

Original Articles

Carbetocin versus Oxytocin in the Prevention of Postpartum Haemorrhage after Caesarean Section

SHAKILA YESMIN¹, FERDOUSI BEGUM², SHORMISTHA BAIN³, A.H.M.IMRUL TAREQ⁴,
SABRINA PARVIN⁵, FARHANA ISRAT JAHAN⁶, HAFIZA FARZANA⁷

Abstract

Background: postpartum haemorrhage is one of the major contributors to maternal mortality and morbidity worldwide. There are many pharmacological options for the management of postpartum hemorrhage, oxytocin being the first line choice of treatment. Carbetocin, a long acting oxytocin agonist, appears to be a promising agent for the prevention of PPH.

This comparative study was between Carbetocin Versus Oxytocin for the Prevention of Postpartum Haemorrhage in Caesarean Section

Objective: To determine the safety and effectiveness of carbetocin and oxytocin for the prevention of post-partum haemorrhage in caesarean section.

Methods: Randomized controlled clinical trial was done in the department of Obstetrics and Gynaecology of Sir Salimullah Medical College Mitford Hospital, Dhaka, between February to July 2015. Study population were 64 pregnant women admitted for delivery and underwent caesarean section, who were randomly selected. Women in the intervention group (group I) received injection carbetocin a bolus of 100 µgm IV; women in the standard treatment group (group II) received 10 IU of oxytocin in IV. Both administered immediately after childbirth. This trial was registered in SSMC MH with reference no-SSMC/2014/76.

Result: Difference of mean age, mean gestational age and indication of C/S were not statistically significant between two groups. Regarding haemodynamic effect, both drugs were almost similar. There was no significant difference in per-operative blood loss, uterine tone, level of uterine fundus, urine output in urobag and hemoglobin level. Need for additional oxytocics required 0(0.0%) vs 5(16.7%) patients in group I and group II respectively and was found statistically significant. Blood transfusion needed was 0(0.0%) vs 3(10.0%) patients and primary PPH 0(0.0%) vs 3(9.4%), though both were not statistically significant. No significant difference regarding side effects and total expense was found.

Conclusion: Administration of single bolus dose of carbetocin (100 µgIV) after delivery of the baby in caesarean section immediately reduces the need for additional oxytocics, occurrence of primary PPH and further blood transfusion. Side effects are mild and similar in both the groups.

Recommendation: Carbetocin can be considered as a good alternative to oxytocin for the prevention of PPH in C/S.

Introduction

Prevention of PPH is a major issue due to its impact on maternal mortality and morbidity. Primary PPH is

defined as blood loss more than 500ml after vaginal delivery and more than 1000ml after C/S, that occurs in the first 24 hours after delivery. In 2017, World

1. Medical Officer, Shaheed Tajuddin Ahmad Medical College, Gazipur
2. Head of Department (Obstetrics and gynaecology), BIRDEM General Hospital-2, Dhaka
3. Medical Officer, Dhaka Medical College Hospital, Dhaka
4. Assistant Registrar, National Institute Of kidney Diseases and Urology, Dhaka
5. Medical Officer, Shaheed Ziaur Rahman Medical College and Hospital, Bogura
6. Medical Officer, National Institute Of Cancer Research And Hospital, Dhaka
7. Junior Consultant, Narayanganj General Hospital, Narayanganj

Address of Correspondence: Dr. Shakila Yesmin, Medical Officer, Shaheed Tajuddin Ahmad Medical College, Gazipur.
Mobile: 01718173232, Email: shuchi.nijhum@gmail.com

Health Organization (WHO) has estimated that around 2,95,000¹ maternal deaths occurring each year on a global scale in association with pregnancy and delivery. Among them, 28.37%¹ resulting from postpartum hemorrhage. The main risk of the primary cause of postpartum hemorrhage is uterine atony which occur in 80.0% cases. The prevalence of PPH in caesarean deliveries is 0.6%.

The decreased prevalence of postpartum hemorrhage in most developed parts of the world is probably due to better management of the third stage of labor. According to, BDHS (2014) MMR is 170/100000 live births, BMMS (2016) 196/100000 live births and WHO (2015) 176/100000 live births (NIPORT).

Caesarian section rate is increasing day by day and getting accessible to every level of health care delivery system even in a country with limited facility like Bangladesh. According to BDHS (2014) delivery rate is 23.0% by caesarean section. Uterine atonicity is the most common cause of PPH. Oxytocic agents are the substances that produce rhythmic contraction of uterine muscle following delivery of the fetus and thus cause caesation of bleeding.

