Carbetocin versus Oxytocin in Prevention of Postpartum Hemorrhage Following Elective Cesarean Section in Low Risk Population

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ABSTRACT

***Objective**: The aim of this study is to compare the efficacy of carbetocin with that of oxytocin in the prevention of uterine atony after elective CS.*

***Study design**: Double-blind randomized clinical trial.*

***Setting**: Kasr Al Aini teaching university hospital, Cairo University, Cairo, Egypt.*

***Population**: A total of 100 pregnant women undergoing elective CS with spinal anesthesia were enrolled in the study. Women were randomly divided into 2 equal groups. One group received a single intravenous dose of 100 µg of carbetocin, and the other group received 10 IU of oxytocin infusion over 2 hours.*

***Main outcome**: The proportion of patients requiring additional uterotonic interventions for uterine atony.*

***Results**: Significantly higher proportion of patients in the oxytocin group required additional uterotonic agents [34 (68%) in the oxytocin group versus 4 (8%) in the carbetocin group, p: <0.001]. Patients in the oxytocin group had 9 times the risk of requiring additional uterotonics as carbetocin group (RR: 0.11, p: <0.001, 95% CI 0.045- 0.307). The mean drop in hemoglobin 24 hours after CS was significantly lower in the carbetocin group (0.74 ± 0.38 g/dl versus 0.92 ± 0.38 g/dl, p: 0.021). No significant changes occurred in the hemodynamic status in either group. Adverse effects were similar in both groups.*

***Conclusion**: carbetocin appears to be more effective than oxytocin infusion in attaining proper uterine contractility following elective CS with the same safety profile.*

***Key words**: carbetocin, oxytocin, post partum hemorrhage, elective cesarean section.*

INTRODUCTION

Hemorrhage remains a major cause of maternal morbidity and mortality in the developed and developing world. Fourteen million cases of postpartum hemorrhage (PPH) occur worldwide each year, with a case-fatality rate of 1%; this is a total of 140.000 women (1).

PPH is excessive blood loss after childbirth, and has been defined as blood loss >500 ml within 24 h of normal vaginal delivery, or > 1000 ml after cesarean section (CS) (2). PPH is most often attributed to uterine atony (3).

The diversity of potential triggers makes the occurrence and severity of PPH difficult to predict. Many cases have no identifiable risk factors (4). PPH in cases of delivery programmed by CS has a quite real gravity. Thus the need for decreasing the rate of PPH is today a concern for all the obstetric units (5).

By stimulating uterine muscle tone, prophylactic uterotonics reduce the incidence of PPH (3).

Which uterotonic drug is preferable for prophylactic use is still being debated (6). Because ergometrine can stimulate smooth muscle contraction and vasoconstriction, it may raise blood pressure, and rarely lead to coronary artery spasm (7). While misoprostol has been shown to be effective in preventing PPH at the community level (8), its efficacy is lower than that achieved by oxytocin and is associated with side effects, including shivering and pyrexia (9).

Oxytocin is the most widely used uterotonic agent and has been shown to be effective in reducing the incidence of PPH (10).

Intravenous oxytocin has a short half life (4-10 minutes); therefore the potential advantage of an oxytocin infusion at CS is in maintaining uterine contractility throughout the surgical procedure and immediate postpartum period, when most hemorrhage occurs (11).

Various newer uterotonic agents have been evaluated (12). Carbetocin (an oxytocin analogue) was prepared to be protected from aminopeptidase and disulfidase cleavage (13). These changes of the oxytocin molecule resulted in prolongation of uterotonic activity of carbetocin[14].

The side-effect profile of carbetocin, in comparison with that of syntometrine (a mixture of 5 IU oxytocin and 0.5 mg ergometrine), may prove to be advantageous (10).

In this study, we aimed to compare the efficacy of a single 100 µg intravenous dose of carbetocin with 10 IU of oxytocin, given as intravenous infusion over 2 hours, in prevention of uterine atony after elective CS in pregnancies at low risk for PPH.

PATIENTS AND METHODS

This prospective randomized clinical trial was conducted at Kasr El Aini University teaching hospital, Cairo University, Egypt. A total of 100 pregnant women attending the delivery unit in the period from January 2012 to July 2013 were enrolled in the study.

