

# Oxytocin vs carbetocin in management of 3<sup>rd</sup> stage at risk of PPH

## Abstract

**Background:** Postpartum haemorrhage occurs in approximately 4% of vaginal deliveries and estimates that it causes significant morbidity and 25% of all maternal childbirth related deaths.

**Objectives:** the aim of the study was to compare between oxytocin and carbetocin in the active management of the 3rd stage of labour after elective cesarean section.

**Subjects and methods:** The study was performed in Obstetrics and Gynecology department of Menoufia University hospital, Menoufia governate, Egypt. A total of 88 women eligible in the study were randomly divided into two equal groups, women who received oxytocin (group 1) and women who received carbetocin (PABAL®FERRING Pharmaceuticals LTD) (group 2). Intra-Operative uterine bleeding is calculated by adding number and weight difference of cloths used during delivery (where 100g increase in the weight of the cloths use is considered equivalent to 100ml of blood lost). Post-operative bleeding in the first 6 hours, calculated by number and weight difference of pads used. The monitoring and anesthetic techniques were identical for all women.

**Results:** The results showed highly significant difference between oxytocin group and carbetocin group as regarding haemoglobin delta change (mean of oxytocin group = -0.0489 Vs. mean of carbetocin group = -0.1148,  $p=0$ ), that carbetocin is more potent and demonstrated in their study an increased use of additional oxytocics in the oxytocin arm. According to blood loss of the women involved in this study in oxytocin group range between 250 and 950ml, with the mean of 434.706ml and SD is 191.799, in carbetocin group range between 250 and 750ml, with the mean of 366.477ml and SD is 165.001 the results showed significant difference between oxytocin group and carbetocin group as regarding blood loss ( $p=0.013$ ).

**Conclusion:** According to the results of this study it is found that there is a good overall agreement that Carbetocin might be effective in controlling the amount of blood loss during cesarean section and giving a better chance in prevention of atonic postpartum Hemorrhage.

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## Introduction

Postpartum haemorrhage is excessive blood loss in excess of 500mL in a vaginal birth and in excess of 1L in a caesarean delivery.<sup>1</sup> PPH should be diagnosed with any amount of blood loss that threatens the haemodynamic stability of the woman. A healthy woman has a 30-50% increase in blood volume in a normal singleton pregnancy and is much more tolerant of blood loss than a woman who has preexisting anemia, an underlying cardiac condition, or a volume contracted condition secondary to dehydration or preeclampsia.<sup>2</sup> Postpartum haemorrhage occurs in approximately 4% of vaginal deliveries and estimates that it causes significant morbidity and 25% of all maternal childbirth related deaths.<sup>3</sup>

Egypt has improved but still has a relatively high maternal mortality ratio of 84 maternal deaths per 100,000 live births. Postpartum haemorrhage is the leading factor contributing to 27% of maternal deaths, with poor obstetric management cited as the most frequent avoidable factor, contributing to 43% of maternal deaths.<sup>4</sup> The World Health Organization (WHO) has examined studies on postpartum haemorrhage published between 1997 and 2002 to arrive at more precise definitions of postpartum haemorrhage and estimates of its incidence, preliminary findings suggest that excessive bleeding

was reported to have occurred in 0.84% to 19.80% of deliveries.<sup>5</sup> Active management of the 3rd stage of labour is the key procedure to protect against atonic PPH. In that study we aimed to compare between oxytocin and carbetocin during Cesarean section in women at risk of PPH

## Patients and methods

### Study design

**Setting:** The study was performed in Obstetrics and Gynecology department of Menoufia University hospital, Menoufia governate, Egypt. The study was done between March 2015 to January 2017.

**Sample size and procedure:** A total of 88 women eligible in the study were randomly divided into two equal groups, women who received oxytocin (group 1) and women who received carbetocin (PABAL®FERRING Pharmaceuticals LTD) (group 2). A single surgeon operated the cesarean section. During cesarean section, women received either of the drugs at delivery of the anterior shoulder, women in oxytocin group (group 1), 20 IU of oxytocin in 1000ml of 0.9% NaCl solution IV (150ml/hour); while in the carbetocin group (group 2), a bolus of 100µg I.V were given

**Patient counseling:** Before participation in the study, the risks and benefits were explained to the volunteered women.

