Prophylactic Carbetocin Improves Outcome of Cesarean Section in Parturient High-Risk for Postpartum Hemorrhage

Hany El-kallaf

Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt
Hanyelkallaf@yahoo.com

Abstract: **Objectives**: Evaluation of the clinical yield of prophylactic carbetocin versus oxytocin single shoot injection in parturient high-risk for developing postpartum hemorrhage (PPH) undergoing cesarean section (CS). **Patients & Methods**: The study included 150 parturient with mean age of 27.6±2.1 years and having at least one high-risk for development of PPH. Patients were randomly allocated into two equal groups to receive slow intravenous injection of single dose of carbetocin 100 µg (Group C) or oxytocin 5 IU (Group O) at time of umbilical cord clamping. Uterine tone was assisted and rated according to the extent of indentation by finger pressure using a 5-point scale. Obstetric hemorrhage was calculated according to postoperative packed cell volume (PCV) deficit. Rescue uterotonic was provided in form of slow injection of oxytocin 5 IU diluted to 3 ml with normal saline. The frequency of rescue uterotonic used since administration of study dose till 24-hrs after surgery was reported. Postoperative hemoglobin concentration and deficit, amount of intraoperative and postoperative blood loss and need for blood transfusion were recorded. **Results**: Both drugs provided successful uterotonic effect; 107 patients (71.3%) had grade-4 uterus and only 3 patients (2%) in group O had grade 0 and one uteri with non-significant difference in favor of group C. Twenty-six patients (17.3%) required rescue uterotonic; 7 in group C and 19 in group O with significantly higher frequency of patients required rescue uterotonic in group O. Postoperative PCV and hemoglobin concentration were significantly lower compared to preoperative estimates in both groups, with significant difference in favor of group C. Thirty-four patients (22.7%) developed side effects of used medications with non-significant difference in favor of group C. **Conclusion**: Single bolus injection of carbetocin reduced the frequency and severity of postpartum hemorrhage in high risk women assigned for elective cesarean section. It also spares the use of rescue uterotonic and blood transfusion with minimal drug-related side effects.

[Hany El-kallaf Prophylactic Carbetocin improves outcome of cesarean section in parturient high-risk for postpartum hemorrhage. *J Am Sci* 2012;8(8):517-522]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 79

Keywords: Oxytocin, Carbetocin, postpartum hemorrhage, high-risk women, cesarean section

1. Introduction

Caesarean section is one of the most commonly performed major operations in women throughout the world. These operations have escalated over the past four decades to between 20% and 30% in most developed countries with increasing frequency in less developed countries. Operative morbidity includes hemorrhage, anemia, risks of transfusion, hysterectomy, and in severe cases, maternal death. Obstetric hemorrhage is the leading cause of maternal mortality worldwide. The commonest cause of primary PPH (PPH <24 hrs following delivery) is uterine atony, **(Martin *et al.*, 2010)**

Postpartum hemorrhage (PPH) is defined by the WHO as postpartum blood loss in excess of 500 ml, **(WHO, 2003)**. However, as other definitions have been suggested, blood loss more than 1000 ml was classified as severe PPH. PPH has an incidence of 19% in nulliparous deliveries in The Netherlands. The diagnosis encompasses excessive blood loss from the uterus, cervix, vagina and perineum, **(Dildy *et al.*, 2002, Bais *et al.*, 2004)**. PPH increased 26% between 1994 and 2006 from 2.3% to 2.9%. The increase primarily was due to an increase in uterine atony, from 1.6% to 2.4%. The increase in PPH could not be explained by changes in rates of cesarean delivery, vaginal birth after cesarean delivery, maternal age, multiple birth, hypertension, or diabetes mellitus **(Callaghan *et al.*, 2010)**.

Oxytocin is a small peptide hormone with multiple sites of action in human body. It regulates a large number of reproduction-related processes in all species. One of the classical biological actions mediated by the posterior pituitary hormone oxytocin is contraction of the uterus at parturition. The ability of oxytocin to stimulate uterine contractility is achieved by multiple mechanisms involving sarcoplasmic reticulum Ca^{2+} release and sensitization of the contractile apparatus to Ca^{2+} **(Shmygol *et al.*, 2006)**.