Patients were eligible if they were scheduled for an elective CS through a lower-segment transverse incision under spinal anesthesia. Only term pregnancies (after 37 weeks) with singleton fetuses were included. Patients were excluded from the study if they have any known risk factor for PPH (severe anemia, antepartum hemorrhage, polyhydramnios, multiple gestation or history of PPH). Patients having any medical disorder contraindicating the use of carbetocin (hepatic disease, renal disease, serious cardiovascular disorder, preeclampsia, eclampsia or epilepsy) were also excluded from the study.

Patients meeting the above inclusion criteria were counseled about the study, and an oral informed consent was obtained.

Full history including age, parity, and gestational age as calculated from the first day of the last menstrual period, and the indication for CS was obtained from each participant. Blood pressure was measured, and weight and height were also measured and hence body mass index (BMI) could be calculated as weight in kilograms (kg)

divided by height in meters squared (m^2). Abdominal examination and auscultation of the fetal heart sounds were carried out. Abdominal ultrasound was performed for all participants for confirmation of the fetal life, maturity (confirmed by a head circumference measuring ≥37 weeks, presence of amniotic fluid turbidity, and the presence of an ossific center of the femur measuring at least 5mm), and for exclusion of multiple gestation, polyhydramnios, placenta previa or the presence of uterine fibroids.

Before initiation of the study, randomization was accomplished using the sealed envelopes method. A series of consecutively numbered opaque envelopes (from 1 to 100) was generated. The sealed envelopes were made available to the assistant nurse present in the operation room and opened. The drug with the same number as that in the envelope was given by the anesthetist, after cord clamping.

Patients in the carbetocin group were given 1 ml of carbetocin (Pabal, 1ml ampoule-100 µg/ml, Ferring pharmaceuticals, Kiel, Germany) containing 100 µg of carbetocin, as a single direct intravenous (IV) injection, and patients in the oxytocin group were given 10 international units (IU) of oxytocin (Syntocinon, Novartis Pharma AG, Basel, Switzerland) into 500 ml of lactated ringer solution as IV infusion over 2 hours. Additional uterotonic drugs were asked for by the surgeon, who was also blinded to the type of drug given, if uterine atony is suspected or diagnosed. Type and dosage of additional uterotonics used, in addition to the time needed to add such uterotonics, were recorded.

The primary outcome was the need for additional uterotonic interventions in the 24 hours following delivery to maintain proper uterine tone. Secondary outcomes included time needed to add uterotonic agents, effect of both drugs used on vital signs, drop in hemoglobin level and change of platelet count on the next day of delivery, occurrence of primary postpartum hemorrhage (defined by blood loss of more than 1000 ml, determined by number of soaked towels used during CS, with each towel being soaked with 150 ml of blood), need for blood transfusion, adverse effect of both drugs used and their effect on liver and kidney functions.

Maternal blood pressure was measured before CS and checked immediately after giving the uterotonic drug, then 30 minutes and 60 minutes later. Pulse was measured before CS and rechecked 60 minutes after the end of CS. Blood was sampled for hemoglobin and platelet count before CS and then rechecked 24 hours after CS. For the safety of both drugs used on liver and kidney functions, blood was withdrawn for AST, ALT and creatinine 24 hours after the end of CS.

At the end of CS and before transfer to the postpartum ward, each patient was asked about some side effects of the used uterotonic drugs as: abdominal pain, back pain, headache, nausea, heat sensation, metallic taste and pruritus. Presence of signs as flushing, sweating, tremors or vomiting was also recorded. The patients were evaluated again for symptoms and signs in the postoperative ward.

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing normally distributed data and Mann Whitney *U* test for independent samples when not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used

instead when the expected frequency is less than 5. *P* values < 0.05 were considered statistically significant.

RESULTS

The baseline characteristics were similar in both groups (table 1). All patients had an elective transverse lower segment CS after 37 weeks' gestation. The main indication for CS in both groups was repeat CS.

