Prophylactic Carbetocin during Elective Caesarean Section in High Risk group for Atonic Postpartum Hemorrhage

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ABSTRACT

Background: Postpartum hemorrhage (PPH) is defined as a blood loss more than 500 ml and serious PPH as a blood loss more than 1,000 ml. PPH is a serious condition remaining the single main cause of maternal morbidity and mortality. Postpartum hemorrhage (PPH) accounts for nearly one-quarter of all maternal deaths worldwide and was the second most frequent cause of maternal death in the UK for the 2000–2002 trienniums.

The most frequent cause of PPH is uterine a tony, contributing up to 80 % of the PPH cases. Although two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, preeclampsia, coagulopathy, multiple gestation and antepartum hemorrhage. Also cesarean section (CS) is a recognized risk factor for PPH and its prevalence is increasing .The administration of oxytocics after the delivery of the neonate reduces the like hood of PPH and 5 IU oxytocin by slow intravenous injection is currently recommended in the UK for all cesarean sections. However, the use of additional oxytocic medication is common to arrest bleeding, or prophylactically if there are risk factors for PPH. Oxytocin is currently the uterotonic of first choice. It has proven to decrease the incidence of PPH by 40 % and has a rapid onset of action and a good safety profile . A disadvantage of oxytocin is its short half life of 4–10 min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections. **Objectives**: was.to evaluate role of carbetocine either i.v or intramyometriam in preventing postpartum haemorrhge. **Patients and methods:** this was Randomized controlled double blind study was held at sayed galal hospital department of obstetrics and gynecology between April 2016 to October 2017 .

Results*:* We observe fall in rate of atonic postpartum haemorrhage after administration of carbetocin either i.v. or intramyometriaum . we found diferrance in blood pressure between two group weher increase og blood pressure in group received carbetocine i.v. .Also we found difference between two group need for additional dose which increase in goup that received carbetocine intramyometraim.

Conclusion: Adminstration of carbetocine either i.v. or intramyometriaum decrease rate of atonic post partum haemorrhage in high risk group for atonic postpartum haemorrhage.

Keywords: Prophylactic Carbetocin during, Elective Caesarean, Atonic Postpartum Hemorrhage.

INTRODUCTION

Postpartum hemorrhage (PPH) is defined as a blood loss more than 500 ml and serious PPH as a blood loss more than 1,000 ml. PPH is a serious condition remaining the single main cause of maternal morbidity and mortality.

Postpartum hemorrhage (PPH) accounts for nearly one-quarter of all maternal deaths worldwide [(1)] and was the second most frequent cause of maternal death in the UK for the 2000–2002 trienniums[(2)]. The most frequent cause of PPH is uterine a tony, contributing up to 80 % of the PPH cases. Although two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, preeclampsia, coagulopathy, multiple gestation and antepartum hemorrhage. Also cesarean section (CS) is a recognized risk factor for PPH and its prevalence is increasing .

The administration of oxytocics after the delivery of the neonate reduces the like hood of PPH and 5 IU oxytocin by slow intravenous injection is currently recommended in the UK for all cesarean sections [(3)] .However, the use of additional oxytocic medication is common to arrest bleeding, or prophylactically if there are risk factors for PPH [(4)]. Oxytocin is currently the uterotonic of first choice. It has proven to decrease the incidence of PPH by 40 % and has a rapid onset of action and a good safety profile [(5)].

A disadvantage of oxytocin is its short half life of 4–10 min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections [(6)]. Carbetocin (Pabal) is a long-acting oxytocin analogue indicated for the prevention of uterine atony after child birth by CS under epidural or spinal anesthesia. Carbetocin has a rapid onset of action (within 1–2 min) and a prolonged duration of action (approximately 1 h) because of sustained uterine response with contractions of higher amplitude and frequency. Its safety profile is comparable to that of oxytocin .

The current pharmacological policy for the prevention of PPH is oxytocin. Most hospitals use a bolus of oxytocin 5 or 10 IU; some add an infusion of oxytocin for a couple of hours.

