Comparative Study between Carbetocin Versus Oxytocin in Prevention of Post-partum Haemorrhage Following Cesarean Section in High-risk Pregnancies

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Abstract: ***Background:*** To compare the effectiveness of carbetocin and oxytocin when they are administered at caesarean section for the routine prevention of postpartum hemorrhage in patients with high risk factors of PPH. ***Study Design:*** This is a comparative prospective, case-controlled, single centre study (1:1 ratio) conducted from **July 2015 and October 2016.** ***Methods:*** two hundred pregnant women between 34 and 42 weeks of gestation with a viable fetus or fetuses and at least one or more risk factor for PPH undergoing elective or emergency caesarean section under regional anaesthesia. Women were randomised to receive either carbetocin (100 cases) - group A or oxytocin (100 cases) group B. (group A) received a bolus of 100 µg IV. (Group B) received 20 IU of oxytocin in 500 ml of 0.9% NaCl solution as infusion (150 mL/hour) by the anaesthetist after the birth of the baby. ***Results:*** The two groups were comparable in the indication of CS ($p = 0.954$). The most frequent indication was previous CS in Carbetocin group and obstructed labor in the oxytocin group. Failed induction of labor was a common indication in the two groups. The amount of blood loss after delivery of the baby ranged between 300 and 1700 ml. Blood loss in Carbetocin group was significantly lower than that in Oxytocin group. The frequency of blood loss ≥ 1000 ml was higher in oxytocin group. There was significance difference between the two groups with p value 0.005. Additional uterotonic drugs were administered to 43 women of Oxytocin group compared to 18 women of Carbetocin group ($p < 0.001$). ***Conclusions:*** The current study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs 18% and $p < 0.001$). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group.

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Introduction

Prevention of post-partum haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. The primary PPH is defined as blood loss more than 500 mL after vaginal delivery and more than 1000 mL after caesarean section that occurs in the first 24 hours after delivery. Almost 500.000 women die for this potentially preventable cause each year, and up to an estimated quarter of these deaths uses to occur as a consequence of haemorrhage at time of delivery. ***(1)***

The first cause of haemorrhage at the time of delivery is uterine atony, therefore there is general agreement that active management of the third stage of labour rather than expectant management is recommended. The third stage of labor is defined as the period that follows delivery and finishes with the delivery of placenta. ***(2)***

The administration of uterotonic drugs widely prevents the PPH, significantly decreases the incidence of PPH and therefore it is the main point of active management. Oxytocin (10 IU), administered intra-muscularly, is the preferred medication for the prevention of PPH in low-risk vaginal and caesarean deliveries. Care providers should administer this medication after delivery of the anterior shoulder. Intravenous infusion of oxytocin (20 to 40 IU in 1000 mL, 150 mL/hour) ***(3).*** Is an acceptable alternative for the active management? Although the oxytocin is the most widely accepted uterotonic agent, other drugs are available, but which agent is ideal for prophylactic use is far to be clearly stated. A single dose of carbetocin given 100 µg as an IV bolus over 1 minute has been hypothesed to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in caesarean section. ***(4)(5).***

Patients and methods

This is a comparative prospective, case-controlled, single centre study (1:1 ratio) conducted from July 2015 and October 2016. At Sheik Zayed Al Nahyan Hospital and El- Hussain university hospital.

After obtaining approval from the local ethical committee and patients consent, Two hundred patients were divided equally in two groups Women were

randomized to receive either carbetocin (100 cases) group A or oxytocin (100 cases) group B. (group A) received a bolus of 100 µg IV. (Group B) received 20 IU of oxytocin in 500 ml of 0.9% NaCl solution as infusion (150 mL/hour) by the anaesthetist after the birth of the baby.

Inclusion criteria: Pregnant women between 34 and 42 weeks gestation with viable pregnancy and at least one or more risk factor for PPH undergoing either elective or emergency C.S.

