Efficacy and Safety of Carbetocin in the Active Management of Third Stage of Labour Following Emergency Caesarean Section

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To evaluate the efficacy and safety of carbetocin in the active management of third stage of labour following emergency cesarean section a clinical study was conducted over a period of six months. A total of 70 patients who had undergone emergency cesarean section in tertiary level hospital was enrolled for this study. Emergency cesarean section was defined as delivery because of an emergency situation in the active phase of labour (e.g. failure to progress, obstructed labour and fetal distress) then the cesarean section was performed. Each patient obtained a single dose of 100 microgram carbetocin intravenously during cesarean section, immediately after the delivery of the baby and prior to the delivery of the placenta. Outcome measures such as primary PPH, massive blood loss, need for additional uterotonic therapy, additional blood transfusion as well as adverse effects were all documented. Massive blood loss did not occur in any patient. No patient was needed for immediate blood transfusion. Among the study population 94% patients did not need any additional uterotonics. No patient had developed fever, arrhythmia, pulmonary edema, tremor, hypotension and pruritus. Nausea complained only 4.3%, abdominal pain only 5.7%, vomiting only 4.3% and headache only 4.3% which was not statistically significant. No patients had developed PPH. Carbetocin appeared to be an effective new drug in the active management of third stage of labour in an emergency cesarean section. Carbetocin has long half-life, which ensures more effective contraction and less adverse effects. Further research is required to assess whether carbetocin is superior to conventional uterotonic agents following vaginal delivery.

[Dinajpur Med Col J 2016 Jan; 9 (1):45-52]

Key words: Emergency Cesarean section, post-partum hemorrhage, uterotonic drugs, carbetocin

Introduction

Active management of the third stage of labour (AMTSL) is a critical intervention for PPH prevention. AMTSL has become a central component for the PPH reduction strategies of governments around the world. In 2012, WHO has issued new recommendations regarding AMTSL, which can be used to strengthen and focus the implementation of this lifesaving intervention. The use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour is recommended for all births.[1] Postpartum haemorrhage (PPH) is the single most important cause of maternal mortality worldwide. It is the leading cause of maternal deaths accounting for nearly one-quarter of all maternal deaths.[2,3] The global prevalence of PPH is approximately 6% of all

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deliveries,[4] whereas in low income countries the prevalence varies from 8.6 to 18.7%.[2,5] In developing countries, mortality from PPH remains high. In low income setting, PPH accounting for 30% of maternal death,[2,5] while in Bangladesh it is 31%.[6] In 1990, the maternal mortality ratio was 574 per 100,000 live births. In 2001 the MMR was 322 per 100,000 live births. In 2010 the ratio was 194 per 100,000. MDG -2015, the target was 143 deaths per 100,000 live births.[7,8] So far the picture is really looking promising for Bangladesh. The key contribution to this decrease was a drop in mortality risk mainly due to improved access and use of health facilities. Postpartum hemorrhage may be primary that occur within 24 hours of delivery and secondary where bleeding appears after 24 hours. Primary PPH is the most common one and up to 80% cases it occurs due to uterine atony,[9,10] while secondary PPH usually related to infection. Conventional uterotonics like oxytocin has used for preventing PPH but it has some limitations like shorter half-life,[8,9] less contraction time and more side effects like fluid overload, convulsion, arrhythmia and pulmonary edema. In addition, the ergot alkaloids cannot be used in 10-15% of women who have hypertensive disorders.[2]

Further, oxytocin and ergot preparation require protection against light to preserve its effectiveness and stability.[11] Bleeding due to uterine atony, can be prevented by active management of third stage labour (AMTSL).[2] Till now it is recommended that oxytocin should be used as oxytocic agent either in form of intramuscular injection or intravenous infusion. But its adverse effects like fluid overload, convulsion, arrhythmia and pulmonary edema limits its random use.[11] Moreover, oxytocin potency deteriorates when it is exposed to temperatures greater than 30°C for prolonged periods of time. For this reason, oxytocin should be distributed and stored along a cold chain.[1] In our country cold chain is not properly maintained for oxytocin. So, there is a chance of its effectiveness and stability problems. As a result, treatment failure may occur.

Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties.[12] Carbetocin has prolonged duration of action (approximately 1 hour) which ensures more contraction time and less adverse effect.[13,14] The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. Carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone.[11]

A single dose of carbetocin has been hypothesis to act as a 16 hours intravenous oxytocin infusion regarding the increase in uterine tone and the reduction of the risk of PPH in elective caesarean section.[15] Moreover, carbetocin ensures more effective contraction and less adverse effect like headache, tremor, hypotension, nausea, abdominal pain, and pruritus.[11] Several data of literature suggest that prophylactic administration of carbetocin may be a good alternative to oxytocin to prevent post-partum haemorrhage.[15,16,17] We conducted this clinical study to evaluate the efficacy and safety of carbetocin in the active management of third stage of labour following emergency cesarean section.