Carbetocin (1-deamino-1-carba-2-tyrosine (O-methyl)-oxytocin) is the parent metabolite of oxytocin. Apart from the parent compound, two metabolites were identified namely desGlyNH2-carbetocin (carbetocin metabolite I) and desLeuGlyNH2-carbetocin (carbetocin metabolite II). Both carbetocin, carbetocin metabolite I and carbetocin metabolite II displayed binding affinities to the myometrial oxytocin receptor of a similar magnitude as oxytocin. All three analogues bound to the myometrial

vasopressin V1 receptor, albeit with much lower affinities than to the oxytocin receptor. Only carbetocin bound to the renal vasopressin V2 receptor though the binding affinity was very low **(Stymiest *et al.*, 2005, Akerlund, 2006, Steckler *et al.*, 2012)**.

The current prospective study aimed to evaluate the clinical yield of prophylactic carbetocin versus oxytocin single shoot injection in parturient high-risk for developing postpartum hemorrhage undergoing cesarean section.

2. Patients and Methods

The present prospective study was conducted at Armed Forces Hospital, King Abdul Aziz, Airbase, Dhahran, KSA since Jan 2010 till Jan 2012. After obtaining written fully informed patients' and husband' consent, the study included 150 non-laboring women with singleton pregnancy and were high-risk for developing postpartum hemorrhage. All enrolled patients were clinically examined for demographic and constitutional data, obstetric history with special regard to the number of previous sections. On day of surgery, all parturient had abdominal ultrasonography for assurance of diagnosis and evaluation of fetal condition and gave blood samples for complete blood counting.

Patients were randomly, using sealed envelops, allocated into two equal groups to receive slow intravenous injection of single dose of carbetocin 100 µg (Group C) or oxytocin 5 IU (Group O). For equalization of the outcome and allow for patients' cooperation, all patients received epidural anesthesia. Also, all patients had low transverse CS.

As soon as the umbilical cord was clamped immediately after delivery, the study drug diluted to 3 ml with normal saline was slowly injected over 30 seconds. Assisted spontaneous placental delivery was used. Uterine tone was assisted before drug administration, immediately after delivery of the placenta and then every 5 minutes until abdominal closure began. Uterine tone was rated according to the extent of indentation by finger pressure using a 5-point scale with 0 indicate soft boggy uterus and 4 indicted rock hard tetanic uterus.

Major obstetric haemorrhage was defined as calculated blood loss of >1000 cc based on the difference between the preoperative and postoperative packed cell volume (PCV), and was calculated as follows: estimated blood volume × (preoperative PCV − postoperative PCV)/preoperative PCV and estimated blood volume = booking weight (kg) × 85, **(Shook *et al.*, 2003)**.

Standard monitoring was used, including noninvasive arterial blood pressure measurement, electrocardiography, and pulse oximetry. Blood pressure measurements were taken every minute starting from the commencement of surgery. The 3 readings immediately before study drug administration were averaged to calculate the baseline and after the bolus, the blood pressure was recorded every minute for 5 minutes to diagnose hypotension if occurred. Hypotension was defined as a decrease in systolic blood pressure ≥20% from baseline within 5 minutes of the bolus administration and was treated with the rapid infusion of lactated Ringer's solution and IV boluses of ephedrine. Heart rate changes (at least 10 bpm) or rhythm were also reported and managed. Patients were observed immediately after the bolus about the presence of any side effects especially facial flushing, headache, nausea and/or vomiting.

Rescue uterotonic was provided in form of slow injection of oxytocin 5 IU diluted to 3 ml with normal saline. The frequency of rescue uterotonic used since administtration of study dose till 24-hrs after surgery was reported. Postoperative hemoglobin concentration and postoperative hemoglobin deficit, amount of intraoperative and postoperative blood loss and need for blood transfusion or need to return to the operating room because of bleeding were recorded.

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using paired Z-test and Chi-square test. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. *P* value <0.05 was considered statistically significant.

3. Results

The study included 150 parturient with mean age of 27.6±2.1; range: 22-33 years. Only 10 were primipara, while 140 women were multipara with mean parity of 2.1±1.2 (0-5). All enrolled women were high-risk for development of postpartum hemorrhage; 38 women had multiple gestations, 32 women had macrosomic fetus, 25 had posterior placenta pravea, 23 women had polyhydramnios, 23 had past history of PPH and 9 women had chorioamnionitis. All patients passed smooth intraoperative course with a mean operative time of 49.6±6.2; range: 35-65 minutes. There was non-significant difference between both groups as regards constitutional, obstetric or operative data, (Table 1).