Received:20 /3 /2018 DOI: **10.12816/0047752**
Accepted:30 /3 /2018

PATIENTS AND METHODS

One hundred pregnant women with the following selection criteria in Sayed Galal Hospital Obstetrics and Gynecology Dept., Alazhar University had been chosen to participate in the study from April 2016 till October 2017. They were divided randomly into two groups A and B. **The study was approved by the Ethics Board of Al-Azhar University.**

Group A: Included fifty women who were injected with 100 ug of carbetocin intravenously after delivery of the anterior shoulder of the fetus

Group B: Included fifty women who were injected with 100 ug of carbetocin intra myometrium after delivery of the fetus.

The identity of using which medication was concealed from the patient, resident physicians who managed the delivery and also who followed up the patients for the next two hours.

Study design:

Randomized controlled double blind study.

Selection criteria:

A) Inclusion criteria

Pregnancy for more than 37 weeks.

Women at risk of atonic postpartum hemorrhage including:-

Parity grater than four.

Multiple pregnancies.

Uterine fibroid.

BMI >30.

Previous postpartum hemorrhage.

History or active antepartum hemorrhage.

Anemia with hemoglobin level <10.5 g/dl. Fetal macrosomia (fundal height 40 cm or clinical ultrasound estimated fetal weight 3.8-4.0 kg).

Polyhydramnios (more than one amniotic fluid pocket 8 cm or AFI 25 cm).

A risk score was done by giving women a score No. for each risk factor of PPH. they have, women who have a risk score of two or more will be included in the study.

B) Exclusion criteria

Coagulation abnormalities.

Preeclampsia.

Hypertension, renal and heart diseases.

Methods:

An informed consent was taken from all women. The selected cases were subjected to the following:

1- History: Proper full history was taken including,

Personal history:

Maternal age.

Parity.

Obstetric history:

Gravidity, parity.

Multiple pregnancies.

Macrosomia.

Pregnancy induced hypertension.

Gestational diabetes.

Previous operative delivery, prolonged difficult labor, or previous PPH.

Any associated complaint during this pregnancy, especially vaginal bleeding and abdominal pain.

Menstrual history:

Last menstrual period

Family history:

Diabetes mellitus.

Hypertension.

Maternal medical history:

DM.

Hypertensive disorders.

Bleeding disorders or coagulopathies.

2- Examination

General examination: Full general examination was done with especial concern to:

Vital signs: Blood pressure, pulse, temperature, and respiratory rate.

Chest and heart examination.

Abdominal examination:

For assessment of gestational age, fetal weight, amount, of liquor, fetal lie and presentation, fetal heart sounds, uterine contractions and scar of previous surgeries.

Vaginal examination:

To assess the progress of labor.

3- Investigations

Routine laboratory investigations: e.g. complete blood count (CBC): To evaluate:

Hemoglobin level (Hb), packed red cell volume (PCV) or Hematocrit value, Rh type.

Urine analysis for protein by dip-sticks.

Trans-abdominal ultrasound study was done for laboring women for assessment of gestational age, implantation site of the placenta and fetal weight.

The following steps were done:-

Blood sample was taken for measurement of hemoglobin level and Hematocrit value on entry into the trial and repeated one day after delivery.

Maternal outcomes

Postpartum hemorrhage.

Blood loss

Pulse and Blood pressure.

Hemoglobin and hematocrit levels.

Blood transfusion.

Use of therapeutic uterotonics (additional dose)

Statistical Methodology

Analysis of data was done by IBM compatible computer using SPSS (statistical program for social science version 12) as follows:-

Pulse rate	**75 +6.2**	**76 +6**	**>0.05 NS**

Description of quantitative variables as mean, SD and range. Description of qualitative variables as number and percentage.
Chi-square and Fisher exact test were used to compare qualitative variables between groups.
Unpaired t-test was used to compare two groups as regard quantitative variable in parametric data (SD<50% mean).
Paired t-test was used to compare quantitative variable in the same group before and after.
P value >0.05 insignificant.
P<0.05 significant.
P<0.01 highly significant.

RESULTS

One hundred women were randomly assigned and were received either 100 ug carbetocin by intravenous IV (n=50) or intramyometrium IMM (n=50). The comparison between carbetocin IV and IMM groups as regard demographic characteristics of the study participants had shown the following results:
No statistically significant difference between carbetocin groups either IV or IMM regarding maternal age (mean ±SD: 24.5 ±3.2 vs 24.8 ±2.3, P>0.05) by using independent sample t-test, table (1) and figure (1).