### Inclusion criteria

- i. Pregnancy duration more than completed 37weeks.
- ii. Patient indicated for elective cesarean section for obstetric and or medical reasons.
- iii. Women at risk of postpartum hemorrhage including:
  - iv. Grand multipara.
  - v. Previous postpartum hemorrhage.
  - vi. Polyhydraminos.
  - vii. History of active antepartum hemorrhage.
  - viii. Anemia with hemoglobin less than 10.5gm/dl.
  - ix. Uterine fibroid.
  - x. Placenta previa.
  - xi. Multiple pregnancy.

### Exclusion criteria

- i. Bleeding disorders and or coagulation defect.
- ii. Patients under anticoagulant therapy.
- iii. Placenta previa, placenta accreta.
- iv. Preeclampsia or HELLP syndrome.
- v. Hypertension, renal and heart diseases.

### For every patient the following was done

1. History taking.
2. Clinical examination.
  - a) General examination including maternal pulse, blood pressure and weight.
  - b) Obstetric palpation and FHS auscultation.
  - c) Local pelvic examination.
3. Laboratory investigations:
  - a) Complete blood picture, renal and liver function tests.
  - b) Any specific investigations if the patient required.
3. Elective cesarean section done by the same surgeon and assistant.

**Table 1** Characteristics of the study population

	Oxytocin(1)(n=44)	Carbetocin(2)(n=44)	P value
Maternal Age(mean, SD)	26.9±4.7	26.09±4.6	0.22

**Table 2** Systolic and diastolic blood pressure during cesarean section

	Oxytocin(1)(n=44)	Carbetocin(2)(n=44)	P value
Systolic(mean, range)	110.1(80-130)	98.8(80-130)	0
Diastolic(mean,range)	71.7(50-90)	65.4(40-80)	0

### Maternal observations during and after cesarean section

1. Maternal pulse and blood pressure.
2. Hematocrit and hemoglobin concentration.
3. Maternal blood loss.
4. Maternal urine output.

### Intra-operative uterine bleeding is calculated by adding

Number and weight difference of cloths used during delivery (where 100g increase in the weight of the cloths use is considered equivalent to 100ml of blood lost) (Chaudhuri et al., 2010). Post operative bleeding in the first 6hours, calculated by Number and weight difference of pads used. The monitoring and anesthetic techniques were identical for all women.

### Results

The study included 88 pregnant women undergoing elective cesarean section at term (completed 37weeks of gestation) divided into 2groups, group 1 was administered oxytocin and group 2 was administered carbetocin (Table 1). No significant difference between oxytocin group and carbetocin group as regarding age (mean of group 1=26.965years vs. mean of group 2=26.091years, p=0.22) (Table 2). Highly significant difference between oxytocin group and carbetocin group as regarding systolic blood pressure (mean of group 1=110.118 mmHg vs. mean of group 2=98.864mmHg, p=0) Highly significant difference between oxytocin group and carbetocin group as regarding diastolic blood pressure (mean of group 1=71.765mmHg Vs.mean of group 2=65.455mmHg, p=0) (Table 3). No significant difference between oxytocin group and carbetocin group as regarding pulse rate (mean of group 1=83.553bpm vs. mean of group 2=83.773bpm, p=0.856) (Table 4). Significant difference between oxytocin group and carbetocin group as regarding blood loss (mean of group 1= 434.706ml Vs. mean of group 2=366.477ml, p=0.013) (Table 5). Highly significant difference between oxytocin group and carbetocin group as regarding Pre Haemoglobin (mean of group 1=9.855gm/dl Vs.mean of group 2=10.91gm/dl, p=0). No significant difference between oxytocin group and carbetocin group as regarding Post Haemoglobin (mean of group 1=9.386gm/dl Vs. mean of group 2=9.641gm/dl, p=0.153) (Table 6). Negative significant correlation between haemoglobin change level and blood loss among oxytocin group (Cr.= -0.277, p=0.01) (Figure 1) (Table 7). Negative no significant correlation between haemoglobin change level and blood loss among carbetocin group (Cr.=0.179, p=0.096) (Figure 2).

