Al-Azhar International Medical Journal

Volume 3 | Issue 5 Article 10

5-1-2022

Carbetocin versus combination of oxytocin and ergometirne for the preventional of post-partum hemorrhage following cesarean section

Abdeldaym Mohammed
Department of Obstetrics & Gynecology, Faculty of Medicine, Al-Azhar University,
drdemo15@gmail.com

Abd El-Azeem Ahmed
Department of Obstetrics & Gynecology, Faculty of Medicine, Al-Azhar University,
abdelazeemahmed55@yahoo.com

Mofeed Mohammad
Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University, Egypt,
mofeedmohammad87@yahoo.com

How to Cite This Article

Mohammed, Abdeldaym; Ahmed, Abd El-Azeem; and Mohammad, Mofeed (2022) "Carbetocin versus combination of oxytocin and ergometirne for the preventional of post-partum hemorrhage following cesarean section," *Al-Azhar International Medical Journal*: Vol. 3: Iss. 5, Article 10.
DOI: https://doi.org/10.21608/aimj.2022.107672.1680

OPEN AIMJ ORIGINAL ARTICLE

Obstetrics & Gynecology

Carbetocin versus combination of oxytocin and ergometirne for the preventional of post-partum hemorrhage following cesarean section

Abdeldaym Sayed Mohammed [1,*] M.B.B.Ch, Abd El-Azeem Mohammad Ahmed [1] MD, Mofeed Fawzy Mohamed [1] MD

**Corresponding Author:*

Abdeldaym Sayed Mohammed

drdemo15@gmail.com

Received *for publication November 23, 2021;* ***Accepted*** *May 27, 2022;* ***Published online*** *May 27, 2022.*

doi: *10.21608/aimj.2022.107672.1680*

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Authorship: *All authors have a substantial contribution to the article.*

ABSTRACT

Background: Postpartum hemorrhage (PPH) is the most basic reason of maternal morbidity and mortality worldwide. Uterine atony is the most common reason of immediate heavy PPH.

Aim of the work: To compare of I.V carbetocin as a long acting oxytocic drug and a combination of intraoperative oxytocin and ergometrine I.V for inhibition of PPH after cesarean delivery.

Patients and methods: a randomized prospective study that was carried out at Alhwamdya General Hospital. After receiving written consent, 100 women were chosen from the obstetrics and gynecology outpatient clinic between May 2020 and February 2021.

Results: In terms of maternal adverse impacts , there was a substantial change among the two groups , 28 % of population of Oxytocin & ergometrine group experienced elevated systolic /diastolic blood pressure more than 10 mmHg from preoperative reading ,while patiants who received carbetocin only show no signficant rise in blood pressure. There was a substantial change in estimated blood loss among the two groups, favouring the carberocin group. Other than that, there was no important change between the two groups in terms of the frequency of PPH, the requirement for extra uterotonic medications, or the incidence of other side impacts like headache.

Conclusion: According to the findings, simultaneous intravenous carbetocin is beneficial in preventing atonic post-partum haemorrhage after caesarean surgery. It's just as effective as a mix of I.V syntocinon and ergometrine. Compared to the combination of syntocinon and ergometrine, carbetocin alone had less side effects on the mother, such as high blood pressure, nausea, and vomiting.

Keywords: *Carbetocin; Oxytocin and ergometirne; Post-partum hemorrhage; Cesarean section.*

INTRODUCTION

Excessive bleeding after or after delivery, known as (PPH), is a potentially dangerous condition that is one of the major reasons of maternal death and morbidity across the world. Due to irreparable shock, maternal death frequently happens within a short amount of time. As a result, avoiding PPH is crucial to improving women's health care [1, 2.]