Table 1: Baseline Characteristics of Both Groups

	Carbetocin Group n= 50	Oxytocin Group n= 50	*P* value
Age (years)	27.1 ± 3.9	26.6 ± 4.6	0.54
BMI (kg/m^2)	25.4 ± 2.2	25.1 ± 2.3	0.62
Gestational Age at Time of CS (weeks)	37.7 ± 1.1	38.1 ± 1.1	0.08
Gravidity	1.92 ± 1.0	2.26 ± 1.6	0.22
Parity	0.72 ± 0.8	0.82 ± 1.1	0.62
History of Miscarriage	0.2 ± 0.49	0.46 ± 0.95	0.91
No. of Previous CS	0.6 ± 0.19	0.58 ± 0.21	0.86
Indications for CS [n (%)]:			
-Repeat CS	30 (60%)	29 (58%)	
-Precious baby (pregnancy by ICSI)	12 (24%)	11 (22%)	0.06
-Malpresentations	6 (12%)	5 (10%)	
-Others	2 (4%)	5 (10%)	
Baseline Hemodynamic Measures:			
-Pulse (bpm)	79.7 ± 4.4	79.8 ± 5.1	0.93
-Systolic blood pressure (mmHg)	114.1 ± 4.9	113.3 ± 6.2	0.49
-Diastolic blood pressure (mmHg)	69.0 ± 5.5	69.2 ± 5.9	0.84
-Baseline hemoglobin level (g/dl)	10.9 ± 0.9	10.6 ± 0.9	0.06
-Baseline platelet count (10^3/dl)	287.8 ± 50.6	278.9 ± 60.6	0.42

Values are presented as mean ± SD, Significance <0.05

A total of 38 patients (38%) required additional oxytocics, 4 (8%) in the carbetocin group and 34 (68%) in the oxytocin group, this difference was statistically significant. Patients in the oxytocin group had 9 times the risk of requiring additional uterotonics as carbetocin group (RR: 0.11, *p*<0.001, 95% CI 0.045- 0.307).

Of the 4 patients in the carbetocin group who required additional uterotonic agents to attain proper uterine contractility, one patient required so during CS and the

other 3 patients received the additional oxytocic in the postpartum ward during the first 3 hours postoperatively. For the oxytocin group, 13 patients required the additional oxytocic intraoperatively and 21 required so in the postpartum ward within 3 hours postoperatively. All patients had proper uterine tone thereafter until discharge from hospital.

The mean dose of additional oxytocin required in non-responders to carbetocin was 20 ± 9.3 IU (range 10-40 IU), and for oxytocin was 17 ± 8.7 IU (range 10-50 IU).

Two patients in the carbetocin group and one patient in the oxytocin group received one ampoule of ergometrine (Methergine, 1ml ampoule, containing 0.2 mg methyl ergometrine maleate per ml, Novartis Pharma AG, Basel, Switzerland) for each. One patient in each group received 4 tablets of misoprostol (Misotac tablets, containing 200 µg of misoprostol, Sigma Pharmaceuticals, Egypt) rectally.

The median time to add extra uterotonic was 93 minutes in the carbetocin group and 50 minutes in the oxytocin group *(p*<0.001).

Two patients developed primary postpartum hemorrhage, one in each group. Both cases occurred while the patient was still in the operation room before abdominal closure. Only the patient in the oxytocin group needed blood transfusion.

The mean drop in hemoglobin level 24 hours following CS was 0.74 ± 0.38 g/dl in the carbetocin group and 0.92 ± 0.38 g/dl in the oxytocin group, the difference was statistically significant *(p*0.021). However, change in platelet count was not significantly different between both groups [2.64 ± 74.3 (10^3/dl) for the carbetocin group and 0.78 ± 3.97 (10^3/dl) for the oxytocin group, *p*=0.86] (table 2).

Table 2: Primary and Secondary Outcomes:

	Carbetocin Group n= 50	**Oxytocin Group n= 50**	***P* value**	**RR**	**95% CI**
Patients who required additional oxytocics [n (%)]	4 (8%)	34 (68%)	<0.001	0.11	0.045 to 0.307
Time elapsed for second dose of oxytocic (min.)*	93	50	<0.001		
Drop in hemoglobin (g/dl)**	0.74 ± 0.38	0.92 ± 0.38	0.021	MD: -0.18	-0.33 to -0.279
Drop in platelet count (10^3/dl)**	2.64 ± 74.3	0.78 ± 3.97	0.86	MD: 1.8	-19.04 to 22.76

*RR: relative risk, MD: mean difference, CI: confidence interval *: median, **: mean ± SD*

All cases that experienced improper uterine contractility and required additional oxytocics responded well to the pharmacological interventions, no surgical interventions were needed.

