Carbetocin in Comparison with Oxytocin in Several Dosing Regimens for Prevention of Uterine Atony after Elective and Emergency Caesarean Section

*Akter A,[1] Uddin MN,[2] Nazneen H[3]

The aim of the study was to compare the prophylactic effects of carbetocin with those of oxytocin for the prevention of uterine atony in patients undergoing elective or emergency caesarean section (CS) in the International Medical College Hospital. The primary aim was to observe the need for additional uterotonic medication. In the International Medical College Hospital, 350 term patients were treated with single dose 100 mg of intravenous carbetocin & 350 patients were treated with 10 IU of intravenous oxytocin followed by 20 IU oxytocin in 1 litre of of intravenous fluid (Hartman or 5% DNS) @ 30 drops/min. In the carbetocin group 350 patients were included and in the oxytocin group 350 patients were included. The proportion of subjects needing additional uterotonic treatment was 2.5 % after carbetocin and 8 % after oxytocin. Carbetocin was most effective compared with 10 IU of intravenous oxytocin followed by 20 IU oxytocin in 1 litre of of intravenous fluid (Hartman or 5% DNS) @ 30 drops/min, with less need for additional uterotonic medication (2.5% vs. 8 %) and blood transfusions (1% vs. 4.5 %). Compared with oxytocin, prophylactic use of single dose 100 mg of intravenous carbetocin for prevention of uterine atony after an elective or emergency CS diminished the need for additional uterotonic drugs .

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Key words: Carbetocin, Oxytocin, Caesarean section, Uterine atony, Post-partum haemorrhage, Blood transfusion

Introduction

Postpartum haemorrhage (PPH) is defined as a blood loss of any amount or more than 500 ml following childbirth which adversely affects the general condition of the mother evidenced by rising pulse rate and hypotension. Still now PPH is a one of the main cause of maternal morbidity and mortality in developing country like Bangladesh.[1] The incidence widely varies mainly because of lack of uniformity in the criteria used in assessment of PPH, incidence is about 4-6% in our subcontinent. In the Netherlands, 1 out of 14 labouring women experiences PPH.[2] The most frequent cause of PPH is uterine atony, contributing up to 80 % of the PPH cases.[3] 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 haemorrhage. Also caesarean section is a recognized risk factor for PPH and its prevalence is increasing.[4,5] The impact of PPH on maternal morbidity and mortality makes active management of the third stage of labour to a critical key.[5,6] To prevent PPH, uterotonic agents are administered immediately after delivery of the baby.[3]

1. *Dr. Afroza Akter, Associate Professor, Department of Gynaecology and Obstetrics, International Medical College and Hospital, Gazipur. drafrozadoly@gmail.com*
2. *Dr. Mohammad Nizam Uddin, Associate Professor(CC), Department of Anaesthesiology, International Medical College & Hospital, Gazipur.*
3. *Dr. Humaira Nazneen, Associate Professor, Department of Community Medicine, International Medical College and Hospital, Gazipur.*

**For correspondence*

Oxytocin is currently the uterotonic of the 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.[3,7-9] A disadvantage of oxytocin is its short half-life of 4-10 min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections.[10]

Carbetocin is a long-acting oxytocin analogue indicated for the prevention of uterine atony after child birth by CS under spinal anaesthesia. 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.[11]

The current pharmacological policy for the prevention of PPH in Bangladesh is oxytocin.[3] Most hospitals use 10 IU intravenous oxytocin, followed by 20 IU oxytocin in 1 litre of of intravenous fluid (Hartman or 5% DNS) at the rate of 30 drops/min; for a couple of hours. The aim of the study was to compare the prophylactic effects of carbetocin with those of oxytocin in several dosing regimens for the prevention of uterine atony in patients undergoing elective or emergency CS under regional anaesthesia in the International Medical College Hospital.

Methods

Design

The study had an prospective observational design, conducted in the International Medical College Hospital from January 2015 to December 2016. Total number of 700 patients were enrolled in this study. Among them 350 term patients were treated with single dose 100 mg of intravenous carbetocin and 350 patients were treated with oxytocin 10 IU intravenous oxytocin, followed by 20 IU oxytocin in 1 litre of intravenous fluid (Hartman or 5% DNS) at the rate of 30 drops/min, for a couple of hours.

Patients

One group of term patients undergoing an elective or emergency CS under spinal anaesthesia were treated with a single injection of 100 mg of intravenous carbetocin. Another group of patients were treated with oxytocin 10 IU intravenous oxytocin, followed by 20 IU oxytocin in 1 litre of of intravenous fluid (Hartman or 5% DNS) @ 30 drops/min, for a couple of hours. Data of patients treated with carbetocin or oxytocin after elective or emergency CS under regional anaesthesia in a previous observational study were merged (140 observations).[12] No extra measurements were performed, other than the procedures routinely performed during CS. No distinction towards risk factors was made. If needed at the discretion of the obstetrician, patients were treated subsequently according to the hospital's guidelines with additional uterotonics, blood transfusions or surgical interventions.