The usage of an uterotonic drug, early cord clamping, and controlled cord traction are 3 parts of active controlling of the third stage of labor. Nowadays, oxytocin and ergometrine are the most often utilized pharmacologic drugs. When compared to oxytocin only, syntometrine (a mix of oxytocin and ergometrine) is related with a notably important decrease in the rate of PPH for blood losing greater than 500 mL but less than 1000 ml. [3]

The unwanted side impacts of nausea, vomiting, and increased blood pressure in previously normotensive women have been widely reported as being significantly greater in syntometrine recipients. In the third stage of labor, prophylactic use of ergot alkaloids is useful in lowering blood loss and PPH. [3, 4]

Syntometrine was also linked to a greater rate of retained placenta when compared to oxytocin, according to some investigators. Syntometrine, furthermore, has been linked to serious side effects such coronary artery spasm and intracerebral hemorrhage. [5, 6]

Furthermore, syntometrine cannot be used in 10percent to 20percent of the obstetric community due to co-existing medical diseases like as pre-eclampsia and cardiac problem. Following that, the women are given oxytocin, as it is less efficient in preventing PPH due to its brief onset of action. Prostaglandins like misoprostol and carboprost, as well as other options, have been investigated. Carbetocin is an agonist-like, long-acting synthetic octapeptide counterpart of oxytocin. Carbamate's clinical and pharmacological qualities are comparable to those of oxytocin, which is found in nature. Carbetocin, like oxytocin, attaches to oxytocin receptors on uterine smooth muscle, generating cyclic uterine contractions, higher incidence of existing contractions, and increased uterine tone. [7]

Intravenous doses of carbetocin generated tetanic uterine contractions within 2 minutes, which lasts 6 minutes followed by rhythmic contractions for

another hour, according to pharmacokinetic studies. Tetanic contractions began just under 2 minutes after the intramuscular injection, continued around 11 minutes, and were accompanied by rhythmic contractions for another 2 h. There was a substantial difference in the period of activity following intramuscular carbetocin versus intravenous carbetocin. [8]

When compared to oxytocin, carbetocin causes a greater uterine effect regarding both amplitude and frequency of contractions when given postpartum. The longer time of im carbetocin therapy compared to im oxytocin treatment may be beneficial. It appears to have less GIT and cardiovascular adverse effects than syntometrine and other ergot alkaloids. [8]

The goal of our randomized study is to compare the superiority, efficiency and adverse effects of I.V carbetocin as a long acting oxytocic analouge versus a combination of intraoperative oxytocin & ergometrine I.V for avoidance of (PPH) following cesarean delivery as regards efficacy and safety of each drug.

PATIENTS AND METHODS

This study is prospective randomized study that was done at Alhwamdya General Hospital. This study enlisted the participation of 100 women after taking their written consent and were selected from the outpatient clinic of obstetrics and gynecology May 2020 to February 2021.

How randomization

Before the study began, a random-number table was used to generate a randomized schedule specifying the group to which each patient would be assigned upon entry into the trial. In case of exclusion, the next patient was randomized per schedule.

Inclusion criteria: Primigravida without any risk for postpartum hemorrhage who did cesarean section under effect of regional anesthesia, and More than thirty seven weeks gestation: the gestational age was calculated using the beginning 24 hour of the last regular menstrual cycle and verified by an ultrasound scan within the first trimester.

Exclusion criteria: Multiparity, vaginal delivery, as carbetocin is only allowed for usage with regional anaesthesia in Egypt, ladies getting caesarean section under general anaesthetic were eliminated. , gestational age less than 37 weeks, and exclusion of any risk factor for postpartum hemorrhage for examples: placenta previa, pregnancy induced hypertension, marked anemia, multiple pregnancy and accidental hemorrhage.

The women in the study were separated into two groups: Group (A) got carbetocin 100g I.V after fetal head delivery, and Group (B) got a mix of intraoperative oxytocin 10 I.U & ergometrine 0.2mg after fetal head delivery.

All patients were subjected to:

Careful and detailed history taking.

General examination.

Abdominal examination: Detect fundal level, and presence of scars of previous laparotomies.

Vaginal examination: Cervical assessment including cervical dilatation, consistency, effacement and position

Investigations: Complete blood count, Rh typing, coagulation profile: Prothrombin time, Partial Thromboplastin Time, INR, liver function tests, and renal function tests.

6-Ultrasound scan: using trans abdominal ultrasound scan to: Confirm gestational age, and detect any risk factors for postpartum hemorrhage as placenta previa.

