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# COMPARATIVE STUDY OF CARBETOCIN VS OXYTOCIN IN PREVENTION OF PPH FOLLOWING VAGINAL DELIVERY

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## ABSTRACT

**Background:** Postpartum haemorrhage [PPH] is the most common cause of maternal death. Oxytocin is the standard therapy for the prevention of postpartum haemorrhage, but it requires cold storage, which is not available in many parts of country. In this study an attempt is made to compare carbetocin [heat stable oxytocin] to the traditional oxytocin in the prevention of postpartum haemorrhage. More such studies may be helpful just to include carbetocin as an additional drug to prevent PPH in rural areas where there is no cold chain.

**Aim:** To study use of heat stable carbetocin in prevention of PPH. To prove heat stable carbetocin is equally effective or no inferior to oxytocin in preventing PPH.

**Methods:** A prospective study carried out from August 2022 - January 2024. The main source of data was collected from the 58 cases and 58 controls attending Ramaiah Medical College and Hospital for delivery, a tertiary care centre in Karnataka, admitted under OBG department of Ramaiah Hospital, Bengaluru . A complete data is collected by history taking, and general, systemic and obstetrics examination. Further haemoglobin of the patient before and after delivery is assessed for effectiveness of carbetocin comparable to oxytocin in preventing PPH. Data was entered into an excel spreadsheet, and descriptive statistics such as mean, standard deviation, frequency, and percentage was computed. The statistical analysis was carried out using "SPSS (Statistical Package for Social Sciences) version 22 (IBM SPASS statistics [IBM corp. released 2011])".

**CONCLUSIONS:** our study shows that a single dose of intravenous carbetocin 100 mcg may be equally effective as compared to a single intramuscular dose of oxytocin 10 IU in reducing postpartum blood loss with a smaller drop in haemoglobin levels and low incidence of adverse effects. Carbetocin has the potential to be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labour following vaginal and caesarean delivery and prevention of postpartum haemorrhage.

**Keywords:** carbetocin, oxytocin, postpartum haemorrhage, third stage of labour

## INTRODUCTION

Maternal mortality is the death of a woman from complications during pregnancy, irrespective of the duration and site of pregnancy, childbirth, or within 42 days of termination of pregnancy, excluding accidental or incidental causes. Maternal mortality is assessed with the help of Maternal Mortality

Ratio (MMR), which is the number of deaths per 100,000 live births.1 About 20% of maternal deaths are reported in South Asia. Among the countries in South Asia with the highest maternal deaths (35000 maternal deaths) estimated globally in 2017, India accounted for 12% of global maternal mortality, trailing Nigeria (23%). Postpartum haemorrhage (PPH) is the most common cause of maternal death worldwide.2 In India, the leading cause of maternal death is the obstetric haemorrhage, accounting to 47% of the cases and this number could be higher in poorer states.3 A critical step towards preventing maternal mortality is timely diagnosis and management of PPH, which is underestimated in primary care facilities in India.4 According to the most recent information from the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) in 2017, India represents 12% of global maternal deaths. In March 2022, the Registrar General of India released a Special Bulletin on Maternal Mortality Ratio (MMR), indicating a reduction of 10 points in MMR, from 113 in 2016-18 to 103 in 2017-19.5 Primary PPH is haemorrhage within the first 24 hours of delivery, while secondary PPH occurs after 24 hours but within 6 weeks of puerperium.6 The Most common cause of postpartum haemorrhage is uterine atony, resulting from poor contraction of the uterus after childbirth.7 The incidence of postpartum haemorrhage has been increasing in developed countries including the USA and Europe for the past 15 years.8 Currently, the World Health Organisation (WHO) recommends active 1management of third stage of labour for prevention of postpartum haemorrhage.7 Prophylactic administration of uterotonic agents is identified as the most important component of active management of third stage of labour, which has reduced the incidence of postpartum haemorrhage nearly by 50%. 9 The most effective method of prophylaxis of atonic postpartum haemorrhage is the use of uterotonic drugs.10 Traditionally, oxytocin is the drug of choice. However, carbetocin, a synthetic analogue of oxytocin, has been recently accepted as an equally effective uterotonic in the prevention of PPH by the WHO as well as the International Federation of Gynaecology and Obstetrics.11 Oxytocin, which has a short half-life and duration of action, is the current standard therapy for the prevention of postpartum haemorrhage. Since it is susceptible to heat, its efficacy cannot be assured in many low- and middle-income countries, where access to cold chain transport and storage is unavailable, and quality issues such as impurity and insufficient active ingredients also compromise its efficacy.12 In contrast, carbetocin, which is a long-acting oxytocin analogue, has been widely used in preventing postpartum haemorrhage since 1997, and heat-stable carbetocin, has been shown to remain active for more than 36 months at 300 C and 75% relative humidity.13 Carbetocin has comparable efficacy to that of oxytocin in prevention of PPH. In addition, it has been found to have a similar onset of action with longer lasting effect on uterine contractility.14 Carbetocin can be given via intravenous or intramuscular injection, with a lower incidence of adverse effects compared to oxytocin. This offers the advantage of reducing the necessity for additional uterotonics in primary or rural healthcare settings. Furthermore, injectable carbetocin remains stable at higher temperatures, unlike oxytocin, which needs refrigeration between 2-8°C. This characteristic makes carbetocin especially suitable for use in developing countries lacking efficient cold chain facilities, where postpartum haemorrhage is prevalent and often fatal. The utilization of carbetocin has risen since its inception in 1997, but research on its effectiveness remains limited.13 Therefore, we aimed to assess the efficacy of carbetocin versus oxytocin in preventing postpartum haemorrhage (PPH) in an urban Indian tertiary care environment.