Immediately after administration of either uterotonic drug, there was a trivial non-significant elevation of systolic (SBP) and diastolic blood pressure (DBP) (a fraction of mmHg) in both groups that returned to preoperative values within 60 minutes. Also, there was non-significant change in maternal pulse before and after CS.

No effect of either drug used was found on liver and kidney functions which were within normal ranges when evaluated postoperatively, and no significant difference was found between both groups.

Adverse effects of both drugs were not significantly different between both groups. Abdominal pain was encountered in about one third of each group. It was mild in all cases and was perceived after cessation of the effect of spinal anesthesia. About one fifth of each group experienced headache, but most probably this symptom was related to spinal anesthesia rather than a side effect of either drugs. Other symptoms and signs were encountered in sporadic cases in both groups (tables 3 and 4).

Table 3: Hemodynamic and Biochemical Effects of Carbetocin and Oxytocin

	Carbetocin group n= 50	Oxytocin group n= 50	*P* value	95% CI
Repeated SBP Measurements (mmHg):				
-Immediately after administration of the uterotonic drug	114.8 ± 4.9	113.9 ± 6.5	0.749	113.0-115.0
-30 minutes later	114.7 ± 4.6	113.6 ± 5.9		
-60 minutes later	114.4 ± 3.9	113.4 ± 6.0		
Repeated DBP measurements (mmHg):				
-Immediately after administration of the uterotonic drug	69.3 ± 5.5	69.7 ± 5.6	0.847	68.4-70.3
-30 minutes later	69.4 ± 5.5	69.4 ± 5.4		
-60 minutes later	69.4 ± 5.6	69.4 ± 5.6		
Change in Maternal Pulse (bpm)	-0.66 ± 2.05	-0.54 ± 1.58	0.74	MD -0.12 (-0.857 to 0.607)
Postoperative Biochemical Values:				
AST (mg/dl)	22.46 ± 3.4	21.7 ± 3.7	0.34	
ALT (mg/dl)	21.7 ± 3.4	22.0 ± 2.9	0.62	
Creatinine (mg/dl)	0.56 ± 0.56	0.57 ± 0.53	0.75	

Values are presented as mean ± SD

Table 4: Adverse Effects of Carbetocin and Oxytocin

	Carbetocin group n= 50	Oxytocin group n= 50	*P* value	RR (95% CI)
Symptoms [n (%)]:				
-Abdominal pain	16 (32%)	15 (30%)	0.5	1.06 (0.594-1.915)
-Back pain	7 (14%)	5 (10%)	0.3	1.4 (0.476-4.117)
-Headache	10 (20%)	12 (24%)	0.4	0.83 (0.379-1.750)
-Nausea	7 (14%)	6 (12%)	0.5	1.16 (0.422-3.227)
-Metallic taste	4 (8%)	4 (8%)	0.6	1.0 (0.265-3.778)
-Heat sensation	5 (10%)	5 (10%)	0.5	0.83 (0.272-2.555)
-Pruritus	3 (6%)	3 (6%)	0.6	1.0 (0.212-4.719)
Signs [n (%)]:				
-Flushing	6 (12%)	6 (12%)	0.6	1.0 (0.346-2.891)
-Sweating	1 (2%)	1 (2%)	0.7	1.0 (0.064-15.548)
-Tremors	3 (6%)	2 (4%)	0.5	1.5 (0.262-8.595)
-Vomiting	5 (10%)	4 (8%)	0.5	1.25 (0.356-4.385)

DISCUSSION

Postpartum hemorrhage is one of the major contributors to maternal mortality and morbidity worldwide (15). Systematic reviews have concluded that active management of third stage of labour, particularly the prophylactic use of uterotonic agents, can significantly decrease the incidence of PPH (16, 17).

This study assessed the efficacy of carbetocin, a long-acting synthetic oxytocin analogue, in preventing uterine atony following elective CS as compared to oxytocin.

Borruto et al, with the use of a sensitive colorimetric method, assessed intraoperative blood loss. They reported that the mean blood loss in patients treated with oxytocin was 30 ml higher than in patients treated with carbetocin (5). However, this is an impractical method for assessing the drug efficacy. We preferred to use "the need for additional uterotonic to implement proper uterine contractility" as a more clinically relevant parameter to assess the efficacy of the drug.