Indications Of Cesarean Section in This Study :

- Breech presentation

Breech presentation is the primary indication for 10% of all CS; However CS rates vary with gestational age, at term 91% women with a breech presentation had a CS.

- Dystocia

Dystocia is abnormal labor resulting from problems related to fetopelvic or cephalopelvic disproportion (CPD), failure to progress, obstructed labor, dysfunctional labor, poor progress, and second stage arrest.

- Fetal distress

Fetal distress used to be a clinical diagnosis based on the passage of meconium, violent fetal movements and changes in the FHR.

- Other indications:which divided into maternal and fetal indications:

Maternal indications

Antepartum hemorrhage

CS is usually necessary when the placenta covers the internal os at 36 weeks (grade 3 or 4 placenta previa). Those women are at increased risk of blood loss of greater than 1000 ml compared to CS for other indications

Abruptio placentae are an absolute indication for section if the hemorrhage is severe and the fetus is not immediately deliverable. In this situation, section may be indicated even in the presence of fetal death.

Vasa previa

In vasa previa, unsupported fetal vessels traverse the fetal membranes in advance of the presenting part.

Delivering by elective cesarean at or about the 35th to 36th week following steroid treatment is ideal.

Fetal indications: e.g:

Multiple pregnancies Cesarean section is often utilized for twins mainly to provide the second twin with maximum safety at birth. Cesarean section is almost always utilized for triplet and quadruplet births.

In all cases, approved ethical committee taken, information sheet completed included Age, Parity, Gestational age at delivery, also the Blood pressure, Pulse, Temperature and Hemoglobin concentration hematocrite value noted before cesarean sections and 24 hours post-partum. The differences between pre- and post C.S values were calculated in each group.

The uterine tone and size were measured by palpating the front wall of the uterus with a hand lying on the fundus. A swampy uterus combined with excessive vaginal bleeding or an increase in uterine size might lead to a diagnosis of uterine atony.

The study medicine (carbetocin or oxytocin) was provided slowly (over 30– 60 seconds) intravenously by the anesthetist after the infant was delivered through CS

Blood loss was estimated by The hematocrit value was measured immediately before delivery and 24 hours after, for more objective of blood loss, Assessment was done according to the following formula **(shook et al., 2003)**:

EBL = EBV X preop Hct – postop Hct

prepo Hct

Estimated blood loss (EBL) = estimated blood volume (EBV) X [preoperative hematocrit (preop Hct) - postoperative hematocrit (postop Hct) / preoperative hematocrit (preop Hct)].

The patient's estimated blood volume (EBV) was calculated as following: woman's weight (in kilograms) X 85.

The side effects of each drug as nausea, vomiting, shivering and headache or others was noted.

All the resulting data from the two groups was collected tabulated and analyzed statistically.

Statistical analysis:

The data will be collected, coded and entered to computer. The data was analyzed with the program (SPSS) statistical package for social science version 25 under windows 10

Statistical tests was used in this thesis :

Description of qualitative variables by frequency and percentage.

Description of quantitative variables in the form of mean and standard deviation (mean ± SD).

Chi-square (x2) test will be used for comparison of qualitative variables with each other.

Comparison between quantitative variables was carried by using :

Student t-test of two independent samples.

Significance level (p) will be expressed as following:

P value > 0.05 is insignificant

P value < 0.05 is significant.

P value < 0.001 is highly significant.

RESULTS

Group	Carbetocin group	Oxytocin & ergometrine group	P value
Gestational age (weeks)	38.95 ±2.64	39.15 ±2.86	0.691
Maternal age (years)	25.83±7.07	27.53±6.81	0.182
BMI	27.5 ± 5.2	27.03 ± 6.0	0.645
Mild PPH	16%	24%	0.154
Moderate PPH	12%	4%	0.59
Severe PPH	4%	12%	0.27

Table 1: Comparison of two groups in terms of the mean values of gestational age, maternal age, BMI, incidence and severity of PPH.

Comparison between two groups as regards the mean values of gestational age, maternal age and BMI were statistically non significant. There was no significance was found between 2 groups as regard mild or moderate PPH (Table 1).

