the coagulation system at delivery [18,19]. Recently, two different studies showed a dose-dependent action on the activation of the haemostatic system, measured using tromboelastography, after oxytocin infusion [16,20]. To date no data are available on carbetocin haemostatic effects in comparison with oxytocin and possible differences on the coagulation system between the two drugs cannot be excluded "a priori" also considering the more prolonged uterotonic action of carbetocin.

To evaluate the haemostatic assessment, in addition to the common coagulation test, recently the thrombin generation test (TGT) has been proposed as global test that measure the kinetic of clot formation and expresses the whole plasmatic balance between hyper- and hypocoagulability [21]. TGT evaluates the whole kinetic of thrombin generation both during the initial phase of thrombin formation as during the phase of thrombin inactivation. Compared to the common coagulation test, such as prothrombin time (PT) and activated partial thromboplastin time (aPTT), that are affected by many variables, TGT is considered more reliable in term of individual haemostatic assessment and better correlated with clinical outcomes [22,23]. Higher thrombin generation has been described in woman with pre-eclampsia [24].

To assess if women treated with carbetocin or oxytocin show differences in haemostatic profile, in addition to haemoglobin measurements used to control blood loss, we evaluated coagulation screening test (PT and aPTT), von Willebrand factor (vWF:Ag) as marker of endothelial activation, D-dimer as marker of fibrin formation and thrombin generation (TGT). The incidence of bleeding and thromboembolic events were registered in the two study groups from delivery to the end of puerperium.

Materials and Methods

Design

This is a prospective, open-label, observational trial conducted during year 2012.

Patients

50 consecutive women, aged between 22-41 years, undergoing elective cesarean section, were enrolled in the study. The first 25 women were treated with oxytocin while the following 25 with carbetocin. All women gave their written informed consent to participate to the study. The patients' characteristics are summarized in Table 1.

	OXYTOCIN Mean (min-max)	CARBETOCIN Mean (min-max)
Age	34 (22-41)	32 (26-39)
Body Mass Index (Kg/m ²)	29 (25-35)	28 (23-34)
Parity	1.0 (0-2)	1.0 (0-2)
Gestational age at delivery	39 ± 2	39 ± 2
Ethnicity	18 caucasian 4 asian 3 afroamerican	19 caucasian 3 asian 3 afroamerican
Previous cesarean section	4/25	5/25

Table 1: Main clinical characteristics of two patient population

Exclusion criteria were: age < 18 years, previous bleeding or thrombotic events, hypertension, pre-eclampsia, cardiac, liver or renal diseases, general anaesthesia, pregnancy-related complications (multiple gestation, placenta praevia, placental abruption).

25 women (control group) were treated with a standard 2-h oxytocin intravenous infusion (10IU), while the 25 women of the case group were treated with a single intravenous injection of 100 µgr carbetocin [13]. We evaluated the incidence of major and minor bleeding and venous thromboembolism (VTE) at delivery and during puerperium through a structured follow up conducted by the Haemostasis and Thrombosis Center. Follow up included two visits at discharge and at the end of puerperium [25]. Major bleeding included haemoglobin decrease of 2 g per deciliter or more, transfusion of 2 or more units of red cells or whole blood, retroperitoneal or intracranial bleeding or bleeding in critical organ, bleeding associated to death. Minor bleeding were considered all clinically relevant episodes not qualified as major [26]. VTE included deep and superficial vein thrombosis, objectively diagnosed by compression ultrasound, pulmonary embolism by computed-tomography lung scan, and thrombosis at other sites (i.e., cerebral or abdominal veins) by computed-tomography, magnetic resonance or magnetic resonance angiography.

Blood samples

Blood samples for coagulation test, TGT and blood cell count were collected just before delivery by cesarean section (T0), 1 hour (T1) and 24 hour (T2) after drug infusion. Venous blood samples, obtained with minimal stasis, were collected using 21g needle into 0.109M citrate Becton Dickinson coagulation tubes (BD, USA). Blood samples were immediately centrifuged at 2000g for 20 minutes and poor platelet plasma (PPP) deeply frozen and stored at -80° before analysis.

Laboratory test

Blood cell count was assessed on automated analyser XE-5000 (Sysmex, Norderstedt, Germany). All coagulation tests were performed on frozen plasma within 3 months from blood collection.

Prothrombin time ratio (PT), activated partial thromboplastin time ratio (aPTT), von Willebrand factor antigen (vWF:Ag), D-dimer (DD) were performed on STA-R (Stago, France) using Stago reagents.

TGT was performed with a full automated commercial assay (Technothrombin TGA, Technoclone, Wien, Austria) on Ceveron a instrument, (Technoclone, Wien, Austria) and lag time (min), peak (nM), velocity (nM/min) and endogenous thrombin potential (ETP) were evaluated. ETP results were expressed as nM.min. The activation of coagulation in TGT was obtained by adding the commercial reagent TECHNOTHROMBIN TGA RC Low (Technoclone, Wien, Austria), containing 5µmol tissue factor (TF).

Statistics

Data were expressed as mean ± standard deviation (SD) and tested for normal distribution. Statistical analysis was performed by using Student's t-test for continuous variables. P-value less than 0.05 (p<0.05) was considered as statistically significant. Analysis was conducted comparing the two study groups at the different time points.

Results

The study was conducted during year 2012. A total of 50 consecutive women were enrolled and assigned to oxytocin or carbetocin treatment. The two patient populations were similar for main clinical characteristics, as shown in Table 1. Major bleeding and thromboembolic events were evaluated at delivery, at hospital discharge and at the end of puerperium (6 weeks after delivery). No major events were observed in the two groups.