Both drugs provided successful uterotonic effect; 107 patients (71.3%) had uteri of grade-4 and only 3 patients (2%) in group O had uteri of grade zero and one with non-significant difference (X^2=1.455, p>0.05) in favor of group C, (Table 1, Fig. 1). Twenty-six patients (17.3%) required rescue uterotonic; 7 in group C and 19 in group O with significantly (X^2=3.23, p<0.05) higher frequency of patients required rescue uterotonic in group O.

Postoperative PCV and hemoglobin concentration were significantly lower compared to

preoperative estimates in both groups. Mean decrease of PCV and percentage of hemoglobin deficit and mean calculated blood loss were significantly lower in group C compared to group O. Five patients required blood transfusion; 2 in group C and 3 in group O with non-significantly (X^2=0.496, p>0.05) higher frequency of patients required blood transfusion, (Table 2, Fig. 2).

Thirty-four patients (22.7%) developed side effects of used medications; 13 in group C (17.3%) and 21 in group O (28%) with non-significant (X^2=1.346, p>0.05) difference in favor of group C. Hypotension was the most frequent event that was reported in 28 patients, followed by headache in 19 patients, facial flushing in 14 patients and tachycardia in 10 patients. Postoperative nausea and vomiting was reported only in 2 patients. The total number of reported side effects was 74 events for a frequency of 2.2 events/patient; so some patients developed postoperative side effects in varied combination, (Table 3).

Table (1): Studied patients data

		Group C	Group O	Total
Age (years)		28±2 (23.6-32)	27.1±2.1 (22-33)	27.6±2.1 (22-33)
Body weight (kg)		85.5±3.5 (80-96)	87.1±2.9 (82-94)	86.3±3.3 (80-96)
Body height (Ht)		167.1±3.2 (162-176)	169±3.9 (161-178)	168±3.7 (161-178)
Body mass index (BMI)		30.6±1.5 (26.1-36.6)	30.5±1.4 (27.7-35.1)	30.6±1.5 (26.1-36.6)
Gravidity		3.2±1 (1-5)	3.4±1.3 (1-6)	3.3±1.2 (1-6)
Parity		2±0.9 (0-4)	2.2±0.9 (0-5)	2.1±1.2 (0-5)
Gestational age (wk)		37±1.9 (34-40)	36.6±2.1 (35-39)	36.8±2 (34-40)
Postpartum hemorrhage risk factor	Multiple gestation	18 (24%)	20 (26.7%)	38 (25.4%)
	Macrosomia	17 (22.7%)	15 (20%)	32 (21.3%)
	Posterior PP	14 (18.7%)	11 (14.7%)	25 (16.7%)
	History of PPH	10 (13.3%)	13 (17.2%)	23 (15.3%)
	Polyhydramnios	12 (16%)	11 (14.7%)	23 (15.3%)
	Parity >5	0	0	0
	Chorioamnionitis	4 (5.3%)	5 (6.7%)	9 (6%)
Neonatal weight (mg)		3778.4±279 (3200-4500)	3496.9±443 (2900-4900)	3637.6±528 (2900-4900)
Duration of surgery (min)		51±6.7 (40-65)	48.3±5.3 (35-60)	49.6±6.2 (35-65)

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis

Table (2): Postoperative hematological changes reported in both groups

		Group C	Group O	Statistical significance
PCV	Pre	0.377±0.024	0.376±0.026	Z=1.070, p>0.05
	PO	0.315±0.019*	0.284±0.023*	Z=7.472, p<0.001
	Pre-PO	0.062±0.01	0.092±0.017	Z=7.409, p<0.001
Blood volume (=BW x 85)		7289.6±302	7374.6±225.5	Z=1.792, p>0.05
Blood loss (ml)		452±78.6	678.4±125.7	Z=7.409, p<0.001
Hemoglobin concentration	Pre (gm/dl)	11.9±0.44	11.8±0.49	Z=0.458, p>0.05
	PO (gm/dl)	10.4±0.4*	9.8±0.7*	Z=5.637, p<0.001
	% of deficit	12.4±3.1	17.2±6.1	Z=5.259, p<0.001