Group	Carbetocin group	Oxytocin & ergometrine group	P value
Need for uterine massage	32%	40%	**0.55**
Need for additional uterotonic drugs	20%	32%	**0.088**
Need for intraoperative ergometrine	16%	-	**0.2**
Need for intraoperative syntocinon	20%	16%	**0.09**
Need for postoperative ergometrine	16%	8%	**0.1**
Need for postoperative syntocinon	**20%**	**32%**	**0.088**

Table 2: Comparison of two groups in terms of requirement for additional uterotoinicmedications.

When we tested the need for additional uterotonic drug comparing both groups it was non significant (Table 2).

Group	Carbetocin group	Oxytocin & ergometrine group
Preoperative Hb (mean)	10.918±0.89	10.77 ±1.035
Postoperative Hb (mean)	10.41±0.924	10.10 ±1.13
Hb difference (mean)	0.508	0.672
P value for Hb difference	0.02	

Table 3: Hb differential between pre- and 24-hour post-operative Hb levels were compared between two groups and their statistical significance.

When comparing the Hb differential between pre- and 24-hour post-operative Hb levels, the carbetocin group was shown to be significantly superior (Table 3).

Group	Carbetocin group	Oxytocin & ergometrine group
Hematocrit (%) preoperative	36.38±5.19	35.63±5.21
Hematocrit (%) 24 h post	32.4±5.22	30.0±5.19
Hematocrit difference (mean)	3.98	5.63
Estimated blood loss	314.86±89.6	447.22±242.88
P value for blood loss	0.003	
P value for Hct diff.	0.048	

Table 4: Comparison of two groups in terms of estimated blood loss, hematocrite pre and 24h postoperative and their statistical significance.

Comparison between two groups as regards estimated blood loss which appear statistically significance (Table 4).

Group	Carbetocin group	Oxytocin & ergometrine group	P Value
Elevated systolic/ diastolic blood pressure	0%	28%	0.001 Sig.
Nausea	20%	36%	0.05 Sig.
Vomiting	12%	32%	0.014 Sig.
Shivering	8%	12%	0.3
Facial flushing	8%	4%	0.5
Headache	4%	8%	0.309
Abdominal pain	8%	16%	0.11
Sweating	8%	4%	0.5

Table 5: Results of Comparison between two groups as regards maternal adverse effects and their statistical significance.

Concerning maternal adverse effects in the form of elevated blood pressure there was statistical significance in which there was 28% elevation in the non carbetocin group. Again concerning nausea and vomiting they were notably important obvious in the non carbetocin group. However, when we tested for shivering, facial flushing, headache, abdominal pain and sweating statistical difference was not significant among the two groups (Table 5).

Group	Carbetocin group	Oxytocin & ergometrin group	P value
PPH further treatment n (%):			
- Uterine artery ligation	(4%)1	(12%)3	0.27
- Compression sutures	(4%)1	(12%)3	0.27
- Hystrectomy	(0.0)	(4%)1	_

Table 6: Comparison between both groups as regard the required additional measures either for prevention or further treatment of postpartum hemorrhage.

In four patients (one in the carbetocin group and three in the oxytocin group), uterotonics failed to stop and control PPH, necessitating surgical intervention. One woman in the carbetocin group developed atonic postpartum hemorrhage, which was treated surgically with bilateral uterine artery ligation and compression sutures. 3 patients in the oxytocin group developed atonic postpartum hemorrhage, which was treated surgically with bilateral uterine artery ligation and compression sutures; one of them required hysterectomy due to intractable bleeding. (Table 6).

DISCUSSION

The present study showed that results of comparison between two groups as regards the mean values of gestational age and maternal age were statistically non significant. As regards incidence and severity of PPH were also non significant. Also when we tested the need for additional uterotonic drug comparing both groups it was non significant.

However, when pre- and 24-h post-operative haemoglobin and hematocrit were compared

between the two groups, statistical significance was shown in favour of the carbetocin group.