In our study, the surgeon was blinded to the drug given to produce uterine contraction following delivery of the baby, and he is the best one to decide if there is a need to add more uterotonic doses in an unbiased manner.

In this study, the need for additional uterotonic agents to produce proper uterine tone was significantly higher in the oxytocin group compared to the carbetocin group. These results are consistent with previous studies that reported significantly higher need for additional uterotonics in the oxytocin group compared with the carbetocin group (5, 12, 18, 19).

In our study, the median time needed to add uterotonic agents was significantly higher in the carbetocin group than in the oxytocin group. This can be explained by the longer half life of carbetocin as compared with oxytocin. This was also similar to Dansereau et al, who reported longer time needed to intervention in the carbetocin group compared to the oxytocin group (19).

Carbetocin is well tolerated, and the monitoring up to 24 hours after the administration showed a great hemodynamic stability, comparable with that of oxytocin (5). A study conducted in 2011 compared the hemodynamic effects of carbetocin with that of oxytocin. The authors reported that at about 30-40 seconds after administration of either drug: the heart rate increased (17.98 ± 2.53 bpm for the oxytocin group, and 14.2 ± 2.45 bpm for the carbetocin group). At the same time interval, systolic blood pressure decreased (-26.8 ± 2.82 mmHg for oxytocin versus -22.98 ± 2.75 mmHg for carbetocin). However, the authors reported that both heart rate and systolic blood pressure recovered slowly to baseline values asymptomatically (20). In our study, the heart rate and systolic and diastolic blood pressure changes before and after CS were trivial and clinically not significant, most probably because we rechecked heart rate 60 minutes following CS and rechecked blood pressure 30 and 60 minutes after administration of either drug when all measurements had returned to baseline readings.

For the minimal effect of carbetocin on blood pressure, Reyes and Gonzalez studied the efficacy of carbetocin versus oxytocin in preventing PPH in patients with severe preeclampsia. The authors reported that carbetocin was as effective as oxytocin in the prevention of PPH in women with severe preeclampsia, and that carbetocin had a safety profile similar to that of oxytocin and was not associated with the development of oliguria or hypertension in the cohort study. They concluded that carbetocin is an appropriate alternative to oxytocin for the prevention of PPH in women with severe preeclampsia (21).

In our study, adverse effects for carbetocin were similar for frequency and nature to those observed with oxytocin. Some adverse effects observed in this study as flushing, heat sensation and metallic taste were observed previously during clinical pharmacology studies with carbetocin (22), and probably represent side effects of the drug. However, nausea and vomiting observed in the postpartum ward may be due to the use of meperidine as analgesic after the cessation of the effect of anesthesia. Also, headache may be related to spinal anesthesia rather than a true side effect of the uterotonic drug. Moreover, abdominal pain may be due to uterine contractility rather than a side effect of carbetocin or oxytocin. It is rather a sign that the drug is effective on uterine tonicity and the required objective is achieved.

A recent study evaluated the safety and adverse effects of carbetocin versus oxytocin after CS. The authors reported that side effects were comparable between both groups, however, the mean ± SD of postoperative pain in the day of surgery in carbetocin group was significantly lower than in oxytocin group and remained significant till the third day after CS (23).

In an overview on all available uterotonics for PPH prevention, Gizzo et al performed a systematic review of the literature and reported these results: oxytocin is the first choice for PPH prophylaxis. Ergot alkaloids, syntometrine and prostaglandins, are second-line uterotonic agents. Misoprostol is not

effective as oxytocin but it may be used when the latter is not available. Carbetocin should be used instead of continuous oxytocin infusion in elective CS for PPH prevention and to decrease the need for therapeutic uterotonics. They concluded that prophylactic use of uterotonics should be individualized (24).

Because of the cost of carbetocin (20 times that of oxytocin in Egypt), its use would not be available in settings where resources are scarce.

In conclusion: a single dose of carbetocin is more effective than oxytocin infusion in maintaining uterine tone following elective CS with comparable safety and side effects. However, its use is limited by its higher cost.