Haemoglobin levels, platelet count, screening coagulation test (PT, aPTT), D-dimer and vWF:Ag, at T1 and T2, were similar in the two groups (Table 2) and no statistical differences were found.

	OXYTOCIN (M ± SD)			CARBETOCIN (M ± SD)			P
	T0	T1	T2	T0	T1	T2	
Hb (g/dL)	11.3 ± 1.33	10.3 ± 1.58	10.2 ± 1.25	11.1 ± 0.93	11.1 ± 1.23	10.4 ± 1.38	n.s.
PLTs (n°/mmc)	218 ± 47.8	221 ± 45.07	252 ± 42.16	229 ± 46.2	226 ± 44.8	256 ± 45.3	n.s.
aPTT (Ratio)	0.99 ± 0.05	1.0 ± 0.07	1.05 ± 0.07	0.94 ± 0.08	0.89 ± 0.10	1.02 ± 0.10	n.s.
PT (Ratio)	0.98 ± 0.06	1.04 ± 0.08	0.99 ± 0.06	0.95 ± 0.06	1.0 ± 0.05	0.96 ± 0.06	n.s.
D-Dimer (ng/mL)	1.73 ± 0.65	1.97 ± 0.83	2.30 ± 0.24	1.98 ± 0.35	2.04 ± 0.61	2.46 ± 0.32	n.s.
vWF:Ag (U/dL)	278 ± 44	254 ± 53	301 ± 46	265 ± 95	257 ± 98	272 ± 77	n.s.

Table 2: Laboratory parameters in the two study groups at: pre-treatment (T0), one hour (T1) and 24 hours (T2) after uterotonic infusion (p values are calculated comparing the two study groups at T1 and T2)

In respect to TGT study no differences were observed at T0, confirming the homogeneity between the two study populations (Table 3). At T1 and T2 increases in ETP, in TGT peak and TGT velocity were observed in the carbetocin group compared with oxytocin treated patients, without, however, reaching a statistical significance.

	OXYTOCIN (M ± SD)			CARBETOCIN (M ± SD)			P
	T0	T1	T2	T0	T1	T2	
Blood collection time							
Time Lag (min)	1.9 ± 0.7	2.1 ± 1.2	1.7 ± 0.6	1.8 ± 0.8	2.0 ± 0.8	1.6 ± 0.8	n.s.
Peak (nM)	697,7 ± 128	743 ± 138	656 ± 191	675 ± 172	740 ± 120	696 ± 200	n.s.
Velocity (nM/min)	252 ± 106	263 ± 102	248 ± 100	272 ± 114	299 ± 129	254 ± 132	n.s.
ETP (nM.min)	3287 ± 443	3588 ± 582	3649 ± 662	3336 ± 581	3811 ± 662	3701 ± 544	n.s.

Table 3: Thrombin generation results in the oxytocin and carbetocin study group. p values are calculated comparing the two study population at T1 and T2

Discussion

PPH is a severe partum related complication frequently associated to undetected risk factors [1] and therefore uterotonic agents are commonly adopted to prevent critical hemorrhages after cesarean section. Oxytocin, a syntetic peptide hormone, is frequently used as uterotonic agent and more recently also carbetocin, an oxytocin analogue, has been introduced in clinical practice because of its longer half-life that can improve patient management.

This study aimed to evaluate if the two uterotonic agents provoke a different activation of the haemostatic system in a clinical condition already known to be at risk not only for bleeding but also for thromboembolic events [27-29]. As known, pregnancy is a physiological condition associated with changes of the haemostatic system that globally cause an hypercoagulable condition [17] and all additional endogenous or exogenous variables should be investigated to assess possible interactions with the coagulation cascade. At our knowledge, no previous studies on a direct comparison of coagulation profile during carbetocin and oxytocin treatment in elective cesarean section have been published.

Our evaluation have shown no clinical differences in term of both early or late bleeding and thromboembolic complications between the two uterotonic agents, confirming the similar effect of the two drugs as already previously reported [14].

Laboratory test, used as marker of haemostatic impairment, didn't show differences in term of haemoglobin concentration, platelet count and coagulation profile suggesting a similar action of both carbetocin and oxytocin on the coagulation system. Moreover, to better define the global haemostatic potential and evaluate possible differences between the two study populations, we performed TGT analyzing the different phases. The two uterotonic agents, characterized for their different half-life, showed a similar action in term of thrombin activation, with no significant increase in patients treated with carbetocin, as measured 1 hour and 24 hours after infusion. This study showed that the increased and prolonged carbetocin uterotonic activity, compared with oxytocin as recently demonstrated [10], is not associated with a significant different activation of the coagulation system, although we observed an increasing trend in ETP, TGT peak and TGT velocity at T1 and T2.

Strengths of our study are the homogeneity of the two study groups, the quality of patient's samples and the evaluation of carbetocin effects on the haemostatic system, firstly described. However some limitations deserve to be addressed. First our study wasn't a double blind randomized study and we didn't include a no treated control group. Moreover, pregnancy and delivery are conditions associated to main haemostatic changes and, consequently, we cannot clearly distinguish the drug effects on haemostasis from physiological variations at delivery and in the immediate post-partum period after cesarean section. However we highlighted a slight, but not significant, increase in the hypercoagulable response in carbetocin group compared with oxytocin.

Conclusion

In conclusion, even if large and prospective trial are necessary to confirm these preliminary data, this observational study suggests that carbetocin acts similarly as oxytocin in term of haemostatic action on patients already known to be at risk not only for bleeding but also for thromboembolic events in the post-partum and puerperium.

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