As regards pre- and post-operative mean values of temperature we found no significance. The results in terms of projected blood loss are statistically significant in favour of the carbetocin group. However, concerning maternal adverse effects in the form of elevated blood pressure there was statistical significance in which there was 28% elevation in the non carbetocin group. Again concerning nausea and vomiting they were important obvious in the non carbetocin group. However, when we tested for shivering, facial flushing, headache, abdominal pain and sweating statistical difference was not significant between the two groups.

Some studies were not in agreement with our thesis concerning need for additional uterotonic drugs, Borruto et al.[11], Boucher et al.[12] and Dansereau et al.[13] compared between carbetocin and oxytocin concerning the necessity for additional uterotonic medications. They found statistical significance between boths groups in favoring of carbetocin group.

However, when they tested the requirement for additional uterotonic agents with carbetocin and oxytocin following vaginal deliveries, they found no statistical significance between both groups. This was in agreement with our thesis despite different mode of delivery. Manner of delivery is an important issue that can effects the treatment outcome. May be ueterine scar make uterus respond in a different manner than in vaginal delivery. Thus, it is recommended to undertake more studies including patients with different modes of delivery and risk factors for PPH.

Concerning pre- and post-operative HB, Askar et al. [14], Attilakos et al. [15] and Boucher et al. [16] found that assessed blood loss in women who experienced cesarean deliveries, was more in the oxytocin group. There was greater drop in HB in this group. This comes in agreement with our thesis.

Borruto et al.[11], Boucher et al. [12] and Dansereau et al. [13] compared the use of carbetocin and oxytocin for maternal adverse effects as elevation of blood pressure after treatment in cesarean deliveries. There was no statistical significance. However, we found in our thesis a 28% elevation in the non carbetocin group. This difference may be that we included other drugs in comparison as ergometrine. This made interpretation of our results different.

Boucher et al. [16] compared carbetocin with oxytocin groups as regards vomiting but found no statistical significance. Again this is not in agreement with our study which may be due to using other drugs. This may prove that carbetocin, concerning maternal adverse effects following use of uterotonic drugs for prevention of PPH is more safe and effective.

In an RCT on 694 women who had an elective caesarean birth, Dansereau et al. 13 evaluated the incidence of PPH in women taking carbetocin as a 100 mcg IV bolus or oxytocin as a continuous infusion for 8 h (25 IU of oxytocin in 1000 mL of Ringer's lactate, 125 mL each hour). In the carbetocin group, PPH and the need for therapeutic oxytocics were less common. (4.7% vs. 10.1%; $P < 0.05$).

Boucher et al. [16] conducted a randomized, double-blind study containing 160 women with minimum one risk factor for PPH and was done at two medical locations. Following placental birth, 83 women got 100 mcg carbetocin IM and 77 women had oxytocin IV infusion. Each group had a comparable population profile and PPH risk factors. There was no discernible change in the number of women who required extra uterotonic medicines (12 in each group).

In a double-blind study, Attilakos et al. [15] randomly assigned women to receive carbetocin 100 mcg or oxytocin 5 IU intravenously after giving birth. Additional oxytocics were administered at the request of the operating obstetrician. In the oxytocin group, significantly more women needed extra oxytocics (45.5 percent versus 33.5 percent, Relative risk 0.74, 95 percent CI 0.57-0.95). Carbetocin was linked to a reduction in the need of additional oxytocics. It's unknown if this will lower PPH and blood transfusion rates.

However, if the extra oxytocics require extended administration in the labour ward or in the recovery area, the lesser usage of additional uterotonic medications is a significant consequence with potential cost savings. However, the increased cost of carbetocin compared to oxytocin may compensate for this.

Given oxytocin's short half-life and the widespread use of extra uterotonic medications (oxytocin administration for the popular of women), the topic of whether a regular oxytocin infusion should be given after a caesarean section arises. If the oxytocin infusion is better to the oxytocin bolus, the next obvious step is to compare carbetocin to the oxytocin bolus, then the oxytocin infusion. The period of stay in the Delivery Suite/Recovery area should be included in the findings of such a study, as this has an influence on the efficiency of busy maternity facilities.

The current study showed no significant difference in the use of additional uterotonic drugs.