Table (1): Comparison between both groups as regard measurement of blood pressure and pulse before delivery

Variables	Carbetocin	Carbetocin	*P*
SBP (mmHg)	112 +9	112 +9.5	>0.05 NS
DBP (mmHg)	**73.5 +6**	**73.7 +6.7**	**>0.05 NS**

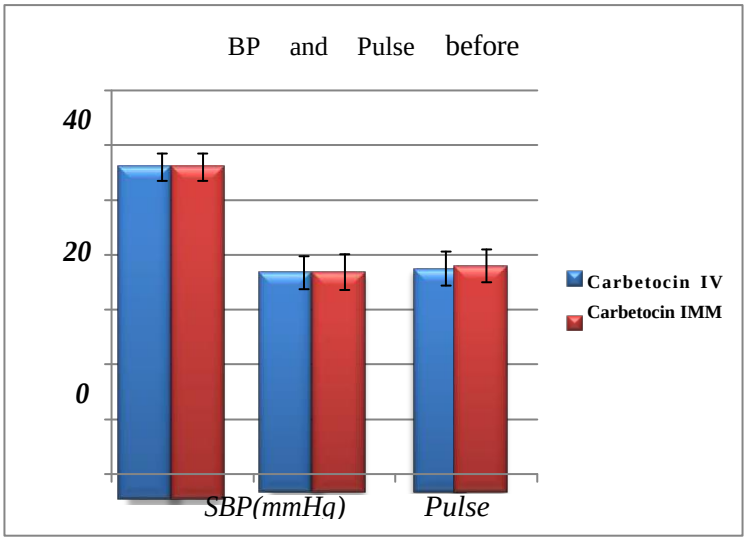

Fig (1): Comparison between both groups as regard measurement of blood pressure and pulse rate before delivery

Table (2): Comparison between both studied groups as regard the need for repeated dose

Repeated dose	**Carbetocin IV** N=50	**Carbetocin IMM** N=50	***P***
Yes	1(2%)	10(20%)	<0.001 *HS*
No	49(98%)	40(80%)	

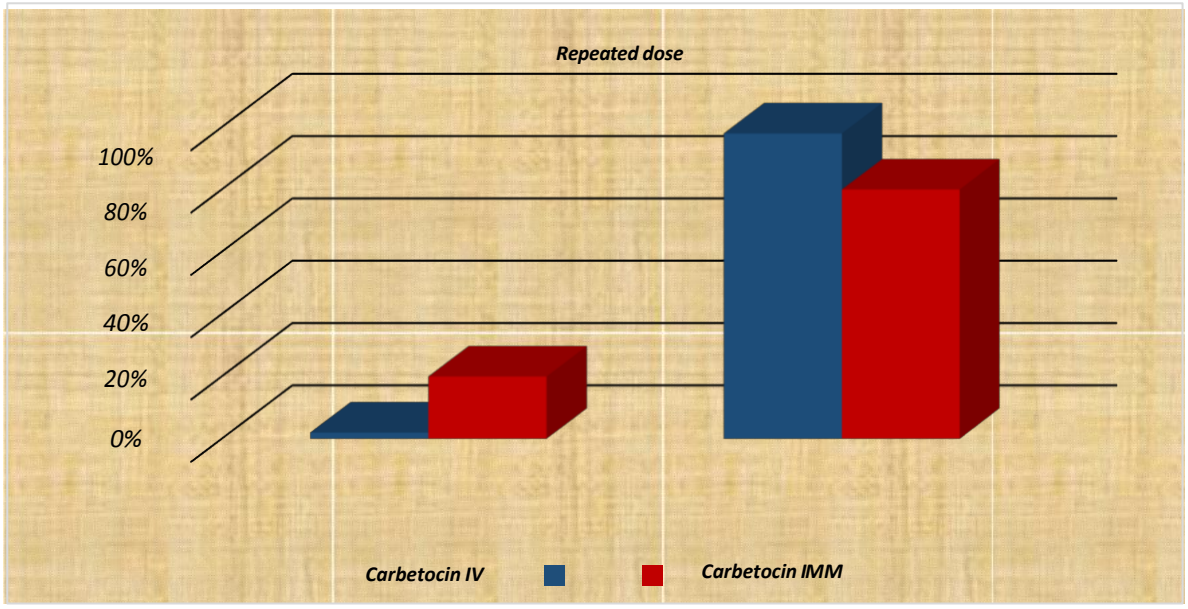

Fig (2): Comparison between both studied groups as regard the frequency of the need for repeated dose.