## MATERIALS AND METHODS

### Source of data:

This is a prospective interventional comparative study conducted in department of obstetrics and gynaecology of Ramaiah Medical College and Hospital, a tertiary care centre in Karnataka, carried out for a period of 18 months from August 2022 - January 2024. The main source of data was collected from the pregnant women attending Ramaiah hospital for delivery.

Study design and method of collection of data:

**Inclusion criteria**: All women who have delivered vaginally. The inclusion criteria are: (1) at or beyond 28 gestational weeks; (2) 18–45 years old; (2) at least one risk factor for developing atony.

Risk factors include: (1) uterine over distension (i.e., suspected macrosomia, amnion fluid index ≥250 mm, multiple pregnancy); (2) intrapartum fever (above 37.8 °C); (3) prolonged labor>12 hours (including the first and the second labour stage); (4) labor induction or augmentation; (5) epidural analgesia; (6) tocolysis utility; (7) precipitate delivery; (8) operative vaginal delivery; (9) antepartum hemorrhage including marginal placenta previa and placental abruption (Grade I); (10) pregnancy complications as hypertensive disorders, gestational diabetes.
**Exclusion criteria:** Participants with cardiovascular disorders, hepatic or renal disease, epilepsy, known allergies to oxytocin or carbetocin.

Random allocation is done by using a technique that chooses individuals for both treatment groups entirely by chance with no regard to the will of the researcher or patient's condition (except taking into consideration patient's willingness and affordability to the cost of the drug) and preference. Random allocation cards using computer-generated random numbers are made. The original random allocation sequences are kept in an inaccessible third place. Allocation concealment is done to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment.
Simple randomization method is followed and subjects are assigned into two groups A and B, subjects are assigned to each group purely randomly for the assignment. As the subject is being recruited the allocation sequences are given and allocation of the treatment would be done according to the random number allocated as defined in the beginning. The study includes all women who have delivered vaginally. Quantification of blood loss is done by making a list of dry weights for delivery items that may become blood soaked with directions on how to calculate blood loss. Quantification of blood loss is begun immediately after the infant's birth (before delivery of the placenta) and the amount of fluid collected in a calibrated under- buttocks drape is assessed and recorded. Most of the fluid collected before delivery of the placenta is amniotic fluid, urine, and feces. If irrigation is used, the amount of irrigation from the total fluid that was collected is subtracted. The total volume of fluid collected in the under-buttocks drape is recorded. The preplacental fluid volume is subtracted from the post placental fluid volume to more accurately determine the actual blood loss. Most of the fluid collected after the delivery of the placenta is blood. The fluid volume collected in the drapes is added to the blood volume measured by weighing soaked items to determine the cumulative volume of blood loss or quantification of blood loss