Data collection

Patient demographics, medical history and information on the current pregnancy, co-morbidities and co-medication were collected by means of data. The study focuses on early or primary PPH, i.e. blood loss during the first 24 h after delivery[13]. During this time span, information on estimated intra-operative blood loss, additional uterotonic medication, blood transfusion, operative interventions related to PPH, haemoglobin status & adverse events was collected after carbetocin or

oxytocin administration.

Statistics

The number of patients treated with carbetocin was 350. This group was compared with 350 patients treated with oxytocin. On the base of the study of Dansereau et al,[14] the power of this comparison is 98 %. To investigate the contributing factors to the need for additional uterotonic medication, was performed: gestational age, parity, H/O PPH, antepartum blood loss and multiple pregnancy.

Results

Out of 350 patients, 140 patients (40%) underwent emergency CS & 210 patients (60%) underwent elective CS in Carbetocin group. On the other hand, among 350 patients, 266 patients (76%) underwent emergency CS & 84 patients (24%) underwent elective CS in Oxytocin group.

Table I: Patients underwent elective or emergency CS, treated with carbetocin and oxytocin following CS for prevention of PPH (n=350)

Type of CS	Carbetocin Group	Oxytocin Group
Emergency	40%(140)	76%(266)
Elective	60%(210)	24%(84)

Table II: Patients underwent primary or repeat CS, treated with carbetocin and oxytocin following CS for prevention of PPH (n=350)

Type of CS	Carbetocin group	Oxytocin group
Primary CS	60% (210)	45%(157)
Repeat CS	40%(140)	55%(193)

Out of 350 patients, 210 patients (60%) underwent primary CS & 140 patients (40%) underwent repeat CS in Carbetocin group. On the other hand, among 350 patients, 193 patients (55%) underwent repeat CS & 157 patients (45%) underwent primary CS in Oxytocin group.

Number of patients required additional uterotonic drugs	%
Carbetocin group (9)	2.5%
Oxytocin group (28)	08%

Table III: Indication of CS, patient treated with carbetocin and oxytocin following CS for prevention of PPH

Indication of CS	Carbetocin	Oxytocin
Prolonged labour	20%(70)	60%(210)
Premature rupture of membrane	20%(70)	15%(53)
Cephalopelvic disproportion	20%(70)	12%(42)
Fibroid uterus	25%(88)	06%(21)
Endometriosis	10%(35)	02%(07)
Placenta previa	03%(10)	04%(14)
Multiple pregnancy	02%(07)	01%(03)

Among 350 patients, in carbetocin group,70 patients (20%) due to prolonged labour, same number of patients due to premature rupture of membrane & cephalopelvic disproportion,88 patients (25%) due to fibroid uterus, 35 patients (10%) due to endometriosis,10 patients (03%) due to placenta previa & 07 patients (02%) due to multiple pregnancy underwent CS. On the other hand, in oxytocin group, among 350 patients, 210 patients (60%) due to prolonged labour, 53 patients (15%) due to premature rupture of membrane, 42 patients (12%) due to cephalopelvic disproportion, 21 patients (06%) due to fibroid uterus,14 patients (04%) due to placenta previa, 07(2%) patients due to endometriosis & 03 patients (01%) due to multiple pregnancy underwent CS .

Table IV: Number of patients needed additional uterotonic drugs after treated with carbetocin and oxytocin following CS for prevention of PPH

Among 350 patients in each group, 09 patients (2.5%) in carbetocin group and 28 patients (8%) in oxytocin group required additional uterotonic drugs following CS for prevention of PPH

Table V: Number of patients needed blood transfusion after treated with carbetocin and oxytocin following CS for prevention of PPH

Number of patients required blood transfusion	%
Carbetocin group (5)	1.4%
Oxytocin group (10)	2.8%

Out of 350 patients ,05 patients (1.4%) in carbetocin group & 10 patients (2.8%) in oxytocin group required blood transfusion following CS for prevention of PPH

Table VI: Number of patients needed additional operative treatment after treated with carbetocin and oxytocin following CS for prevention of PPH

Number of patients required additional operative treatment	%
Carbetocin group (00)	00%
Oxytocin group (03)	0.8%

Out of 350 patients, NO patient (0%) in carbetocin group & 3 patients (0.8%) in oxytocin group required additional operative treatment following CS for prevention of PPH.