Data are presented as mean±SD, PCV: packed cell volume, Pre: preoperative, PO: postoperative, BW: body weight

Table (3): Frequency of side effects reported in both groups

	Group C	Group O	Total
Hypotension	11 (14.7%)	18 (24%)	29 (19.3%)
Tachycardia	3 (4%)	7 (9.3%)	10 (6.7%)
Facial flushing	5 (6.7%)	9 (12%)	14 (9.3%)
Headache	8 (10.7%)	11 (14.7%)	19 (12.7%)
Nausea	0	1 (1.3%)	1 (0.7%)
Vomiting	0	1 (1.3%)	1 (0.7%)
Total	27	47	74

Data are presented as numbers; percentages are in parenthesis

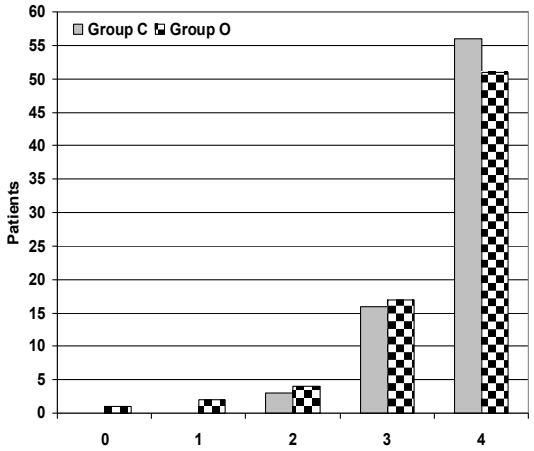

Fig. (1): PAtients' distribution according to intraoperative uterine tone grade

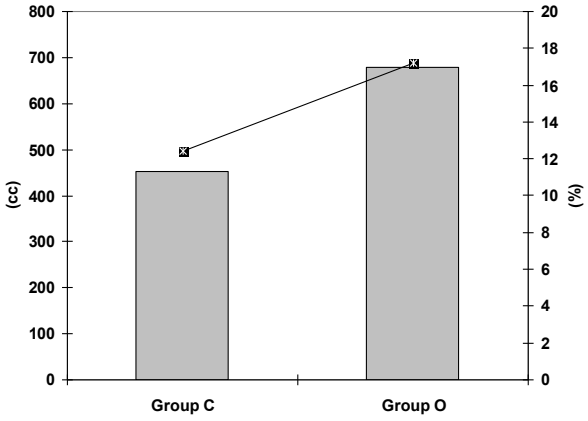

Fig. (2): Mean blood loss and percentage of hemoglobin deficit recorded in both groups

4. Discussion

The study included 150 parturient high-risk for developing PPH, all underwent elective cesarean section without trial for vaginal delivery so as to minimize the risk of PPH and other complications. In line with such policy, **Holm *et al.* (2012)**, reported that compared with intended vaginal delivery, planned caesarean delivery was associated with a reduced risk of severe postpartum hemorrhage indicated by use of red blood cell transfusion in total population including high-risk, low-risk nulliparous women and in women with a previous section.

Single bolus injection of carbetocin provided significant control of uterine bleeding manifested as significantly lower hemoglobin and PCV deficit with significantly lower blood loss. Moreover, it improved uterine contractile status manifested as significantly higher frequency of patients had uteri of score 4 and no patient had uteri scored zero or one with significant reduction of consumption of rescue uterotonic.

Carbetocin provided better hemodynamic stability compared to oxytocin manifested as minimal frequency of patients developed hypotension and tachycardia, despite the difference being non-significant versus oxytocin. Subsequently, carbetocin induced fewer headaches and facial flushing thus provided more safety profile compared to oxytocin.

These findings go in hand with that previously reported in literature; **Borruto *et al.* (2009)** documented that carbetocin makes possible to obtain, with a single IV injection, results equivalent to those of oxytocin on the maintenance of uterine tonicity and the limitation of blood losses, in the peri- and in the post-operative period, during a delivery by CS. **Attilakos *et al.* (2010)** found carbetocin is associated with a reduced use of additional oxytocics.