Exclusion criteria: Women younger than 18 years old, history of significant heart disease, chronic illness or hypersensitivity to oxytocin or carbetocin. Women undergoing caesarean section with general anaesthesia were excluded, because carbetocin is licensed for use with regional anaesthesia only. **(6).**

Technique:

A- *Patient preparation:* On admission, the enrolled patients were subjected to proper full history including; personal, Maternal and Obstetric history, full general examination was done with especial concern to vital signs (blood pressure, plus, temperature). Routine laboratory investigations were requested and repeated as needed including blood group typing and cross matching, chemistry panel, complete blood count (CBC) and coagulation panel. Continuous pulse oximetry, heart rate and blood pressure measurements and a foley catheter should be placed. The patient vital signs are noted in three readings pre, intra and post-operative.

B- The procedure: **Carbetocin (group A)** 100 micrograms was diluted in 10 ml normal saline and adminitered slowly (over 30–60 seconds) intravenously, Women in the control group **(group B)** received 20 IU of **oxytocin** in 500ml of 0,9% NaCl solution as infusion by the anaesthetist after the birth of the baby. Measurement of blood loss was started immediately after drug administration, defining as haemorrhage a blood loss in excess of 1000 ml or more *(7).*

Primary outcome measures:

Need for additional uterotonic treatment during the first 24 hours after carbetocin or oxytocin administration, which may be administered by us for perceived inadequate uterine tone with or without hemorrhage in the first 24 hours after delivery.

Secondary outcome measures:

1. Need for blood transfusion during the first 24 hours.
2. Need for operative interventions other than the initial CS during the first 24 hours.
3. Hemoglobin post versus pre CS.
4. Amount of intraoperative blood loss.
5. Incidence of intraoperative blood loss > 500 ml.
6. Incidence of intraoperative blood loss > 1000 ml.
7. Uterus tone after uterotonic treatment.
8. Incidence of adverse effect.
9. Association between high risk factors and incidence of PPH and additional uterotonics.

Results

The current study provides sufficient evidence that carbetocin is more effective than oxytocin in reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs 18% and $p < 0.001$). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group. Since the present study demonstrated a lower rate of additional oxytocic usage after carbetocin compared with oxytocin, carbetocin may be more effective in preventing uterine atony and thereby PPH.

Table 1 shows the demographic and clinical characteristics of the two studied groups. The two groups were comparable regarding baseline characteristics. The type of cesarean delivery is shown in figure10. Emergency CS were more common in the two groups, but there was no significant difference between the two groups regarding type of CS done ($p = 0.390$).

Table 1: Demographic and clinical characteristics of the two studied groups.

	Carbetocin (n=100)	**Oxytocin (n=100)**	**pvalue**
Age (yrs)	29.7±7.9	29.5±6.5	0.891
Weight (kg)	86.6±13.3	85.2±13.2	0.329
Gestational Age (weeks)	37.9±2.3	37.4±2.3	0.149
Birth weight(gm)	2934±569	2906±590	0.730
Gravidity	4 (1 - 10)	3 (1 - 11)	0.182
Parity	2 (0 - 7)	2 (0 - 9)	0.283

Data are presented as mean ± SD or median (range)

Table 3 shows a detailed list of the risk factors detected in the two groups. The two groups were comparable in the risk factors of PPH (p = 0.938). The most frequently encountered risk factor was uterine over distension followed by prolonged labor trial. Uterine overdistension was caused by hydramnios, twins or macrosomic fetus. History of PPH in a previous delivery was a common risk factor as well as antepartum hemorrhage in the current pregnancy. The number of patients with previous cesarean delivery is shown in figure 11. There was no significant difference between the two groups in history of previous CS (p = 0.193).