**Table 3** Pulse rate during cesarean section

	Oxytocin(1)(n=44)	Carbetocin(2)(n=44)	P value
Pule rate(mean, SD)	83.5±7.6	83.7±8.2	0.8

**Table 4** Maternal blood loss

	Oxytocin(1)(n=44)	Carbetocin(2)(n=44)	P value
Maternal blood loss(mean, SD)	434.7±171.7	366.4±165	0.01

**Table 5** Haemoglobin levels before and after cesarean section

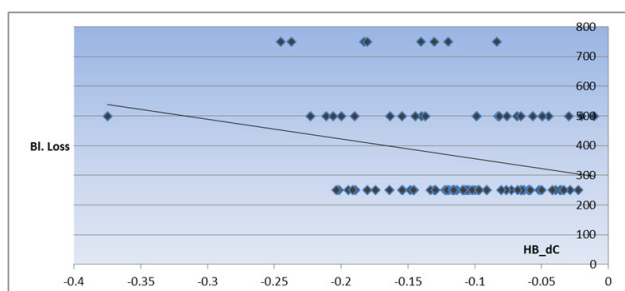
	Oxytocin(1)(n=44)	Carbetocin(2)(n=44)	P value
Pre-Operative Hb(mean, SD)	9.8±1.1	10.9±1.1	0
Post-Operative Hb(mean, SD)	9.3±1.2	9.6±1.04	0.15

**Table 6** Correlation study among oxytocin group between Haemoglobin change level and blood loss

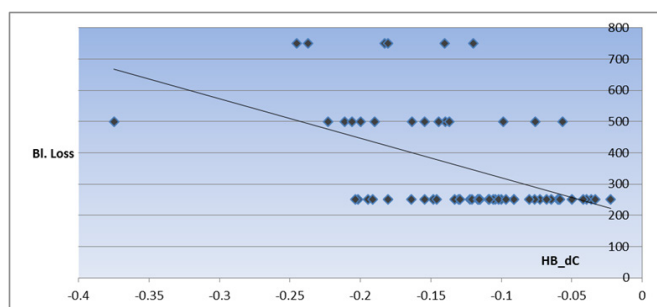
	Oxytocin(1)(n=44)	P value
(r.)	-0.277	0.01

**Table 7** Correlation study among carbetocin group between Haemoglobin change level and blood loss

	Carbetocin(1)(n=44)	P value
(r.)	-0.179	0.096



**Figure 1** Correlation study between Haemoglobin change level and blood loss among oxytocin group.



**Figure 2** Correlation study between Haemoglobin change level and blood loss among carbetocin group.

## Discussion

In our study the aim is to compare the difference between receive 20IU of oxytocin in 1000ml of 0.9% NaCl solution IV (150ml/hour) or 100µg of carbetocin (PABAL®FERRING Pharmaceuticals LTD) which are the standard clinical doses. Both drugs were administered by the anesthetist after the delivery of the baby and before delivery of the placenta. The ages of the women involved in this study, in oxytocin group range between 18 and 37years, with the mean age is 27years and SD is ±4.7, in carbetocin group range between 19 and 39years, with the mean age is 26years and SD is ±4.6, and that showed a no significant difference between the two groups (p=0.22). In our study the delta change of hemoglobin (Hb dC) of the women involved in this study, in oxytocin group range between -0.26 and 0.02gm/dl, with the mean of -0.0489 and SD is ±0.04932, in carbetocin group range between -0.38 and -0.01gm/dl, with the mean of -0.1148 and SD is ±0.06272. The results showed highly significant difference between oxytocin group and carbetocin group as regarding haemoglobin delta change (mean of oxytocin group=-0.0489 Vs. mean of carbetocin group=-0.1148, p=0), and these results are matching with Attilakos et al.,<sup>6</sup> that carbetocin is more potent and demonstrated in their study an increased use of additional oxytocics in the oxytocin arm.