Methods

The clinical study was conducted in Rangpur Medical College Hospital, Bangladesh from 1 November 2014 to 30 April 2015. About 70 pregnant women were included in this study. The participants were enrolled in the study after fulfilling the inclusion and exclusion

criteria. A written informed consent was taken from eligible women on admission.

Inclusion criteria were women with a single pregnancy undergoing emergency caesarean section due to some indications like fetal distress, prolonged labour, obstructed labour, APH etc.

Exclusion criteria were multiple gestations, hypertensive disorders in pregnancy.

Study medication was a single dose of 100 microgram carbetocin intravenously by anesthetist during cesarean section, immediately after the delivery of the baby and prior to the delivery of the placenta.

Primary outcome is primary postpartum haemorrhage (PPH) defined as blood loss from genital tract of 500 ml or more in the first 24 hours after normal delivery and 1000 ml or more in case of cesarean section. Blood loss was estimated by the surgeon in the usual way (visual estimation, number of used sanitary pad and amount of aspirated blood (BJOG 2010; 117:929-36). The secondary outcomes were massive blood loss, need for additional uterotonic therapy, additional blood transfusion as well as adverse effects within 24 hours of delivery. Uterine tone was evaluated by palpation and administration of additional uterotonics was the decision of the investigator.

Statistical Analysis

Analysis was performed by using a computer based statistical program SPSS (Statistical Package for Social Sciences) version 16. Quantitative data were shown as mean and standard deviation and qualitative data as frequency. Comparison of qualitative and quantitative data was performed by chi-square and t-student tests. $P \leq 0.05$ was considered statistically significant.

Results

A total of 85 pregnant women with a single pregnancy were initially recruited for inclusion in this study. 15 cases were excluded (8 had pre-eclampsia, 4 eclampsia, 3 multiple gestation).Thus 70 women formed the final study group and were included in the final analysis. Mean age of study population were 25.8 ± 4.5 years where minimum age was 18 years and maximum age was 38 years(Table I). Among the study population 67.1% patients had mild anemia before delivery. Mean systolic BP of patients were120±12 mm of Hg and mean diastolic BP were 78 ±10 mm of hg (Table III). Mean gestational age at delivery was 38±1.3 weeks (Table IV).Massive blood loss did not occur in any patient (Tab V).No patient was required immediate blood transfusion (Table VI). Among the study population 94% patients did not need any additional uterotonics (Table VII). Mean body weight of baby was 2.96±0.4 Kg. No patient had developed fever, arrhythmia, pulmonary edema, tremor, hypotension, and pruritus. Nausea complained only 4.3%, abdominal pain only 5.7%, vomiting only 4.3% and headache only 4.3% which was not statistically significant. No patients had developed PPH (Table IX – XI).

Table I: Distribution of the study population by Age (n=70)

Total number of patient	70
Mean	25.86
Std. Deviation	4.56
Minimum	18
Maximum	38

Mean age = 25.8 ± 4.5 years

Table I shows that the mean ±SD ages of the caesarean patients were25.8 ± 4.5 years where

minimum age was 18 years and maximum age was 38 years

Table II: Distribution of study population by anemia (n = 70)

Anemia	Frequency	Percent
Absent	23	32.9
Mild	47	67.1
Total number of patient	70	100.0

Table II shows that among the study population 32.9% (n=23) had no anemia.67.1% (47) patient had mild anemia before delivery.

Table III: Distribution of study population by Blood pressure (n = 70)

	Systolic BP	Diastolic BP
Total Number of Patients	70	70
Mean	120.36	78.86
Std. Deviation	12.75	10.84

Table III: shows that the mean ±SD systolic BP of patients were120±12 mm of Hg and Diastolic blood pressure were 78 ±10mm of Hg

Table IV: Distribution of study population by Gestational age at delivery (n = 70)

Total patient number	70
Mean	38.10
Std. Deviation	1.3
Minimum	35
Maximum	43

Table IV shows that the mean ±SD of gestational age at delivery 38±1.3 where minimum gestational age were 35 weeks and maximum gestational age were 43 weeks.

Table V: Outcome of Third stage of Labour (n = 70)

Outcome of 3rd stage of Labour	Yes/No	Frequency	Percent
Massive blood loss	No	70	100.0

Table V shows that massive blood loss did not occur in any patient

Table VI: Outcome after Third stage of Labour (n = 70)

Outcome after 3rd stage of Labour	Yes/No	Frequency	Percent
Immediate blood transfusion	No	70	100.0

Table VI shows that no patient was required immediate blood transfusion

Table VII: Outcome after Third stage of Labour (n = 70)

Additional uterotonics	Frequency	Percent
Need for additional uterotonics	4	5.7
Did not need for additional uterotonics	66	94.3
Total number of Patient	70	100.0

Table VII shows that among the study population 94% (n= 66) patients did not need any additional uterotonics. Only 6% (n=4) patients need additional uterotonics.