Table 2: Risk factors for postpartum hemorrhage detected in the two studied groups

	Carbetocin (n=100)	**Oxytocin (n=100)**
Overdistended Uterus	17 (17.0%)	19 (19.0%)
Prolonged labor	15 (15.0%)	14 (14.0%)
Induction of labor	14 (14.0%)	16 (16.0%)
Previous CS	14 (14.0%)	14 (14.0%)
History of Postpartum Hemorrhage	12 (12.0%)	15 (15.0%)
Antepartum hemorrhage	8 (8.0%)	6 (6.0%)
Fibroid uterus	5 (5.0%)	5 (5.0%)
Use of Anticoagulant	4 (4.0%)	7 (7.0%)
Two Risk Factors	11 (11.0%)	4 (4.0%)

The amount of blood loss after delivery of the baby ranged between 300 and 1700 ml in the whole studied group. Blood loss in Carbetocin group was significantly lower than that in Oxytocin group (p = 0.005) as shown in table 4. There was a tendency towards significant difference between the two groups regarding the proportion of cases with PPH, i.e. blood loss ≥ 1000 ml (p = 0.067). The frequency of blood loss ≥ 1000 ml was higher in oxytocin group. Considering severe PPH vs. mild plus moderate bleeding (< 1000 ml), there is no significant difference between the two groups (p = 0.093).

Table 3: Amount of postpartum blood loss in the two studied groups

	Carbetocin (n=100)	**Oxytocin (n=100)**	**p value**
Volume of blood loss (mL)	29.7±7.9	29.5±6.5	0.005
< 500 mL	57 (57.0%)	42 (42.0%)	0.067
500 to < 1000 mL	34 (34.0%)	41 (41.0%)	
≥ 1000 mL	9 (9.0%)	17 (17.0%)	

Data are presented as mean±SD or No. (%)

Table 4 shows uterine response to the test drugs during the intraoperative and postoperative periods. In the two periods, more cases of Oxytocin group showed uncontracted uterine muscle in response to the test drug (p < 0.001, and = 0.004, respectively). Consequently, additional uterotonic drugs were administered to 43 women of Oxytocin group compared to 18 women of Carbetocin group (p < 0.001) as shown in figure 1. This result was adjusted to the type of CS, emergency vs. elective. Carbetocin was still more effective in reducing need for additional uterotonics with an Odds Ratio of 3.7 (95%CI: 1.9-7.1).

Table 4: Response of the uterine muscles to test drugs during the intra- and postoperative periods in the two studied groups

	Carbetocin (n=100)	**Oxytocin (n=100)**	**p value**
Intraoperative			< 0.001
Uterus Contracted	87 (87.0%)	57 (57.0%)	
Uterus Not contracted	13 (13.0%)	43 (43.0%)	
Postoperative			0.004
Uterus Contracted	82 (82.0%)	64 (64.0%)	
Uterus Not contracted	18 (18.0%)	36 (36.0%)	

Data are presented as No. (%)