Table (3) Comparison between both groups as regard measurement of blood pressure and pulse rate after delivery:

Variables	Carbetocin IV N=50	Carbetocin IMM N=50	*P*
SBP (mmHg)	108 +9	107 +10	>0.05 ***NS***
DBP (mmHg)	70 +5	70 +7	>0.05 ***NS***
Pulse rate	76 +7	88 +21	<0.05 ***S***

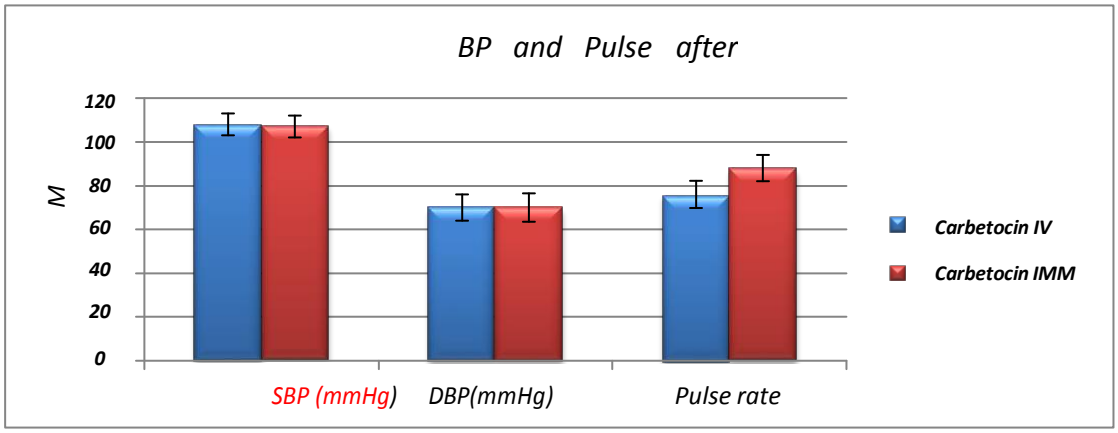

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Fig (3) Comparison between both groups as regard measurement of blood pressure and pulse rate after delivery

Table (4) Comparison between measurement of antepartum and postpartum pulse rate and blood pressure among intravenous carbetocin groups:

Variables	Before delivery	After delivery	*% of change*	*P*
SBP (mmHg)	112 +9	108 +9	3.5%	>0.05 ***NS***
DBP (mmHg)	73.5 +6	70 +5	2%	>0.05 ***NS***
Pulse rate	75 +6.2	76 +7	1.5%	>0.05 ***NS***

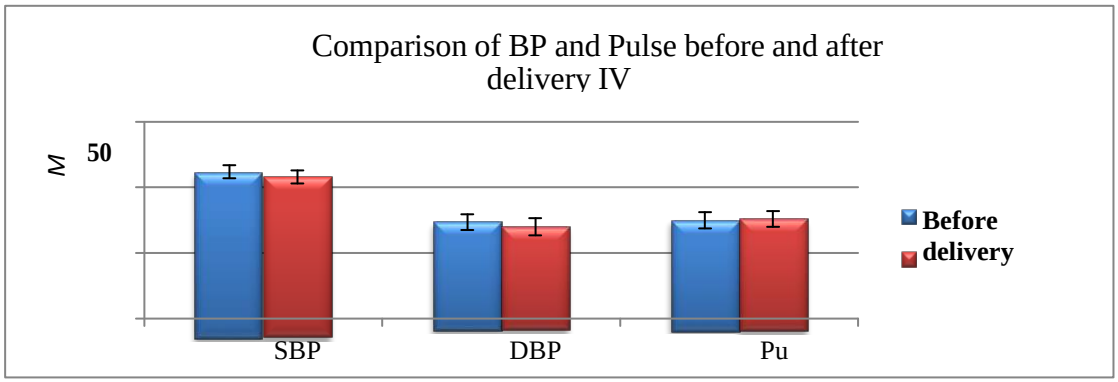

Fig (4) Comparison between measurement of antepartum and postpartum pulse rate and blood pressure among intravenous carbetocin group

Table (5) Comparison between both groups as regard the incidence of blood transfusion:

Blood transfusion	Carbetocin IV N=50	Carbetocin IMM N=50	*P*
Yes	0(0%)	3(6.0%)	**<0.001 *HS***
No	50(100.0%)	47(94.0%)	

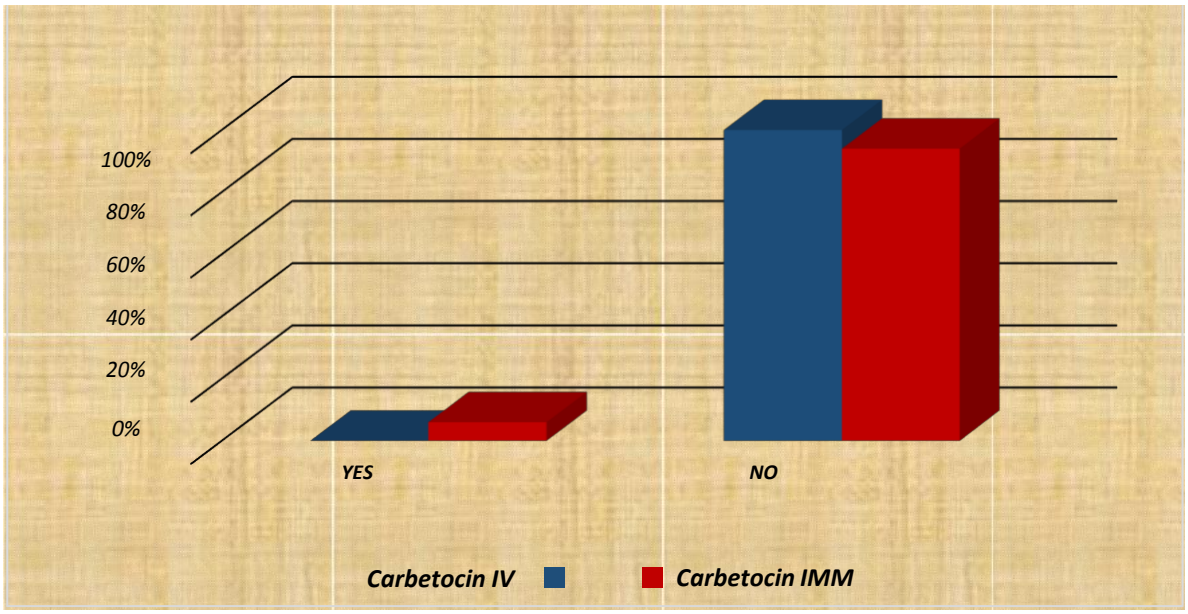

Fig (5) Comparison between both groups as regard the incidence of blood transfusion

Table (6) Comparison between both groups as regard Hb level (gm/dl) after delivery

	Carbetocin		p-value
Hb after delivery	**IV(N=50)**	**IMM (N=50)**	
Mean +SD	**10.1+0.8**	**10 +0.6**	**>0.05 *NS***
Range	**8.7-12**	**8.2-11.9**	

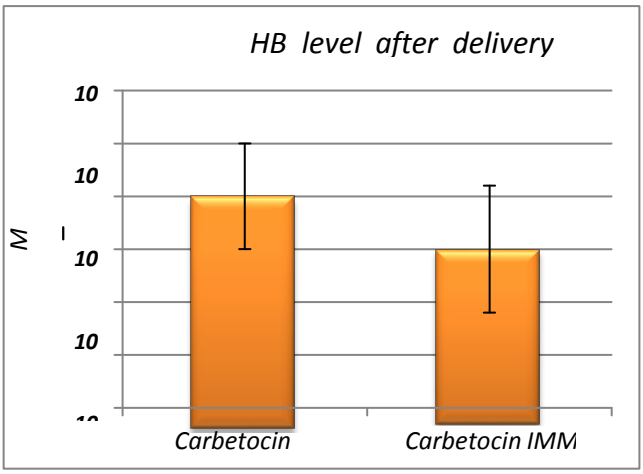

Fig (6) Comparison between both groups as regard Hb level (gm/dl) after delivery

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Table (7): Comparison between both groups as regard PCV (%) after delivery

	Carbetocin		p-value
PCV (%) after delivery	IV **(N=50)**	IMM **(N=50)**	
Mean +SD	40.2 ±3.4	38.1 ±3.1	<0.05 S
Range	35.7-44.3	32-41	