Table VII: Number of patients needed uterine message after treated with carbetocin and oxytocin following CS for prevention of PPH

Number of patients required uterine message	%
Carbetocin group (12)	3.4 %.
Oxytocin group (88)	25%

Among 350 patients, 12 patients (3.4%) in carbetocin group & 88 patients (25%) in oxytocin group required uterine message following CS for prevention of PPH

Table VIII: Number of patients in whom, the fundus of uterus was at or below the umbilicus at the end of operation after treated with carbetocin and oxytocin following CS for prevention of PPH

Number of patients required uterine message	%
Carbetocin group (12)	92.9 %.
oxytocin group (88)	75%

Out of 350 patients, in carbetocin group 325 patients (92.9%) & in oxytocin group 263 patients (75%), the fundus of uterus was at or below the umbilicus at the end of operation after treated with carbetocin and oxytocin following CS for prevention of PPH

Table IX: Number of patients experienced a mild adverse effects (nausea, vomiting headache, abdominal pain, hypotension.) after treated with carbetocin and oxytocin following CS for prevention of PPH

Number of patient experienced a mild adverse effect	%
Carbetocin group (02)	0.5%
Oxytocin group (06)	1.7%

Out of 350 patients, in carbetocin group 02 patients (0.5%) & in oxytocin group 6 patients (1.7%), experienced a mild adverse effects (nausea, vomiting headache, abdominal pain, hypotension) after treated with carbetocin or oxytocin following CS for prevention of PPH

Discussion

The present study showed that the need for additional uterotonic drugs after elective or emergency CS under regional anaesthesia was more in oxytocin group compared with 100 mg intravenous carbetocin for prevention of uterine atony . Estimated peri-

operative blood loss, changes in haemoglobin as well as the need for blood transfusions or additional operative interventions was more in oxytocin group. Carbetocin seemed to be most beneficial compared with the oxytocin. Carbetocin led to a prompt and sustained uterine involution with firm uterine tone.

The results are in line with those of the four existing clinical studies comparing carbetocin with oxytocin in CS. Compared with intravenous oxytocin administration for several hours, carbetocin resulted in a more rapid and sustained uterine involution[15,16], less need for additional utero- tonic medication,[14,15,17] less need for uterine massage[15] and more often mild blood loss (200-500 ml). [15,16]

Since all previous studies as well as 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. Estimated peri-operative blood loss, changes in haemoglobin as well as the need for blood transfusions or additional operative interventions were more in oxytocin group. Use of carbetocin did result in a reduction in the need for therapeutic uterotonic drugs as well as the need for uterine massage after CS.[18]

In addition to treatment with oxytocin or carbetocin, the factors 'antepartum haemorrhage' and 'multiple pregnancy' had an independent and significant impact on the need for additional uterotonics drugs. These are indeed known risk factors for PPH.[4,5]

The need for additional uterotonics drugs indicates a diagnosis of uterine atony which implies intensified monitoring and possibly prolonged observation time in the postoperative recovery area with an increased use of medical staff time. The lesser use of additional oxytocics after carbetocin found in this study is therefore an important surrogate outcome measure with possible financial savings. To date, two studies have compared the cost-effectiveness of prophylactic carbetocin and oxytocin following CS. In low-risk women undergoing elective CS, carbetocin was not cost saving.[19] In contrast, in patients with risk factors for PPH, the mean cost per woman was significantly lower following carbetocin treatment compared with oxytocin treatment.[20]

In addition to effectivity, the administration of a single injection of carbetocin is more convenient than an oxytocin bolus injection that needs to be followed by several hours of oxytocin infusion. The latter requires preparation of intravenous infusion and is therefore more prone to dosing errors.[21]

Considering oxytocin bolus 5 IU infusion, a recent study demonstrated that the need for an additional uterotonic agent after oxytocin bolus 5 IU followed by 40 IU oxytocin infusion over 4 h was lower than that in the oxytocin bolus 5 IU only group.[22] A bolus of oxytocin 10 IU could theoretically have more cardiovascular side effects compared with a bolus of oxytocin 5 IU[23] or carbetocin.[17]

Nevertheless, we chose the design of the study to be observational because of the following reasons: it allows collecting 'real life' data obtained in an unselected patient population according local treatment routines and protocols. As a result an observational design reflects more closely the real clinical situation.[24] Cases with either elective or emergency CS were included in the study, to minimize variation in the outcome measures due to other factors. The observational design allowed us to recruit a rather large number of patients in a limited time frame. The cohort

was large enough to make in addition comparisons between carbetocin and oxytocin subgroups. Recent studies show that carbetocin and oxytocin have comparable haemodynamic effects and both drugs have the same acceptable safety profile.[11,17]

In conclusion, compared with oxytocin in several dosing regimens, this study demonstrates that prophylaxis of uterine atony with carbetocin after an elective CS reduced the need for additional uterotonics by more than 50%.

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