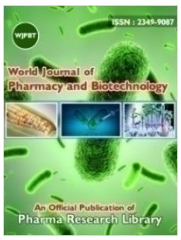

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A prospective study on outcomes of heat stable carbetocin vs. Oxytocin on prevention of postpartum haemorrage

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A B S T R A C T

Background: Postpartum haemorrhage contributes 27% of all maternal fatalities that occur globally each year and 14 million women worldwide suffer with postpartum bleeding annually. **Objective:** To study the efficiency of heat stable carbetocin over the oxytocin in the prevention of the postpartum haemorrhage. **Patients and methods:** This study included 130 women and were assigned into two groups of 65 patients: Group 1 includes carbetocin single dose recipients of 100ug- IM in vaginal delivery and 100ug-IV in caesarean delivery, administered slowly for 1minute and Group 2 includes oxytocin drug recipients of 10IU-IV, infused in 500(ml) of Nacl solution, administered for about 15- 60 minutes until desired dilatation and 10IU-IM after child birth. **Results:** Regarding predelivery haemoglobin and HCT, there was no statistically significant difference and postdelivery there was statistically significant differences between the two study groups. There was significant increase in frequency of blood transfusion and need of additional uterotonic drugs in oxytocin group regard to carbetocin group. There was statistically significant increase pain perception in oxytocin group than carbetocin group. There was statistically significant increased incidence of pruritus in carbetocin group than oxytocin group. There was statistically significant increase in frequency of nausea, vomiting, sweating in oxytocin group compared to carbetocin group. There was significant increase in frequency of elevated temperature in carbetocin group compared to oxytocin group. Conclusion: Carbetocin has the non- inferiority effect on oxytocin for prevention of postpartum haemorrhage.

Keywords: Carbetocin, Oxytocin, Postpartum haemorrhage, Pruritus, Pain perception

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Postpartum haemorrhage [PPH]- is defined as greater than 500ml estimated blood loss in the vaginal delivery or than 1000ml estimated blood loss at the time of caesarean delivery (i.e.) excessive blood loss after the childbirth.

Category of PPH:

PPH can be categorised based on the amount of blood loss and when the bleeding occurs:

- Minor PPH: A blood loss of 500-1000ml has occurred without any noticeable symptoms of shock.
- Major PPH: More than one 1000ml of blood lost, or less than one 1000ml of visible blood lost together with clinical shock symptoms.

- Primary PPH (Acute phase): PPH occurring immediately from the genital tract in excess to 500ml within 24 hours of delivery.
- Secondary PPH (Late phase): PPH occurring from the genital tract in excess 500ml from 24 hours up to 12 weeks post-delivery.

Figure 1. Postpartum haemorrhage

Epidemiology

- According to projections, 287000 maternal fatalities occurred globally in 2020, with the majority of those deaths taking place in the least developed nations of the world. More specifically, South Asian and sub-Saharan African nations accounted for 87% of global maternal fatalities.
- The primary cause of maternal mortality, responsible for 27% of all maternal fatalities that occur globally each year, is obstetric haemorrhage. PPH is the primary cause of these fatalities. According to estimates from the World Health Organization (WHO), 14 million women worldwide suffer with PPH annually.

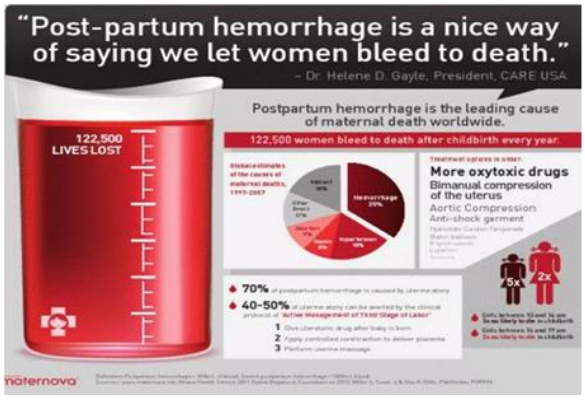


Figure 2. Epidemiology of Postpartum haemorrhage

Causes:

Uterine Atony: This is when uterine muscles do not contract enough to clamp the placental blood vessels shut. This leads to a steady loss of blood after delivery.

Prolonged Labour: When the combined duration of the first and second stage is more than arbitrary time limits of 18hours. They are two phases

Latent Phase: This is the period from 0-3cm dilatation of the cervix, Latent phase is about 8hours in primigravida and 4hours in multi gravidas.

Active Phase: The period from 3 – 10cm full dilation of the cervix.

Uterine Rupture: Is a serious complication where uterus tears and break open. Uterine rupture can allow a part of the umbilical cord to enter the peritoneal cavity or broad ligament also cause abdominal pain vaginal bleeding a change in the contraction pattern and a non-reassuring fetal heart rate tracing.

Gestational Diabetes Mellitus

Degree of impaired glucose tolerance of with onset of first recognition during pregnancy, there is a state called diabetogenic state peak 24 – 28 weeks.