Conventional oxytocic agents used include oxytocin, ergometrine, syntometrine and prostaglandins. Oxytocin has been used routinely for many years. It is a short acting synthetic oxytocin.

Carbetocin is a long-acting synthetic oxytocin analogue, 1-deamino-1 monocarbo-(2-0-methyl-tyrosine)- oxytocin firstly described in 1987. The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. It has a half-life of 40 mins, around 4-10 times longer than oxytocin. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increases frequency of existing contractions and increases uterine tone. In pharmacokinetic studies, intravenous injections of carbetocin produces tetanic uterine contractions within two minutes, lasting six minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produces tetanic contractions in less than two minutes, lasting about 11 minutes and followed by rhythmic contractions for an additional two hours. In comparison to oxytocin, carbetocin induces a prolonged uterine response when administered postpartum and also ahead in terms of both amplitude

and frequency of contractions².

Till now it was recommended that Oxytocin should be used as oxytocic agent either in the form of intramuscular injection or I/V bolus or I/V infusion³. With the use of Carbetocin uterine contractions occur in less than two minutes after intravenous administration of optimal dosage of 100 µgm³. Several data of literature⁴ suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum haemorrhage. Aim of this study was to compare the haemodynamic effects of carbetocin and oxytocin, to assess the efficacy of carbetocin and oxytocin in terms of intraoperative blood loss and the need of additional uterotonic in caesarean section for management of post-partum haemorrhage and to compare side effects of them.

Materials and method:

This was a randomized controlled clinical trial from February to July 2015, carried out in the Department of Obstetrics & Gynecology, Sir Salimullah Medical College Mitford Hospital, Dhaka. Sixty four pregnant women undergoing C/S were enrolled by lottery method using different colored cards in sealed envelopes. Inclusion criteria were women at term pregnancy undergoing elective or emergency caesarean section under spinal anaesthesia in women with risk factors for PPH like multiple pregnancy, two or more previous caesarean section, uterine fibroids, past history of PPH and myomectomy.

Exclusion criteria were hypertension, preeclampsia, eclampsia, placenta previa, gestational age less than 37 weeks, cardiac, renal or liver diseases, epilepsy and general anaesthesia, as well as women with history of hypersensitivity to carbetocin or oxytocin.

A written informed consent was asked from eligible women on admission. 32 pregnant women were recruited in intervention group who received bolus dose of 100 µg of carbetocin intravenously immediately after delivery of the baby and another 32 pregnant women in control group who received bolus dose of 10 IU of oxytocin intravenously immediately after delivery of the baby.

The primary outcome of this study was the evaluation of vital signs during and after the operation, estimated blood loss (per operative and within first 24 hours after surgery), difference in preoperative and postoperative haemoglobin, uterine tone, uterine

position, urinary output, use of additional oxytocics, occurrence of primary PPH, requirement of blood transfusion adverse effects and cost. All patients received spinal anaesthesia.

To evaluate the haemodynamic effects between carbetocin and oxytocin the study was considered the drop in a blood pressure comparing the BP after spinal procedure and 5 minutes after drug administration. Occurrence of nausea, vomiting, flushing, haedache, dyspnea and tachycardia were recorded.

The latter important outcome of this study was the need for additional uterotonic agents and the evaluation of the drop in haemoglobin level by comparing the haemoglobin concentration on admission with the measure at 24 hours after delivery. Also the blood loss is checked immediately after caesarean, defining as haemorrhage a blood loss in excess of 1000 ml or more⁵. Blood loss were estimated by visual estimation, measuring collected fluid/blood in suction container before and after delivery of the placenta and weight of all blood soaked materials and clots. Calculated by (wet item in gram wt-dry item in gram wt=blood loss in gram wt. 1gram wt=1ml blood loss)⁶. Blood pressure (in mmHg), uterine tone (standardized as Very good, Good, Sufficient, Atony), uterine position (with respect to the umbilical point, UP) were monitored at 2 hours, 12 hours and 24 hours after caesarean section⁷. All patients had the Foley catheter and urobag in situ for 12 hours after caesarean section. Finally, incidence of PPH, requirement of blood transfusion and total costs are measured.

Results:

Total 70 pregnant women were initially recruited in this study. Among them 6 cases were excluded 5-

not meeting inclusion criteria, 1-other reason. Thus 64 women were included in the final analysis.

Demographic characteristics of the study patients showed- Mean age was found 26.5±4.9 years in group I Carbetocin and 27.2±4.8 years in group II Oxytocin. Majority 22 (68.8%) patients were multi gravida in group I and 23 (71.9%) in group II. The mean gestational age was found 38.6±1.6 weeks in group I and 38.9±1.6 weeks in group II. The difference were not statistically significant ($p>0.05$) between two groups. That is the groups were homogenous.