All blood-soaked materials and clots are weighed to determine cumulative volume. 1 gram weight=1 millilitre blood loss volume. The equation* used when calculating blood loss of a blood-soaked item is WET Item Gram Weight - DRY Item Gram Weight=Millilitres of Blood Within the Item. Randomized controlled trials with outcome measure of blood loss ≥500ml are eligible if they compared carbetocin with oxytocin to prevent postpartum hemorrhage during prophylaxis of PPH in women following vaginal delivery. The primary outcome is blood loss of at least 500ml after vaginal delivery. The secondary outcomes will be blood loss of at least 1000ml; use of additional uterotonic agents; blood transfusion; uterine massage; flushing; vomiting; abdominal pain; nausea; dizziness; headache; palpitation; itching; shivering. Side-effects are also an important concern when choosing uterotonic agents. Although carbetocin seems to be an ideal agent compared to other uterotonic agents, some side-effects, such as vomiting, nausea, and dysarteriotony, are still concerning. Side-effects are also considered as secondary outcomes in these trials. Clinicians do not fully understand the side-effects of carbetocin to PPH, particularly the unanticipated ones. There seems to be a gap in the detailed presentation of the side-effects of carbetocin. Therefore, this study also aims to assess the side-effects of carbetocin compared to oxytocin in the prevention of PPH. Carbetocin 100mcg IV will be administered without any other confounding factor to subjects and then compared with the subjects who have been administered oxytocin 10IU with additional uterotonic agents. From the literature review it has been observed in a study that blood loss exceeding 500ml with carbetocin vs oxytocin was 18.5% vs 25.8%. The present study expects to get similar results with 80% power, 95%

confidence level and minimum detectable difference between 2 groups as 19%. This study requires a minimum of 58 subjects in each group.

**Sample size:** 116 (58 in each group)

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**Study Conduct**

A total of 58 subjects who were given Carbetocin and 58 subjects who were given oxytocin were enrolled in the present study. In our study a heat stable carbetocin 100 mcg intravenous is used as a part of active management of third stage of labour, in preventing PPH, in a tertiary care hospital. The study includes 58 cases where carbetocin 100 mcg intravenously was used with another group of 58 women, where oxytocin was used as a part of active management of third stage of labour. Blood loss was assessed by measuring the haemoglobin concentration before and after delivery in both groups.

## DISCUSSION

PPH is the most important cause for maternal mortality in India. Most common cause being atonic PPH, which can be prevented by using uterotonics like oxytocin immediately after birth as a part of active management of third stage of labour. Now recently newer uterotonic, heat stable carbetocin, an analogue of oxytocin, with no cold chain requirement is being used. In our study a heat stable carbetocin 100 mcg intravenously is used as a part of active management of third stage of labour, in preventing PPH, in a tertiary care hospital. The study includes 58 subjects where carbetocin 100 mcg intravenously was used with another group of 58 women, where oxytocin was used as a part of active management of third stage of labour. Blood loss was assessed by measuring the haemoglobin concentration before and 24 hours total after delivery in both cases and controls. The mean age group of study subjects among carbetocin and oxytocin group, was 27.9 years and 27.1 years respectively. Majority of subjects were belonging to lower socioeconomic class, in 30 (51.7%) subjects in Carbetocin group and 26 (44.8%) subjects in oxytocin group. Majority of subjects were educated upto degree in 34 (58.6%) subjects in Carbetocin group and 32 (55.2%) subjects in oxytocin group. 43 (74.1%) subjects in Carbetocin group and 41(70.7%) subjects in oxytocin group had no risk factors. 6 (10.3 %) subjects from each group had hypothyroidism 2(3.4%) subjects from each group had oligohydramnios and 2(3.4%) subjects from Carbetocin group had polyhydramnios. Study subjects from Carbetocin (50%) and oxytocin (50%) group were both Multigravida and Primigravida . Considerations were done for conditions which might be a relative risk factor for PPH such as induction of labour, regional analgesia and mode of labour. 44 (75.9%) subjects from Carbetocin group and 41 (70.7%) subjects from oxytocin group underwent induction of labour while the remaining had spontaneous onset of labour. 30(51.7%) subjects from Carbetocin group and 33 (56.9%) subjects from oxytocin group opted for combined spinal epidural analgesia and 13 (22.4%) subjects from Carbetocin group and 14 (24.1%) subjects from oxytocin group were given Intrathecal analgesia. Among Carbetocin group , 42 (72.4%) underwent normal delivery, 16 (27.6%) underwent instrumental delivery. Among oxytocin group 55 (94.8%) underwent normal delivery, 3 (5.2%) underwent instrumental delivery. In our study we observed that the mean blood loss with the Carbetocin group was 227 ml and with the oxytocin group was 234 ml with no statistically significant difference. In Carbetocin group , other uterotonics used along with carbetocin were oxytocin, methergine, carboprost, misoprostal, and tranaexemic acid and in oxytocin group along with oxytocin other uterotonics used were methergine, carboprost, Misoprostol and tranaexemic acid. 42 (72.4%) subjects among Carbetocin group and 40 (69.0%) subjects among oxytocin group needed no additional uterotonics. In the Carbetocin group 8 (13.8%) subjects needed only one additional uterotonic whereas in the oxytocin group 8 (13.8%) subjects required additional 2 uterotonics and 7 (12.1%) subjects needed 5 additional uterotonics, therefore the oxytocin group requiring more additional uterotonics compared to the Carbetocin group. 3 subjects in the oxytocin group required ballon tamponade and 2 subjects in the Carbetocin group required balloon tamponade. Mean