Duthie et al. (1992), in their study to measure intra-operative blood loss during elective lower segment cesarean section by using alkaline hematin method, that included forty women (mean age 29years) with singleton pregnancies (mean gestation 38weeks) delivered by elective lower segment cesarean section under general anaesthesia (mean birth

weight 3177g). Certainly, there was no significant difference in the estimated blood loss, there was also no difference in the postoperative fall in haemoglobin. This method can be imprecise especially for blood loss more than 600 ml, meanwhile this study included 172 patients who had previous one cesarean section (mean age 26) with singleton pregnancy delivered by elective lower segment cesarean section under spinal anaesthesia patients and blood loss was measured by other more accurate means. As for the delta change of the drapes' weight (Wt dC) of the women involved in this study, in oxytocin group range between 1 and 3.8gm, with the mean of 1.739 and SD is 0.7672, in carbetocin group range between 1 and 3gm, with the mean of 1.443 and SD is 0.6407. Significant difference between oxytocin group and carbetocin group as regarding weight delta change (mean of oxytocin group=1.739 Vs. mean of carbetocin group=1.443,  $p=0.007$ ).

Prasertcharoensuk et al.,<sup>7</sup> considered it a gold-standard against which they compared other methods of determination of blood loss during CS. According to blood loss of the women involved in this study in oxytocin group range between 250 and 950ml, with the mean of 434.706ml and SD is 191.799, in carbetocin group range between 250 and 750ml, with the mean of 366.477ml and SD is 165.001 the results showed significant difference between oxytocin group and carbetocin group as regarding blood loss ( $p=0.013$ ). Su et al. (2012) said that mean blood loss was observed to be greater in the oxytocin group compared to the carbetocin group, but the difference was not statistically significant in their study which included 2653 women, by four trials comparing carbetocin with Oxytocin. Khan et al.,<sup>8</sup> suggested that carbetocin may be a more potent oxytocic, but it is unclear whether this will reduce the rate of PPH and in particular major PPH.

All the previous studies of carbetocin Dansereau et al.<sup>9</sup> and Boucher et al.,<sup>10</sup> demonstrated a lower rate of additional oxytocic usage, but no study has demonstrated a significant difference in the rate of PPH, which is arguably a more important outcome. The reason for this is that only a very large study with many thousands of women would have adequate power to demonstrate a significant difference in this relatively rare outcome. Perhaps, large retrospective studies from countries or institutions where carbetocin is used routinely may provide interesting data, although such studies would be prone to bias. The diastolic blood pressure of the women involved in this study, in oxytocin group range between 50 and 90 mm Hg, with the mean of 71.765 and SD is 7.7423, in carbetocin group range between 40 and 80 mmHg, with the mean of 65.455 and SD is 6.4164. Highly significant difference between oxytocin group and carbetocin group as regarding diastolic blood pressure ( $p=0$ ). The systolic blood pressure of the women involved in this study, in oxytocin group range between 80 and 130mm Hg, with the mean of 110.118 and SD is 9.9396, in carbetocin group range between 80 and 130 mmHg, with the mean of 98.864 and SD is 9.3994. Highly significant difference between oxytocin group and carbetocin group as regarding systolic blood pressure ( $p=0$ ).

The pulse rate of the women involved in this study, in oxytocin group range between 70 and 110bpm, with the mean of 83.553bpm and SD is 7.6119, in carbetocin group range between 70 and 110bpm, with the mean of 83.773bpm and SD is 8.2848. Pisan et al.,<sup>11</sup> showed a reduction in mean blood pressure, a reduction of total vascular resistance and an increase of cardiac output and of stroke volume were seen, while heart rate values remained stable in both treatment groups. No statistically significant differences were found. The haemodynamic

data are reassuring with no clinically significant differences between the two interventions. However, many of the haemodynamic changes resulting from oxytocin occur within the first 5minutes<sup>12</sup> and our study outcomes did not include continuous haemodynamic monitoring during this time period, as it was previously demonstrated<sup>9</sup> that the two drugs had similar haemodynamic profiles. Although, the slow intravenous administration of oxytocics appears to reduce their haemodynamic effects<sup>12</sup> further studies comparing the haemodynamic profiles of carbetocin and oxytocin by invasive monitoring with arterial line will provide more robust data on this subject.