Posadas Robledo (2011), evaluated the usefulness of carbetocin to prevent uterine bleeding complications and maternal deaths and assessed the benefits, effectiveness and side effects, and reported that hemoglobin showed a reduction of 17% after delivery, and only 17.5% of patients required blood transfusion and no side effects were documented. **Reyes & Gonzalez (2011)**, documented that carbetocin is an appropriate alternative to oxytocin for the prevention of PPH in women with severe pre-eclampsia and considering that it appears not to have a major hemodynamic effect in women with severe pre-eclampsia and that it uses a lower volume per dose than oxytocin, it should be considered a valid option in the management of the third stage of labor in women with hypertensive disorders of pregnancy. **Moertl *et al.*(2011)**, reported that both oxytocin and carbetocin have comparable hemodynamic effects and are uterotonic drugs with an acceptable safety profile for prophylactic use and minimal differences in the recovery phase beyond 70 seconds are in keeping with the fact that carbetocin has an extended half-life compared with oxytocin.

Moreover, **De Bonis *et al.* (2012)**, reported that a single carbetocin injection is efficacious and safe for the maintenance of uterine tone and on the limitation of blood losses, in peri- and in postoperative period; in addition, carbetocin was able to reduce pain perception during postoperative days thus improving quality life of women. **Su *et al.* (2012)**, retrospectively tried to determine if the use of oxytocin agonist is as effective as conventional uterotonic agents for the prevention of PPH and suggested that 100 µg of intravenous carbetocin is more effective than oxytocin for preventing PPH in women undergoing caesarean deliveries and is associated with less blood loss compared to syntometrine in the prevention of PPH for women who have vaginal deliveries and is associated with significantly fewer adverse effects.

As regards dosage form of oxytocin, the current study used single bolus intravenous dosage without

oxytocin infusion to be repeated according to requirement as a rescue uterotonic. In support of this option, **Macrus *et al.* (2010)** tried to determine dosages and routes of administration of oxytocin during cesarean section in Germany using hospital survey questionnaires and found that 85.3% of departments administer oxytocin as a bolus and a bolus of 1-3 IU is administered at 51.8% of departments, 5-9 IU at 20.9%, 10 IU at 11.6%, and 12-40 IU at 1.8% of departments. **Kim *et al.* (2011)**, found bolus-continuous injection of oxytocin resulted in more hemodynamic changes than continuous injection, bolus-continuous injection had a greater effect on uterine contraction and two IU bolus-continuous injection showed lower hemodynamic changes than in the five IU bolus-continuous injection. **Dyer *et al.*(2011)**, suggested that the effective dose of oxytocin for prophylaxis against uterine atony during caesarean delivery is significantly lower than the historically used 5-10 IU dose and slow administration of small bolus doses minimizes maternal hemodynamic disturbance.

The reported significantly higher clinical yield of single bolus carbetocin versus oxytocin could be attributed to the difference in pharmacokinetics and pharmacodynamics of oxytocin and its metabolite carbetocin. In support of such attribution; **Engstrøm *et al.*(1998)**, experimentally reported that carbetocin was found to have agonistic properties on isolated myometrial strips and it was found to exert this effect through generation of inositol phosphates, as is the case for oxytocin. However, maximal contractile effect of carbetocin was approximately 50% lower than that of oxytocin (2.7 g compared to 5.22 g) and EC50 (the concentration of a drug that gives half-maximal response) was approximately ten times higher (48±8.2 nM compared to 5.62±1.22 nM). Additionally, the well documented extended half-live of carbetocin, approximately 4-10 times longer than oxytocin, **(Borruto *et al.*, 2009, Rath *et al.*, 2009, Moertl *et al.*, 2011)** is another factor and could be attributed to the stronger receptor affinity for carbetocin.

It could be concluded that single bolus injection of carbetocin reduced the frequency and severity of postpartum hemorrhage in high risk women assigned for elective cesarean section. It also spares the use of rescue uterotonic and blood transfusion with minimal drug-related side effects.