Clinical manifestations:

- The main clinical manifestation of PPH is heavy bleeding from the vagina (or directly from the uterus at caesarean section).
- There may also be signs of haemodynamic instability, such as tachycardia, hypotension, prolonged capillary refill time or cool peripheries.
- Other clinical manifestations are dependent on the underlying cause of the haemorrhage**.**

Diagnosis:

Assessment and measurement of blood loss-

- **Clinical:** The golden hour is the time at where resuscitation has to begin to achieve maximum survival before the metabolic acidosis.
- Rule of 30- 30% blood loss - SBP fall by 30% -- HR increase by 30/min – RR > 30/min – Hb/HCT drop by 30% - urine output fall to < 30ml/hr.
- **Visual methods:** Brass-V method, soaked pads, Gravimetric method, Acid- Hematin method, Measurement of Isotope Cr51 tagged erythrocytes, Plasma volume changes by radioactive tracer.

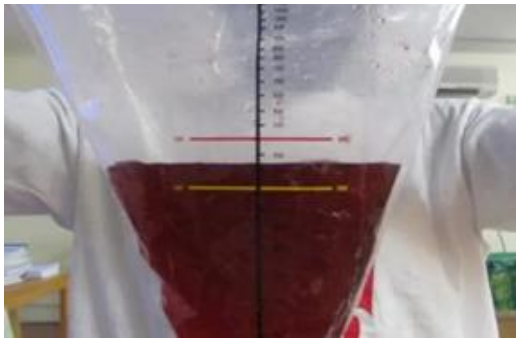


Figure 4: Brass V method

Management and prevention of PPH:

Healthcare providers treat PPH as an emergency in most cases. Stopping the source of bleeding as fast as possible and replacing blood volume are the goals of treating postpartum haemorrhage. T-stat and K-stat is been used.

- ABCDE approach should be adopted when managing patients with PPH.
- **Airway:** Consider airway adjuncts and call for anaesthetic support if there is an airway problem.
- Breathing: Assess respiratory rate and oxygen saturation as well as performing auscultation of the chest. Consider supplemental oxygen.

Carbetocin

Carbetocin is a long-acting, synthetic, uncharged peptide agonist substitute for oxytocin and is employed to manage excessive bleeding and postpartum haemorrhage following childbirth.

Indication: Duratocin (carbetocin injection) is indicated for the prevention of postpartum haemorrhage by controlling uterine atony.

- Paediatrics - Paediatrics (< 18 years of age)
- Geriatrics - Geriatrics (≥65 years of age)

Contraindications:

- Intentional or medical inducement of labor, prior to baby's delivery.
- In patients with a history of hypersensitivity to oxytocin or carbetocin.
- In patients with serious cardiovascular disorders**.**

Clinical pharmacology:

Mechanism of Action- Carbetocin is a synthetic analogue of oxytocin that lasts for a longer period of time. It selectively binds to oxytocin receptors in the uterine smooth muscle, thereby stimulating rhythmic uterine contractions and increasing both frequency of existing contractions and uterine tone. Additionally, it enhances uterine involution early in postpartum.

Pharmacodynamics:

Onset: 1.2 ± 0.5 minutes (IV).

Duration: Approx 60 minutes(IV); approx. 120minutes (IM).

Pharmacokinetics:

Absorption: Bioavailability- 77% (IM), Plasma concentration- 30 minutes (IM).

Half-life- 40minutes: Distribution: Enters breast milk (small amount), Volume of distribution: 22 L. Excretion: Via urine (<1% as unchanged drug), Elimination half-life: 33 minutes (IV); 55 minutes (IM).

2. Methodology

Study Site: The current study was conducted in Obstetrics and Gynaecology department at CKM Government Maternity Hospital, Warangal and Laxmi Narsimha hospital, Hanamkonda.

Study Design: A prospective cohort study.

Study Period: The current study was carried out for 6 months period of time from May- 2023 to November-2023.

Study Sample: The study was conducted on 130 total samples, out of 65 are of carbetocin recipients and the other 65 are of oxytocin recipients.

Study criteria:

Inclusion criteria:

- Patients with lower risk of pregnancy.
- Patients with higher risk pregnancy.
- Patients with gestational diabetes mellitus(>24weeks).
- Patients with gestational hypertension (>20 weeks).
- Patients with polyhydramnios (>20cm AFI).
- Patients with twin pregnancy.
- Exclusion criteria:
- Pediatrics (< 18 years of the age).
- Geriatrics (> 65 years of age).
- Gestational age less than 28 weeks.
- Patients with eclampsia, pre-eclampsia, epilepsy.
- Patients with coronary artery disease.
- Patents with past medical history of renal disorders or known coagulopathy disorders.
- Patients allergic to carbetocin and the oxytocin.
- Patients using carbetocin and the oxytocin prior to delivery.