haemoglobin before delivery in carbetocin group was about 12.04gm/dl and in oxytocin group was 12.29/dl, and after delivery mean haemoglobin in Carbetocin group was 11.16gm/dl and in oxytocin group was 11.05gm/dl. The fall in haemoglobin is not very significant with p value of 0.042 and a mean difference of only 0.4 gm/dl between the two groups. 22(37.9%) subjects among carbetocin group had blood loss less than 200 ml, 32 (53.4%) had blood loss between 200 – 400 ml, and 5 (8.6%) subjects had blood loss greater than 400ml. Among oxytocin group 17 (29.3%) had blood loss less than 200 ml, 41 (70.7%) subjects had blood loss between 200-400 ml and no subject had a blood loss greater than 400 ml, thereby implying that larger group of subjects among the oxytocin group had blood loss of 200 – 400 ml compared to the oxytocin group.

1. Maternal and obstetric characteristics and labour

| | CARBETOCIN N = 56 | OXYTOCIN N = 56 | P value |
|---|---|---|---|
| Age (Mean) years | 27.91 | 27.10 | 0.32 |
| Multigravida | 29 | 31 | 0.85 |
| Induction of labour | 44 | 41 | 0.52 |
| Regional anesthesia | 43 | 47 | 0.67 |
| Duration >20 hrs | 2 | 4 | 0.53 |
| Instrumental delivery | 16 | 3 | 0.002 |
| Birth weight (mean) | 2.8358 | 2.8351 | 0.992 |

1. Primary and secondary outcomes

| | CARBETOCIN N = 56 | OXYTOCIN N = 56 | P value |
|---|---|---|---|
| 1.Primary outcomes | | | |
| HB reduction post delivery | 0.88 | 1.23 | 0.042 |
| Estimated blood loss > 400 ml | 5 | 0 | |
| Embolization | 0 | 0 | |

| | | | |
|---|---|---|---|
| Vascular ligation | 0 | 0 | |
| Blood transfusion | 0 | 0 | |
| Hysterectomy | 0 | 0 | |
| Maternal death | 0 | 0 | |
| 2.Secondary outcomes | | | |
| Estimated blood loss > 200 ml | 36 | 41 | 0.030 |
| Additional uterotonics | 8 | 17 | 0.016 |

We have compared our results with the study conducted by others.

In our study 58 subjects received carbetocin and 58 subjects received oxytocin, who underwent vaginal delivery. According to akriti Anurag et al, a prospective randomized interventional study where 250 women with singleton pregnancy undergoing vaginal delivery were divided into two groups, group A and B receiving carbetocin and oxytocin respectively. carbetocin has a longer duration of action. Moreover, carbetocin was also found to be more effective as a single and safe intramuscular/intravenous dose. The cost of carbetocin in India is higher than that of oxytocin, with 100mcg carbetocin costing 300 rupees and 10 units of oxytocin costing 100 rupees. However, the non-requirement of cold chain as well as the efficacy of single dose make carbetocin a useful drug in the developing countries such as India.

Mean haemoglobin before delivery in carbetocin group was 12.04gm/dl and oxytocin group was 12.29/dl, and after delivery mean haemoglobin in carbetocin group was 11.16gm/dl and in oxytocin group was 11.05gm/dl. The fall in haemoglobin was not very significant with p value of 0.042 and a mean difference of only 0.4 gm/dl between the two groups. Among oxytocin group 17 (29.3%) subjects had blood loss less than 200 ml, 41 (70.7%) subjects had blood loss between 200-400 ml. As per M. Widmer et al,[126] the frequency of blood loss of at least 500ml or the use of other uterotonic agents was 14.5 % in the carbetocin group and 14.4 % in the oxytocin group, a finding that was consistent with non-inferiority. The use of other uterotonic agents, interventions to stop bleeding, and adverse effects did not differ significantly between the two groups. Heat stable Carbetocin was non inferior to oxytocin for the prevention of blood loss of at least 500ml or the use of additional uterotonic agents.