The adverse effect profiles of the two drugs appear to be reassuringly comparable. The risks of headache, chills, stomach discomfort, dizziness, tremor, back pain, metallic taste, sweating, shortness of breath, and premature ventricular contractions were comparable in women administered oxytocin and carbetocin during caesarean birth. These findings agree with Dansereau et al. [13].

As a result, large-scale trials may be necessary to demonstrate any differences in the adverse effects of the two drugs. Syntometrine, a popular uterotonic drug, has been linked to greater negative side effects than oxytocin. [3] It is possible that carbetocin has the benefit of having fewer adverse effects than syntometrine.

It's reassuring to know that there are no clinically significant differences between the two treatments.

Many of the oxytocin-induced hemodynamic changes, however, happen within the first 5 minutes. Unlike Thomas et al.[9] and Moertl et al.[17], we did not use continuous hemodynamic monitoring during this time period.

Reyes and Gonzalez [18] conducted a prospective double-blind randomized controlled trial in 60 women with severe preeclampsia. They discovered that carbetocin is an effective alternative for oxytocin in avoiding postpartum bleeding in women with severe preeclampsia. Because it does not appear to have a significant hemodynamic effect in women with severe preeclampsia and is not related to the development of oliguria or hypertension, it should be considered a viable option in the management of the third stage of labor in women with hypertensive disorders of pregnancy.

Following vaginal delivery, three randomized investigations of carbetocin versus Syntometrine have been conducted. [14, 19, 20]

Leung et al. [19] and Su et al. [20] found no significant differences in the usage of extra oxytocics, hemoglobin drop, incidence of PPH, or estimated blood loss between the two groups. However, carbetocin was shown to be linked with a much decreased rate of adverse effects in all investigations. Carbatocin was linked to a decreased prevalence of hypertension at 30 and 60 minutes, but a greater incidence of maternal tachycardia, according to a previous research by Leung et al. [19.]

Askar et al. [14] did a study at Al-Azhar University Hospital that included 240 healthy women with viable normal singleton pregnancies who delivered normally vaginally at or after 37 weeks of pregnancy. There was important change in estimated mean blood loss between the carbetocin and syntometrine groups, with the syntometrine group losing 81.5 ml more. The average haemoglobin concentration dropped by 0.8 g/dl in the carbetocin group and 1.1 g/dl in the syntometrine group 24 hours after delivery, a statistically significant difference. Carbetocin users were less likely to have nausea and vomiting. [14] Because all of the trials for this rare complication have been underpowered, it's hard to establish whether carbetocin reduces the risk of PPH following vaginal delivery.

Aside from medical concerns, the most acceptable uterotonic drug will be determined by criteria such as cost, which will be especially important in nations with limited resources. Carbetocin is not justified as a standard first-line uterotonic drug in many countries due to a lack of strong proof of advantages on major clinical outcomes such as PPH. However, because of the reduced requirement for uterine massage and therapeutic uterotonics in some circumstances, it may be a choice for particular physicians.

It is recommended after this study to investigate use of carbetocin in cardiac and hypertensive patients for prevention of PPH. Also, it is essential to search for cost-effectiveness of using carbetocin in developing countries. More studies are required for proving our results using patients with one or more risk factors for PPH as mentioned above in the review of literature. In addition, route of administration and doses of the drug are so important for outcome of studies. Thus, more studies are required for finding the most suitable dose and route of administration of carbetocin in inhibition of PPH.

More studies are needed for the need of addition of other uterotonic agents to carbetocin. Leduc et al.[21] stated that according to the canadian society of gynecologists and obstetricians, 100 micro gram of carbetocin given as intravenous bolus over one minute is used instead of continous oxytocin infusion in inhibition of PPH and decrease the need for uterotonic agents following cesarean deliveries. However, concerning the need for addition of other uterotonic drugs our thesis results were non-significant between both groups.

CONCLUSION

According to the findings, simultaneous intravenous carbetocin is beneficial in preventing atonic post-partum hemorrhage after caesarean surgery. It's just as effective as a mix of I.V syntocinon and ergometrine. Compared to the combination of syntocinon and ergometrine, carbetocin alone had less adverse effects on the mother, such as high blood pressure, nausea, and vomiting.