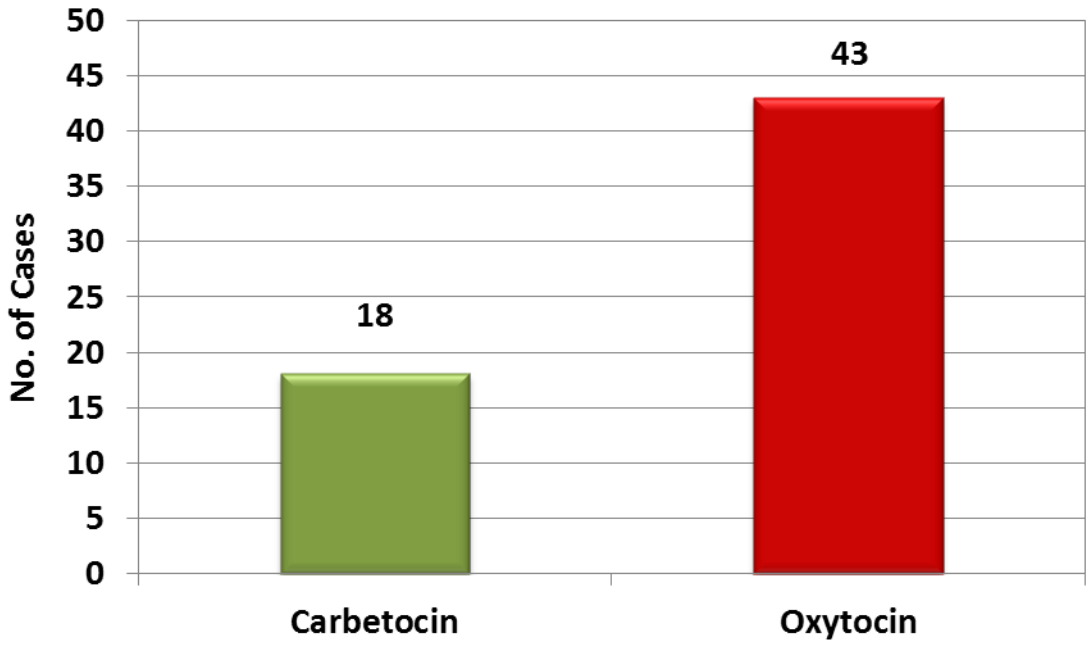

Figure 1: Number of women in need for additional uterotonic in the two studied groups

Table 5 shows pre-, intra- and postoperative levels of systolic and diastolic blood pressure. In all readings, Oxytocin group showed significantly higher values of blood pressure statistically. However, all values in the two groups were within the clinically accepted ranges (Figure 2, 3).

Table 5: Blood pressure before, during and after surgery in the two studied groups

	Carbetocin (n=100)	Oxytocin (n=100)	p value
Systolic Blood Pressure (mmHg)			
Preoperative	110±17	115±9	0.005
Intraoperative	96±9	93±7	0.045
Postoperative	106±11	109±8	0.005
Diastolic Blood Pressure (mmHg)			
Preoperative	73±7	75±7	0.024
Intraoperative	64±5	62±4	0.038
Postoperative	69±7	71±6	0.012

Data are presented as mean±SD

Table 6: Postoperative side effects of test drugs in the two studied groups

Data are presented as No. (%)

	Carbetocin (n=100)	Oxytocin (n=100)	p value
Abdominal pain	14 (14.0%)	10 (10.0%)	0.384
Nausea	13 (13.0%)	8 (8.0%)	0.249
Headache	8 (8.0%)	4 (4.0%)	0.234
Vomiting	5 (5.0%)	6 (6.0%)	0.756
Flushing	4 (4.0%)	4 (4.0%)	1.000
Pruritus	2 (2.0%)	4 (4.0%)	0.687