Table VIII: Birth weight of baby (n=70)

Total number of baby	70
Mean body weight	2.96
Std. Deviation	0.427

Table VIII shows that the mean ±SD weight of baby was2.96±0.4 kg

Table IX: Side effects (n = 70)

Side effects	Yes/No	Frequency	Percent
Fever	No	70	100.0
Arrhythmia	No	70	100.0
Pulmonary edema	No	70	100.0
Tremor	No	70	100.0
Hypotension	No	70	100.0
Pruritus	No	70	100.0

Table IX shows that no patient developed fever, arrhythmia, pulmonary edema, tremor, hypotension, and Pruritus.

Table X: Side effects

Xa: Nausea: (n = 70)

Nausea	Frequency	Percent
Yes	3	4.3
No	67	95.7
Total	70	100.0

Table Xa shows that among the study population 95.7% (n= 67) patients did not complain Nausea . Only 4.3% (n=3) patient complain it.

Xb: Vomiting: (n = 70)

Vomiting	Frequency	Percent
Yes	3	4.3
No	67	95.7
Total number of Patient	70	100.0

Table Xb shows that among the study population 95.7% (n= 67) patients did not complain vomiting only 4.3% (n=3) patient complain it.

Xc: Abdominal Pain :(n = 70)

Abdominal Pain	Frequency	Percent
Yes	4	5.7
No	66	94.3
Total number of Patient	70	100.0

Table Xc shows that among the study population 94.3% (n= 66) patients did not complain abdominal pain. Only 5.7% (n=4) patient complain it.

Xd: Headache :(n = 70)

Headache	Frequency	Percent
Yes	3	4.3
No	67	95.7
Total number of patient	70	100.0

Table Xd shows that among the study population 95.7% (n= 67) patients did not complain headache. Only 4.3% (n=3) patient complain it.

Table XI: Outcome of the patient: Primary PPH (n = 70)

Outcome of the patient	Yes/No	Frequency	Percent
Primary PPH	No	70	100.0

Table XI shows that no patients had developed PPH

Discussion

The risk of postpartum hemorrhage is much higher for women undergoing cesarean section, particularly in developing countries, where the majority of operations are carried out as an emergency procedure.[18] Globally postpartum haemorrhage (PPH) accounts for nearly one-quarter of all maternal deaths while in Bangladesh it is 31%.[6] It is the most common maternal morbidity in developed countries and a major cause of death worldwide.[19,20] The most common point at which PPH occurs is during the third stage of labour, when the uterus may suddenly lose its ability to contract. Around 80% of cases of postpartum hemorrhage due to uterine atony. [21,22]

Bleeding due to uterine atony, can be prevented by active management of third stage labour(AMTSL).[3,23] For the successful management of third stage of labour we need an effective uterotonic drug like carbetocin which has long half-life, which ensures more effective contraction and less adverse effect like nausea, vomiting, headache, tremor, hypotension, abdominal pain, and pruritus.[11] Carbetocin is a long-acting synthetic analogue of oxytocin with agonist properties.[24] The clinical and pharmacological properties of carbetocin are similar to those of naturally occurring oxytocin. Like oxytocin, carbetocin binds to oxytocin receptors present on the smooth musculature of the uterus, resulting in rhythmic contractions of the uterus, increased frequency of existing contractions and increased uterine tone.[25] As compared to oxytocin, the carbetocin molecule is better protected from the effects of aminopeptidases and disulfidases, prolonging the half-life and decreasing enzymatic degradation. Carbetocin is effective in preventing postpartum hemorrhage in both high- and low-risk groups. [26]

In pharmacokinetic studies, intravenous injections of carbetocin produced tetanic uterine contractions within two minutes, lasting six minutes, followed by rhythmic contractions for a further hour.[25] A single dose of 100 Microgram of intravenous carbetocin is more effective than 10 IU of oxytocin given to the uterine muscle during caesarean delivery to prevent PPH.[27]

However, oxytocin must be requires cold storage from the time of its manufacture until the moment it is used.[1] In our country cold chain does not properly maintained for oxytocin. So, there is a chance of its effectiveness and stability problems. As a result, treatment failure may occur. Due to maintenance of cold chain in preservation of carbetocin there is no chance of its effectiveness and stability problems. In the present study, we observed that massive blood loss did not occur in any cases and no women were required immediate blood transfusion. Additional uterotonics was needed only for 6% (n=4) patients. No major side effect was observed among the study population. No patients had developed PPH.

Postpartum haemorrhage is most preventable and treatable through active management of the third stage of labour (AMTSL) by effective uterotonics. Carbetocin appears to be an effective new drug in the active management of third stage of labour in an emergency cesarean section. Carbetocin has long half-life, which ensures more effective

contraction and less adverse effects. So, it may be a good alternative to prevent post-partum haemorrhage. Further multi-centre research is required to verify our findings.

Acknowledgments
This study was conducted by Department of Gynecology and Obstetrics, Rangpur Medical College and Hospital, Bangladesh. The preparation of carbetocin was Duratocin manufactured by Beacon Pharmaceuticals Limited, Bangladesh. The research team would like to thank all doctors, health staff and patients for participating in the clinical trial.

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