| | | |
|---|---|---|
| Need for additional uterotonics | CARBETOCIN | OXYTOCIN |

| | | |
|---|---|---|
| Widmer et al | 10.4 % | 10.4% |
| Ben tareef et al [134] | 8.8 % | 12% |
| Sergio Rosales et al | 1.5% | 5.8% |
| Caglar cetin et al[135] | 20% | 37.3% |
| Present study | 27.6 % | 31% |

| | | |
|---|---|---|
| Blood loss | | |
| Korb et al[133] (> 500ml) | 4% | 5.8% |
| Sergio Rosales et al [135.] (>500ml) | 18.4% | 25.8% |
| Caglar cetin et al[135] (>500ml) | 10.7% | 12% |
| Present study (>400ml) | 8.6% | 0 |
| Blood transfusion | | |
| Widmer et al | 1.6% | 1.3% |
| Ben tareef et al [134] | 0.3% | 1.4% |
| Sergio Rosales et al | 1.7% | 2.6% |
| Caglar cetin et al[135] | 1.3% | 5.4% |

| | | |
|---|---|---|
| Present study | 0 | 0 |
| Surgical procedures | | |
| Widmer et al | 1.1 % | 0.9% |
| Present study | 0 % | 0 % |
| Reduction in HB | | |
| Caglar cetin et al[135] | 1.03 | 1.3 |
| Ahmed Maged et al | 0.6 | 0.56 |
| Present study | 0.88 | 1.23 |

In our study, blood loss was assessed by measuring the haemoglobin concentration before and 24 hours after delivery in both groups. It was found to be not very significant with p value of 0.042. S.A.Esseiah et al,[127] a randomized controlled trial, where 120 patients with multiple pregnancies undergoing caesarean delivery under regional anaesthesia, studied by comparing amount of haemoglobin 24 hours post operative period in the assessment of carbetocin and oxytocin was found that, carbetocin is more powerful and beneficial in avoiding atonic postpartum haemorrhage than the oxytocin and ergometrine combination.

In the study by, Alsaeed A. Askar et al,[130] a prospective double blind randomized controlled study, 2 drugs were compared and concluded that a single dose of intramuscular carbetocin 100mcg may be more effective as compared to a single intramuscular dose of syntometrine (5IU of oxytocin and 0.5 mg of ergometrine) in reducing post-partum blood loss with a smaller drop in haemoglobin levels and low incidence of adverse effects. Carbetocin has the potential to be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labour following vaginal delivery and prevention of postpartum haemorrhage.

According to Xin-Hang Jin et al,[125] according to latest evidence suggested that, due to insufficient amounts of active ingredient, nearly 45.6% to 74.2% of oxytocin samples failed quality tests in many countries.

D.Mannaerts et al,[128] concluded that oxytocin and carbetocin have a similar effect on nausea and vomiting, if there is any difference it would be that carbetocin probably results in less nausea and vomiting, which may be clinically relevant although the difference did not reach statistical significance due to lack of sufficient power in this study. Both products have similar influence on BP, heart rate, the need for vasopressor, and blood loss.

Fiona J. Theunissen et al,[129] concluded that heat stable carbetocin is being investigated as a potential alternative to oxytocin in prevention of PPH in vaginal deliveries. Two clinical trials with 3 drug comparison are used here.

## CONCLUSION

Our study used carbetocin in prevention of PPH in one group and Oxytocin in prevention of PPH in another group as a part of active management of labour. Blood loss , need for additional uterotonics, adverse effects and haemoglobin before and after delivery of both groups were compared.

This study shows that a single dose of intravenous carbetocin 100 mcg may be equally effective as compared to a single intramuscular dose of oxytocin 10 IU. The study also reveals that, the reduction in postpartum blood loss and a smaller drop in haemoglobin levels and low incidence of adverse effects, of carbetocin is comparable and similar to oxytocin used in active management of third stage of labour.

Carbetocin has the potential to be considered as a good alternative to conventional uterotonic agents used in managing the third stage of labour following vaginal delivery and prevention of postpartum haemorrhage, with its additional advantage of its heat stability and prolonged duration of action. We also conclude that Carbetocin is preferable to oxytocin in developing countries, as no cold chain management is needed and also reduces the financial burden associated with cold chain management.