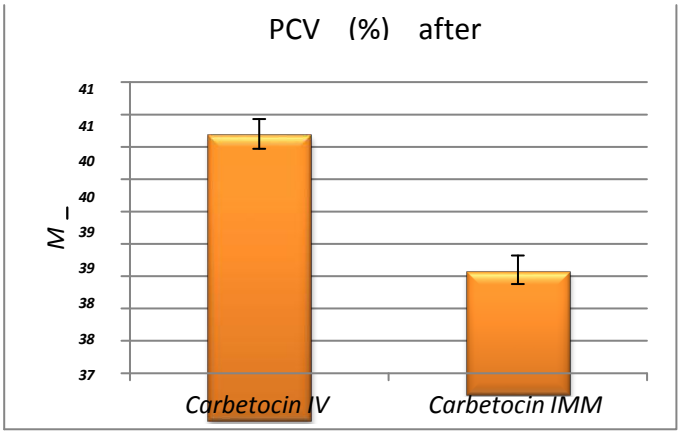

Fig. (7) Comparison between both groups as regard PCV value (%) after delivery

DISCUSSION

Postpartum hemorrhage (PPH) is defined as a blood loss >500 ml and serious PPH as a blood loss >1,000 ml. PPH is a serious condition remaining the single main cause of maternal morbidity and mortality.

All pregnant women are at risk of complications during the 3rd stage of labor [(7)]. Maternal risk factors contribute to the development of postpartum hemorrhag. For women undergoing delivery by cesarean section, there is an increased risk of postpartum hemorrhage compared to vaginal delivery

The most frequent cause of PPH is uterine atony, contributing up to 80 % of the PPH cases [(8)]. Athough two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, pre-eclampsia, coagulopathy, multiple gestation and antepartum hemorrhage. It is therefore reasonable to advise routine administration of a uterotonic drug immediately after the baby has been delivered by cesarean section[(9)].11h impact of PPH on maternal morbidity and mortality makes active management of the third stage of labour to a critical key [(10)].

Thus, the administration of a uterotonic medication soon after the delivery of the fetus is an essential part of the AMTSL that is capable of decreasing the incidence of PPH by 40% [(11)].

However, these medications pose some challenges, in that individually and collectively they have side-effects, contraindications and problems with storage and administration. As such, the search for the ideal uterotonic continues, and today the main uterotonic agents are oxytocin, ergonovine, carboprost, carbetocin and misoprostol [(12)].

Thus, this case controlled randomized study was conducted on *100* pregnant women after 37 weeks who were undergoing elective caesarean section under spinal anesthesia to compare the prophylactic effects of carbetocin i.v with those of carbetocin intramyometrium in the prevention of uterine atony in patients undergoing repeated elective CS under spinal anesthesia. The patients were divided into 2 equal groups where 50 patients received a single dose of 100 microgram intravenous carbetocin, the other 50 patients received 100 ug of carbetocin intramyometrium.

During the study, the postoperative blood loss was significantly lower in carbetocin i.v group when compared to the carbetocin intramyometrium group. Also, there was no statistically significant difference between the two groups regarding the occurrence of postpartum hemorrhage. The

carbetocin i.v group showed less occurrence of hemorrhage.

In accordance with the present study, demonstrated a lower rate of additional oxytocic usage after carbetocin compared with oxytocin, carbetocin may be more effective in preventing uterus atony and thereby PPH. Also, another recent study found that The estimated blood loss was significantly lower in the carbetocin group (mean 585mL versus 702.8mL, P=.026)[13]. In addition, showed that blood loss was significantly higher in the oxytocin group compared to carbetocin group but no to the degree of PPH and this could be attributed to that carbetocin causes a tetanic uterine contraction produced 2min after an intravenous injection of 8-30mg or intramuscular injection of 10-70mg, which persists for approximately 1 min. Rhythmic uterine contractions persist for 60 and 120min after intravenous and intramuscular injection respectively which decrease the uterine atony . Furthermore, a prospective double-blinded randomized study conducted on 200 pregnant women randomized into two groups: Group 1 (100 women) received single 100 µg IM dose of carbetocin and Group 2 received of 5 IU oxytocin IM. Both groups received their drug after fetal and before placental delivery concluding that carbetocin is a better alternative to traditional oxytocin in prevention of PPH after vaginal delivery with minimal hemodynamic changes and similar side effects [14].