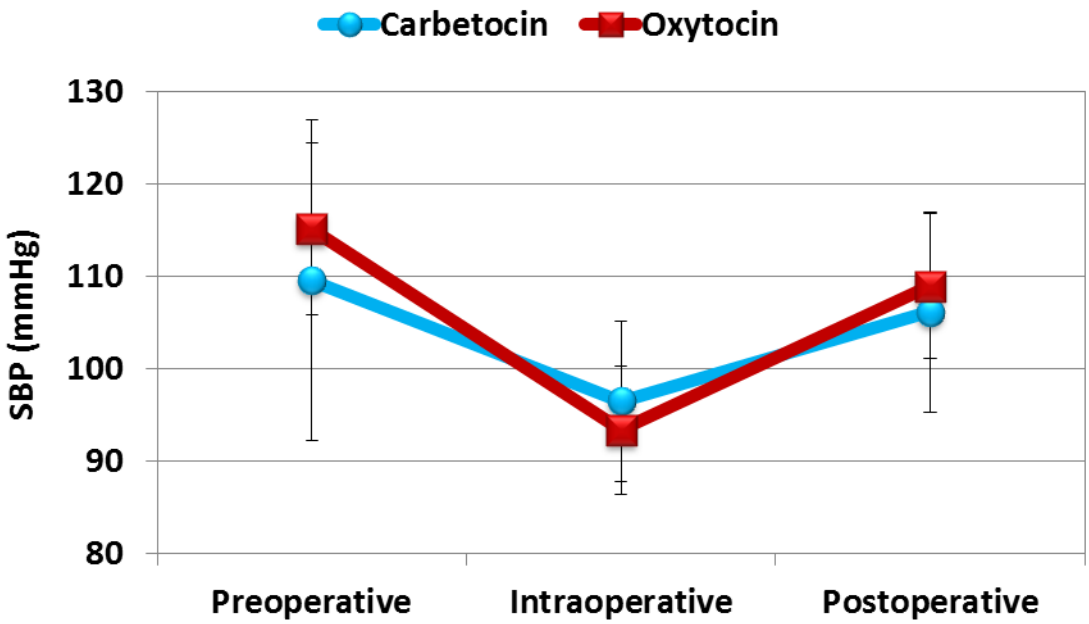

Figure 2: Change of systolic blood pressure during cesarean section in the two studied groups

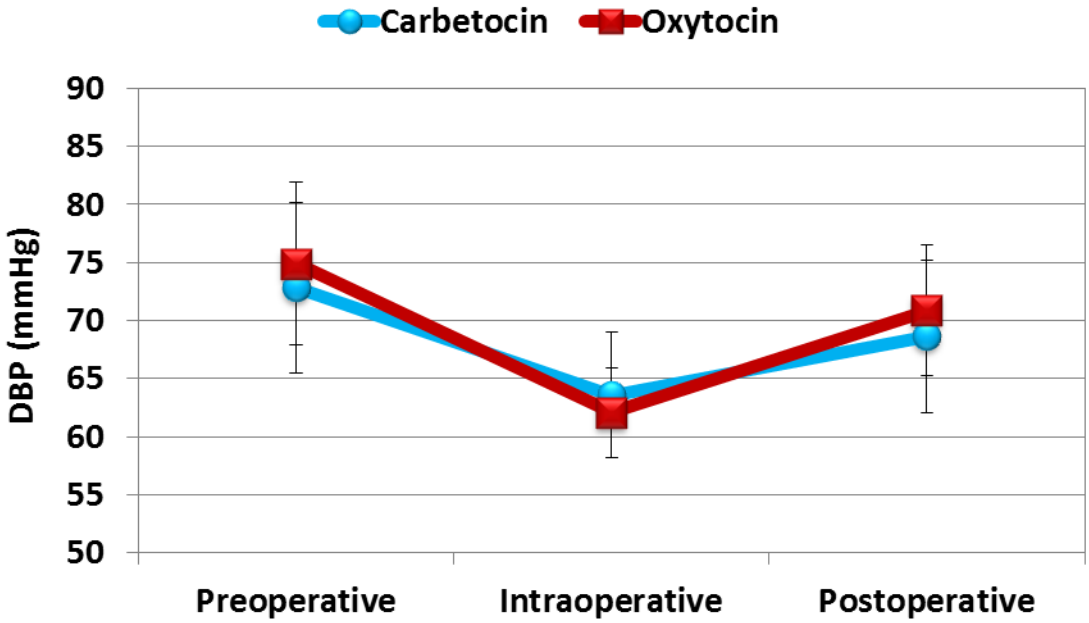

Figure 3: Change of diastolic blood pressure during cesarean section in the two studied groups

Discussion

Postpartum hemorrhage (PPH) is one of the most frequent causes of mortality and morbidity in obstetric population worldwide, causing about 25% of maternal deaths each year ***(8,9)*** and 66% of deaths due to PPH are still due to "substandard care" ***(10).*** Moreover, PPH is also the cause of 73% of all serious morbidity during pregnancy and is the most frequent obstetrical cause of admission to intensive care units ***(11).***

As the unterine atony the most common case of PPH). Active treatment during third stage of labor seems to be the chosen treatment to prevent PPH,

which reduces maternal blood loss and the risk of PPH.

The active treatment of the third stage of labor is made up of three interventions:

1. Early clamping of the umbilical cord
2. Controlled cord traction
3. Prophylactic oxytocic drug as the anterior shoulder is delivered.