No significant difference between oxytocin group and carbetocin group as regarding frequency of postpartum Hemorrhage ( $p>0.05$ ) i.e. total percentage=100%. Nevertheless, the lower use of additional oxytocics is an important outcome with possible financial savings if the additional oxytocics require prolonged administration on the labor ward or in the recovery area. However, this may be offset by the higher cost of carbetocin in comparison to oxytocin. The UK cost of a carbetocin ampoule (one dose) is £17.64 (although a reduced price may be available), whereas the cost of a 10IU ampoule of oxytocin is £0.86.<sup>6</sup> According to the current study, there is insufficient evidence that 100microg of IV carbetocin is as effective as oxytocin to prevent PPH. In comparison to oxytocin, carbetocin was associated with reduced need for additional uterotonic agents, and uterine massage. Carbetocin appears to be more effective than a continuous infusion of oxytocin and has a similar safety profile (Silcox et al., 1993). A single 100microg IV injection of carbetocin is as effective and more reliable than a standard continuous infusion of oxytocin in maintaining adequate uterine tone and preventing excessive intraoperative blood loss during CS after delivery of the placenta. It makes possible to prevent excessive bleedings, which are increased in cases of insufficient uterine tonicity. Its activity begins quickly with valid contractions obtained in 2-3min. Patients receiving carbetocin require less intervention. It is well tolerated<sup>13</sup> and it has a longer time of action (approximately 5h) than oxytocin (1h and 30min). To our knowledge, there are not specific studies of the interactions carried out with carbetocin. Nevertheless, we did not observe any pharmacological interaction with the drugs used in the peri-operative period by the anesthetists or with the drugs used in the postpartum period. From now on, it is enough to make an injection of carbetocin in the operating room; the post-operative follow-up is then simplified (Bose et al., 2009).

## Summary

In the present study 88 pregnant women at term (completed 37 weeks of gestation) were recruited to perform lower segment cesarean section. After delivery of the placenta, the volume of blood loss was assessed by weight or saturation assessment techniques by subtracting the dry weight of absorbing materials (pads, sponges, etc) from the weight of blood-containing materials and using the conversion 1gm weight=1ml to quantify the blood volume contained in the materials. Both drugs (Oxytocin and Carbetocin) were administered by the anesthetist after the delivery of the baby and before delivery of the placenta. The monitoring and anesthetic techniques were identical for all women. Significant difference between Oxytocin group and Carbetocin group as regarding blood loss (mean of group 1=434.706 vs. mean of group 2= 366.477,  $p=0.013$ ). Significant difference between Oxytocin group and Carbetocin group as regarding weight delta change (mean of group 1=1.739 vs. mean of group 2=1.443,  $p=0.007$ ). According to these results of this study it is concluded that

Carbetocin is more effective in controlling the amount of blood loss during cesarean section and eventually help in prevention of atonic postpartum Hemorrhage.

## Conclusion

The most frequent cause of PPH is uterine atony, therefore, active management of the third stage of labor rather than expectant management is recommended (Chong et al., 2004). After delivery of the placenta, the volume of blood loss assessed by weight or saturation assessment techniques by subtracting the dry weight of absorbing materials (pads, sponges, etc) from the weight of blood- containing materials and using the conversion 1gm weight=1ml to quantify the blood volume contained in the materials (Lyndon et al., 2010). According to the results of this study it is found that there is a good overall agreement that Carbetocin might be effective in controlling the amount of blood loss during cesarean section and giving a better chance in prevention of atonic postpartum Hemorrhage.<sup>14</sup>

## Recommendations

- i. Multicenter studies are needed to determine with greater certainty the potential advantages of Carbetocin.
- ii. Studies are needed to ensure the efficacy of Carbetocin superiority as regards prevention of atonic postpartum Hemorrhage.
- iii. Multicenter studies are needed to determine with greater certainty the cost effectiveness of Carbetocin.
- iv. Carbetocin is recommended to be a superior routine modality in the initial management of postpartum blood loss due to uterine atony.
- v. Efficacy of Carbetocin should be compared to other drugs such as Prostaglandins and Misoprostol.

## Acknowledgements

None.

## Conflict of interest

The author declares no conflict of interest.

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