Performed a randomized controlled trial (RCT) in Canada comparing the incidence of PPH in women undergoing elective caesarean section who received either carbetocin as a 100 microgram IV bolus or oxytocin as a continuous infusion for 8 hours. The carbetocin group had a decreased incidence of PPH .

In partial accordance with our results, Su and associates observed greater blood loss in the oxytocin group compared to the carbetocin group, but the difference was not statistically significant. On the other hand, there were no statistically significant differences between carbetocin and oxytocin in terms of risk of any PPH (blood loss greater than 500 ml) or in risk of severe PPH (blood loss greater than 1000 ml).

In contrast to this study, some results for women who underwent vaginal delivery showed that the risk of having PPH was similar in both the oxytocin and carbetocin .

In our present study, the levels of Hb and HT were evaluated pre and post-operative in both groups. The levels of preoperative Hb and HT showed non-significant difference between the two groups while the levels of postoperative Hb and HCT were significantly higher in carbetocin i.v group than carbetocin intramyometrium group concluding that carbetocin i.v showed the best results in controlling the blood loss and maintaining the levels of Hb and HCT values. Also, the change in pre and postoperative HCT and Hb levels were significantly lower in carbetocin i.v group in comparison with carbetocin intramyometrium.

In agreement with these results, postoperatively, hemoglobin and hematocrit levels in the carbetocin group were statistically higher .

During the present study, the need for repeated dose is higher in carbetocin intramyometrium group than in carbetocin i.v group 20%). The need for uterine massage is higher in carbetocin intramyometrium group than in carbetocin i.v group of uterotonic agents and uterine massage was significantly lower in carbetocin group. In our present study there was no significant differences between two groups in blood pressure and pulse rate before delivery while there was significant difference in pulse rate after delivery where higher in carbetocin intramyometrium group than in carbetocin i.v group (*76 ±7* vs *88 ±21*).

In consistence with our results, carbetocin seemed to be most beneficial compared with the oxytocin group 5 IU bolus with thrice less need for additional uterotonic medication (3.1 vs. 9.3 %) and significantly less need for blood transfusions (2.2 vs. 3.6 %).

Other studies, evaluated the effect of an I.V. injection of carbetocin after caesarean delivery under regional anesthesia, showed that a single intravenous injection of carbetocin significantly reduced the need for additional uterotonic interventions to maintain adequate uterine tone and prevent/treat excessive bleeding following caesarean delivery versus intravenous oxytocin.

During this study, there was statistiacly significant difference between carbetocin group either i.v or intramymetrium as regard the incidence of blood transfusion. Carbetocin intramyometrium group had higher incidence of blood transfusion compared to carbetocine i.v group with statisticaly significant difference in between (No 100% vs 94% . yes 0%vs 6%).

In contrast with our results, showed that the two studied groups did not significantly differ in neither terms of blood transfusion requirements nor the occurrence of sever .

Also, at study**,** there were no significant differences in the number of women requiring blood transfusions between oxytocin and carbetocin groups.

In agreement with this, carbetocin seemed to be most beneficial compared with the subgroup oxytocin 5 IU bolus with significantly less need for blood transfusions (2.2 vs. 3.6 %).

In conclusion, carbetocin intravenous appears to be more effective than carbetocin intramyometrium for prevention of postpartum hemorrhage in patient undergoing elective cesarean section. In conclusion carbetocin either i.v or intramyometrium appears to be more effective than oxytocin for prevention of postpartum hemorrhage in patient undergoing elective cesarean section.

But in developing countries as Egypt, the cost of medical service and specially the drug cost is a very important issue while dealing with the quality of the medical service, we found in this study that carbetocin use is not associated with the use of additional oxytocics but to be the drug of choice for the active management of the third stage of labour, this may be offset by the higher cost of carbetocin in comparison to oxytocin.

In our study, the cost of the oxytocin ampoule is 5 LE, meanwhile the cost of the carbetocin ampoule is 110 LE, which may be not applicable in most of the hospitals and among the Egyptian population as Egypt is considered one of the developing countries.

Hencefor, many studies are recommended on large population to report the incidence of adverse effects, uterine involution beyond the 24 hour. The effect of carbetocin on also the hemodynamic states, blood pressure, cardiovascular disease risk, and major PPH should be assessed to evalaute if the efficiency and benefits of carbetocin exceeds its cost.

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