Corresponding author
Hany El-kallaf
Department of Obstetrics & Gynecology, Faculty of Medicine, Benha University, Egypt
Hanyelkallaf@yahoo.com

References

1. Akerlund M: Targeting the oxytocin receptor to relax the myometrium. Expert Opin Ther Targets. 2006; 10(3):423-7.
2. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, Hunt LP, Draycott T: Carbetocin versus oxytocin for the prevention of postpartum hemorrhage following caesarean section: the results of a double-blind randomised trial. BJOG. 2010; 117(8):929-36.
3. Bais JM, Eskes M, Pel M, *et al.* Postpartum hemorrhage in nulliparous women: incidence and risk factors in low and high risk women. A Dutch population-based cohort study on standard (≥500 ml) and severe (≥1000 ml) postpartum hemorrhage. Eur J Obstet Gynecol Reprod Biol 2004; 115:166-72.
4. 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(5):707-12.
5. Callaghan WM, Kuklina EV, Berg CJ: Trends in postpartum hemorrhage: United States, 1994-2006. Am J Obstet Gynecol. 2010; 202(4):353.e1-6.
6. De Bonis M, Torricelli M, Leoni L, Berti P, Ciani V, Puzzutiello R, Severi FM, Petraglia F: Carbetocin versus oxytocin after caesarean section: similar efficacy but reduced pain perception in women with high risk of postpartum hemorrhage. J Matern Fetal Neonatal Med. 2012; 25:732-5.
7. Dildy GA III. Postpartum hemorrhage: new management options. Clin Obstet Gynecol 2002; 45:330-44.
8. Dyer RA, Butwick AJ, Carvalho B: Oxytocin for labor and caesarean delivery: implications for the anaesthesiologist. Curr Opin Anaesthesiol. 2011; 24(3):255-61.
9. Engstrøm 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(2-3):203-10.
10. Holm C, Langhoff-Roos J, Petersen K, Norgaard A, Diness B: Severe postpartum hemorrhage and mode of delivery: a retrospective cohort study. BJOG. 2012 Feb 8. doi: 10.1111/j.1471-0528.2011.03267.
11. Kim TS, Bae JS, Park JM, Kang SK: Hemodynamic effects of continuous intravenous injection and bolus plus continuous intravenous injection of oxytocin in cesarean section. Korean J Anesthesiol. 2011; 61(6):482-7.
12. Marcus HE, Fabian A, Lier H, Dagtekin O, Böttiger BW, Teschendorf P, Petzke F, Valter M, Spöhr F: Survey on the use of oxytocin for

cesarean section. Minerva Anestesiol. 2010; 76(11):890-5.
13. Martin JA, Hamilton BE, Sutton PD, Ventura MA, Mathews TJ, Kirmeyer S, et al. Births: final data for 2007. Natl Vital Stat Rep 2010; 58:24.
14. 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(11):1349-56.
15. Posadas Robledo FJ: Carbetocin use to prevent obstetric hemorrhage. Ginecol Obstet Mex. 2011; 79(7):419-27.
16. Rath W: Prevention of postpartum hemorrhage with the oxytocin analogue carbetocin. Eur J Obstet Gynecol Reprod Biol. 2009; 147(1):15-20.
17. Reyes OA, Gonzalez GM: Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe pre-eclampsia: a double-blind randomized controlled trial. J Obstet Gynaecol Can. 2011; 33(11):1099-104.
18. Sheehan SR, Montgomery AA, Carey M, McAuliffe FM, Eogan M, Gleeson R, Geary M, Murphy DJ; ECSSIT Study Group: Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial. BMJ. 2011 Aug doi: 10.1136/bmj.d4661.
19. Shmygol A, Gullam J, Blanks A, Thornton S: Multiple mechanisms involved in oxytocin-induced modulation of myometrial contractility. Acta Pharmacol Sin. 2006; 27(7):827-32.
20. Shook PR, Schultz JR, Reynolds JD, Spahn TE, DeBalli P. Estimating blood loss for cesarean section: how accurate are we? Anesthesiology 2003;98:1
21. Steckler D, Naidoo V, Gerber D, Kähn W: Ex vivo influence of carbetocin on equine myometrial muscles and comparison with oxytocin. Theriogenology, 2012 Apr 24, Epub ahead of print.
22. Stymiest JL, Mitchell BF, Wong S, Vederas JC: Synthesis of oxytocin analogues with replacement of sulfur by carbon gives potent antagonists with increased stability. J Org Chem. 2005; 70(20):7799-809.
23. Su LL, Chong YS, Samuel M: Carbetocin for preventing postpartum hemorrhage. Cochrane Database Syst Rev. 2012; 4:CD005457.
24. World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors. Integrated Management of Pregnancy and Childbirth 2003.

522