REFERENCES

1. Estimates developed by WHO, UNICEF, and UNFPA. Geneva: Department of Reproductive Health and Research, World Health Organization, 2004. WHO. Maternal mortality in 2000.
2. WHO guidelines for the management of postpartum hemorrhage and retained placenta. World Health Organization, 2009.
3. Cotter AM, Ness A, Tolosa JE. Prophylactic oxytocin for the third stage of labour. Cochrane Database Syst Rev 2001. DOI 10.1002/14651858.CD001808.
4. Arulkumaran S, Mavrides E, Penney GC. Prevention and management of postpartum hemorrhage. Royal College of Obstetricians and Gynecologists Green-top Guidelines 52, 2009.
5. Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. Arch Gynecol Obstet 2009; 280: 707-712.
6. Elbourne DR. Prophylactic oxytocin vs ergot derivatives in third stage of labour: pregnancy and childbirth module. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, editors. Cochrane database of systematic reviews. Oxford: Update Software; 1994. Disk Issue No. 1. Review No. 03000.
7. Carey M. Adverse cardiovascular sequelae of ergometrine. Br J Obstet Gynecol 1993; 100: 865.
8. Derman RJ, Kodkany BS, Goudar SS et al. Oral misoprostol in preventing postpartum hemorrhage in resource-poor communities: a randomized controlled trial. Lancet 2006; 368(9543): 1248-1253.
9. Glümezoglu AM, Villar J, Hofmeyr GJ. Prostaglandins for postpartum hemorrhage (Cochrane review). The Cochrane Library 2004, 3.
10. Chong YS, Su LL, Arulkumaran S. Current strategies for the prevention of postpartum hemorrhage in the third stage of labour. Curr Opin Obstet Gynecol 2004; 16: 143-150.
11. Sheehan SR, Montgomery AA, Carey M, McAuliffe FM, Eogan M, Gleeson R, Geary M, Murphy DJ. Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective cesarean section: double-blind, placebo controlled, randomized trial. BMJ 2011; 343: d4661 doi: 10.1136/ bmj.d4661.
12. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. Carbetocin versus oxytocin for the prevention of postpartum hemorrhage following cesarean section: the results

of a double-blind randomized trial. BJOG 2010; 117: 929-936.

13. Flegel M, Lebl M. From oxytocin to carbetocin. Journey from development to production. In: Peptides, M. Flegel (ed), Geneva, Kenes International 2005; pp.117-122.
14. Engstrem T, Barth T, Melin P, Vilhardt H. Oxytocin receptor binding and uterotonic activity of carbetocin and its metabolites following enzymatic degradation. Eur J Pharmacol 1998; 355: 203-210.
15. Wandabwa J, Doyle P, Todd J, et al. Risk factors for severe postpartum hemorrhage in Mulago hospital, Kampala, Uganda. East Afr Med J 2008; 85: 64-71.
16. Prendivillie W, Elbourne D, Chalmers I. The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. Br J Obstet Gynecol 1988; 95:3-16.
17. Prendivillie WJ, Elbourne D, McDonalds S. Active versus expectant management in the third stage of labour (Cochrane review). In: The Cochrane Library. Oxford, UK: Update Software; 2003.
18. Boucher M, Horbay GLA, 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: 202-207.
19. 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: 670-676.
20. 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 cesarean delivery: a randomized trial. BJOG 2011 Oct; 118(11): 1349-1356.
21. Reyes OA, Gonzalez GM. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double-blind randomized controlled trial. J Obstet Gynaecol Can 2011 Nov; 33(11): 1099-1104.
22. Hunter DJ, Schulz P, Wasenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther 1992; 52: 60-67.
23. De Bonis M, Torricelli M, Leoni L, Berti P, Ciani V, Puzzutiello R, Severi FM, Petraglia F. Carbetocin versus oxytocin after cesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum hemorrhage. J Matern Fetal Neonatal Med 2012 Jun; 25(6): 732-735.
24. Gizzo S, Patrelli TS, Gangi SD, Carrozini M, Saccardi C, Zambon A, Bertocco A, Fagherazzi S, D'Antona D, Nardelli GB. Which uterotonic is better to prevent the postpartum hemorrhage? Latest news in terms of clinical efficacy, side effects, and contraindications: a systematic review. Reprod Sci 2013 Jan 7 [Epub ahead of print].