REFERENCES

1. Kane TT, El-Kady AA, Saleh S, Maternal mortality in Giza, Egypt: magnitude, causes and prevention. *Studies in Family Planning*. 2013; 23(1):45-7.
2. Weindling AM, The confidential enquiry into maternal and child health (CEMACH). *Arch Dis Child*. 2012; 88:1034–7.
3. McDonald SJ, Prendiville WJ, Blair E, Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of the third stage of labour. *Cochrane Database of Systematic Reviews*. 2015; 307:1167-71.
4. Liabsuetrakul T, Choobun TPeeyananjarassri K, Prophylactic use of ergot alkaloids in the third stage of labour. *Cochrane Database of Systematic Reviews.* 2017; 1:3-6.
5. Carey M, Adverse cardiovascular sequelae of ergometrine. *Br J Obstet Gynaecol*. 2014; 100:865-9.
6. Dumoulin JG, A reappraisal of the use of ergometrine. *International Journal of Obstetrics & Gynaecology*. 2013; 8: 178–181.
7. Postina R, Fahrenholz F, Reinheimer T, Binding domains of the oxytocin receptor for the selective oxytocin receptor antagonist barusiban in comparison to the agonists oxytocin and carbetocin. *European Journal of Pharmacology*. 2015; 9:16-21.
8. Barth T, Engstrom T, Melin P, Oxytocin receptor binding and uterotonic activity of carbetocin and its metabolites following enzymatic degradation. *European Journal of Pharmacology*. 2015; 21: 203–10.

9. Thomas JS, Koh SH, Cooper GM, Hemodynamic effects of oxytocin given as IV bolus or infusion on women undergoing caesarean section. *Br J Anaesthesia*. 2017; 98: 116–9.
10. Shook PR, Schultz JR, Reynolds JD, Estimating blood loss for cesserian section: how accurate are we?. *BMC Pregnancy and Childbirth*. 2014; 20: 98-103.
11. Borruto F, Treisser A, Comparetto C, Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. *J Obstet Gynaecol*. 2019; 280:707–12.
12. Boucher M, Nimrod CA, Tawagi GF, Comparison of carbetocin and oxytocin for the prevention of postpartum hemorrhage following vaginal delivery:a double-blind randomized trial. *Int J Gynaecol Obstet*. 2014; 26(5): 481–8.
13. Dansereau J, Joshi AK, Helewa ME, Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. *Arch Gynecol Obstet*. 2011; 180:670–6.
14. Askar AA, Ismail MT, El-Ezz AA, Carbetocin versus syntometrine in the management of third stage of labor following vaginal delivery. *Int J Reprod Contracept Obstet Gynecol*. 2011; 284(6):1359-65.
15. Attilakos G, Psaroudakis D, Ash J, Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomised trial. *BJOG*. 2010; 117: 1665–6.
16. Boucher M, Horbay GL, Griffin P, Deschamps Y, Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. *Arch Gynecol Obstet*. 2017; 18:202–7.
17. Moertl MG, Friedrich S, Kraschl, J, Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. *Int J Gynaecol Obstet*. 2018; 118(11): 1349–56.
18. Reyes OA, Gonzalez GM, Carbetocin versus oxytocin for prevention of postpartum hemorrhage in patients with severe preeclampsia: a double-blind randomized controlled trial, *BJOG*. 2011; 33(11):1099-104.
19. Leung SW, Ng PS, Wong WY, Cheung TH, A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. *Am J Obstet Gynecol*. 2016; 113:1459-64.
20. Su LL, Rauff M, Chan YH, Carbetocin versus syntometrine for the third stage of labour following vaginal delivery; a double-blind randomised controlled trial. *Cochrane Database Syst Rev*. 2019; 116:1461-1466.
21. Leduc D, Senikas V, Lalonde AB, Active management of the third stage of labour: prevention and treatment of postpartum haemorrhage. *Journal of Obstetrics and Gynaecology Canada*. 2012; 31: 980-93.