Oxytocin (Syntocinon®) 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 ***(12, 13).*** 5 IU oxytocin by slow intravenous injection is currently recommended in the United Kindom (UK) for all caesarean sections ***(14).*** On the other hand, a significant limitation for its clinical use is represented by its short half-life of 4–10 min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections ***(15, 16)*** and the use of additional oxytocic medication is common to arrest bleeding, or prophylactically if there are risk factors for PPH ***(17).***

Over the past two decades, several other alternatives have been explored. Among the other agents or interventions that have been studied for prevention of PPH, the oxytocin agonist (carbetocin) was suggested as a promising agent for this indication ***(18).*** Carbetocin (Pabal®) is a long-acting oxytocin analogue indicated for the prevention of uterine atony after childbirth by CS under epidural or spinal anaesthesia. Carbetocin has a rapid onset of action (within 1–2 min); a prolonged duration of action (approximately 1 h) with a half-life approximately 4-10 times longer than oxytocin ***(19).*** Its standard dosage is a slow single intravenous (over 1 min.) or intramuscular injection of 100 µg. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus.

The primary end point of the current study was the need for additional uterotonic treatment during the first 24 postoperative hours. The carbetocin group was superior to oxytocin group in reducing the use of additional uterotonic drugs ($p < 0.001$). After adjustment to the type of CS, carbetocin was still more effective in reducing need for additional uterotonics with an Odds Ratio of 3.7 (95%CI: 1.9-7.1). We found a definitively and significantly reduced additional uterotonic need after CS in the carbetocin-receiving women compared to oxytocin group at high risk for PPH (43% vs 18% and $p < 0.001$). ***(17);*** approximately 20% of clinicians reported routine use of oxytocin infusions whereas 80% reported selective use in the presence of risk factors. In our study, most of the women who were given additional oxytocics received additional oxytocin bolus or infusion, which was typically given over 4 hours. The reason for administering additional oxytocics in the oxytocin group was likely to be more liability to develop PPH and hence more blood loss and PPH treatment. This study demonstrates that prophylaxis of uterine atony with carbetocin after CS reduced the need for additional uterotonics by more than 50 % with a power of the test of 98%, which is in accordance with the results of Holleboom ***(20).*** Borruto Lower rate of additional oxytocic need in women undergoing carbetocin administration during CS and we do reach the same conclusions ***(21, 22, and 23)***

On this item, **Su LL in the Cochrane of 2007** and in the ***Cochrane 2012*** **regarding** *"Carbetocin for preventing post-partum haemorrhage"*, conclude that the use of carbetocin is more effective than oxytocin for preventing PPH in women undergoing CS ***(24, 25).*** The amount of bleeding and occurrence of PPH were significantly lower in carbetocin group. They concluded that Carbetocin is a better alternative to traditional oxytocin in prevention of PPH in women with at least 2 factors of PPH according to Maged AM ***(26).***

The secondary outcome of the current study is the evaluation of immediate haemodynamic effects of carbetocin administration. The current study demonstrated that; the haemodynamic data are reassuring with no clinically significant differences between the two interventions and that the two drugs had similar haemodynamic profiles. Although, the slow intravenous administration of oxytocics appears to reduce their haemodynamic effects ***(27).*** The results of the present study demonstrated that carbetocin was more effective at preventing PPH than oxytocin in patients at a high risk of PPH undergoing cesarean delivery. Apparently, fewer cases needed blood transfusion for management of PPH in Carbetocin group ($p = 0.091$). In fact; the frequency of severe PPH was significantly associated with the risk factors in the affected patient ($p = 0.01$). The presence of more than one risk factor was the most frequent association followed by uterine overdistension. In our study, there was no statistically significant difference between the 2 groups regarding the occurrence of nausea, vomiting, tachycardia, flushing, headache and itching. Overall, the adverse effect profiles appear reassuringly similar between the two medications. It could be argued that some of these are not 'true' adverse effects, but rather are the effect of hypotension or surgery.

Conclusion:

The current study provides sufficient evidence that carbetocin is more effective than oxytocin in

reducing the need for additional uterotonic agents in patients at high risk for PPH undergoing CS (43% vs 18% and $p < 0.001$). A single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to maintain adequate uterine tone with statistically significant better uterine contractility in carbetocin group.

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