Indications of C/S were not statistically significant ($p>0.05$) between two groups. P/H/O 1C/S with other obstetrical indication was common in both groups, which was 9(28.1%) in group I and 13(40.6%) in group II. Other indications were CPD, mal-presentation, FD, obstructed labor etc.

Regarding vitals, BP (systolic & diastolic), urine output were more or less similar in both groups.

Though the difference in blood loss between two groups were not statistically significant, loss of blood was 70-100 ml less in group I.

Uterine tone and level of uterine fundus were almost similar in both groups and difference were not statistically significant ($p>0.05$).

Haemoglobin level is a proxy indicator of blood loss. The mean difference were not statistically significant ($p>0.05$) between two groups.

Administration of additional oxytocics, blood transfusion & side effects of drugs were less in group I but not statistically significant

Total cost of primary oxytocic, additional oxytocics & blood transfusion per person in group I is 140 taka & in group II is 220 taka. The difference was not statistically significant ($p>0.05$) but much higher in oxytocin group.

Table-I
Distribution of the study patients by maternal blood loss at different follow up (n=64)

Maternal blood loss (ml)	Group-I (n=32) Mean±SD	Group-II (n=32) Mean±SD	P value
Per operative	363.3±107.4	441.3±209.6	0.066 ^{ns}
Range (min-max)	250-650	300-900	
2 hrs after caesarean section	389.7±113.8	463.3±238.0	0.120 ^{ns}
Range (min-max)	270-700	330-1100	
12 hrs after caesarean section	423.8±121.2	504.0±243.3	0.100 ^{ns}
Range (min-max)	290-770	350-1150	
24 hrs after caesarean section	452.8±122.8	526.3±234.1	0.121 ^{ns}
Range (min-max)	300-800	390-1200	

s= significant, ns= not significant

P value reached from unpaired t-test

Table-II
Distribution of the study patients by hemoglobin in different follow up (n=64)

Hemoglobin (g/dl)	Group-I (n=32)		Group-II (n=32)		P value
	Mean±SD		Mean±SD		
Before administration of drug	10.7±0.9		10.9±0.8		0.351 ^{ns}
Range (min-max)	9-12.4		9.2-13		
24 hrs after caesarean section	10.2-0.8		10.0±0.9		0.351 ^{ns}
Range (min-max)	8.8±11.8		8.4-12.2		

Table-III
Distribution of the study patients by outcome (n=64)

Outcome (primary PPH)	Group-I (n=32)		Group-II (n=32)		P value
	n	%	n	%	
Yes	0	0.0	3	9.4	0.119 ^{ns}
No	32	100.0	29	90.6	

The difference was not statistically significant ($p>0.05$)

Discussion:

This randomized controlled clinical trial was carried out to determine the safety and effectiveness of carbetocin and oxytocin for the prevention of post-partum haemorrhage in caesarean section. Majority of the patients were in 3rd decade, multipara and gestational age belonged to 37 – 40 weeks in both groups. P/H/O 1C/S with other obstetrical indication, P/H/O 2C/S with scar tenderness, breech presentation with other obstetrical indication and prolonged labour with fetal distress were the commonest indication in both groups. Blood pressure, maternal blood loss, uterine tone, position of uterine fundus to the umbilical point, urine out put in urobag and hemoglobin level were almost similar between two groups. Additional oxytocics not needed in carbetocin group ($p<0.05$). On the other hand, no need of any blood transfusion, side effect and no primary PPH observed in carbetocin group. Though initial cost of oxytocin was found less but total expense was much higher than carbetocin.

Conclusion:

A single intravenous injection of carbetocin (100 µgm) appears to be more effective than a single intravenous injection of oxytocin (10 IU) for maintaining adequate uterine tone, less blood loss, no need of additional oxytocics and blood transfusion and no incidence of PPH, with a similar safety profile and

minor side effects, in the third stage and in the first 24 hours after delivery.

Limitations of the study

1. The study population was selected from one selected hospital in Dhaka city, for a very short period of time, so that the results of the study may not reflect the exact picture of the country.
2. The sample size was limited. If the study could be done in a large group of people then the results of the study would be more producible.
3. The amount of blood loss was assessed clinically and not by quantitative parameters.

Recommendation

A single intravenous injection of 100 µgm of carbetocin immediately after birth of the baby in pregnant women undergoing caesarean section under spinal anesthesia can be used effectively and safely to prevent post-partum hemorrhage.

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