Study procedure:

Patients who meet the required criteria for the study especially, GDM(>24weeks), gestational hypertension (>20 weeks), polyhydramnios (>20cm AFI), twin pregnancy and in cases of low risk or high-risk patients are registered and included in the study. These categorized patients were assigned into two groups as- Group 1 which includes the carbetocin single dose recipients of 100ug-IM in vaginal delivery and 100ug-IV in caesarean delivery, administered slowly for about 1minute and Group 2 includes the oxytocin drug recipients of 10IU-IV, infused in 500(ml) of Nacl solution, administered for about 15- 60 minutes until the desired dilatation and 10IU-IM after the child birth.

Monitoring:

All the patients were in stable condition were subjected to full history through clinical and obstetric examination, including Vital signs, blood pressure (BP), were checked before delivery and immediately after placental delivery, for 24 hours. The blood pressure was measured; immediately after delivery and every hour after delivery for 24 hour and if any fluctuations noticed were noted and the patients prone to eclampsia or with any potential higher risk during the delivery were excluded from the study. If any potential side effects of the drugs were present are recorded.

Laboratory investigations:

Blood group and RH type, complete blood picture with Hb level and Hct. Coagulation profile, PLT, bleeding time, clotting time are noted. Blood sugar profile is derived which includes FBS, PPBS, HbA1C before and after the delivery. Renal function tests, Liver function tests were analyzed for safety. Trans abdominal ultrasonography is assessed for gestational age, site of placenta, fetal weight, CFMF, AFI, fetal presentation.

Assessment of efficacy:

Efficacy will be assessed as the primary outcome measures by blood loss volume (includes estimation of blood loss by visual estimation (padding and brass v method during the delivery and within 24hrs of the delivery, Hb values) and development of PPH that requires induction of blood transfusion and utilization of additional uterotonics.

Assessment of safety:

Secondary outcomes which indicate the safety were incidence and amount of Hb and HCT changes pre-and post-delivery, vital signs during and after delivery, time of discharge from hospital, side effects post-delivery (pruritus, fever, pain perception, nausea, vomiting, sweating were included in the study).

Source of the study:

- Patient medical records. Laboratory data.
- Scanning reports.
- Assessments from the patients. OBGYN specialists.
- Midwifery staff.

Case report form:

- A written informed consent form (annexure-1) was prepared which consisted of a description of the study, was obtained from participants who met the

inclusion criteria of the study and were enrolled in the study.

- The study suitable designed data collecting form or case report form was prepared (annexure-2) which includes patients' demographics, other background information, treatment and other requirements of the study.

Statistical analysis:

The collected data throughout history of the patient, basic clinical examination, laboratory investigations and outcome measures were coded, entered in Microsoft Excel software. Data was primarily analyzed and then imported into Domatics- graph pad software for analysis. As per the type of data, where numbers and percentages are qualitative represented, while the quantitative data is represented in Mean ± SD. To calculate the difference between two or more groups of qualitative variables, Chi square test ($\chi 2$) is used. To compare distributed variables difference between two independent groups paired t-test is used. P-value had set at <0.05 for significant results, and <0.001 for highly significant difference.

3. Results and Discussion

Table 1: Primary data of study groups

Variable	Group 1 (n=65)	Group 2 (n=65)	t-test value	P- value
Age (years) Mean ± SD	25.72±4.0	25.54 ± 4.1	0.3	0.7
Gravidity Mean ± SD	1.94 ±0.8	2.0±1.0	0.7	0.4
Gestational age (weeks) Mean ± SD	34.8±1.9	34.5±2.2	1.6	0.1

Table 2.Vital sign of pre and post administration of drug in two groups

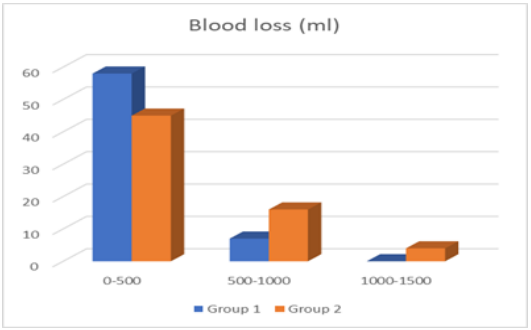
Vital sign	Group 1 (n=65)	Group 2 (n=65)	t-test value	P- value
Pre delivery systolic blood pressure Mean ± SD	135.25± 9.08	128.93± 13.97	1.7	0.09
Post- delivery systolic blood pressure Mean ± SD	122.50± 7.8	128.21± 13.89	1.8	0.08
Pre delivery diastolic blood pressure Mean ± SD	95.79±13.3	93.07± 10.7	0.8	0.4
Post delivery diastolic blood pressure Mean ± SD	85.32± 11.6	83.93± 7.86	0.7	0.5

Table 3. Haemoglobin, HCT values of pre and postdelivery in two study groups

Variable	Time		Group 1 (n=65)	Group 2 (n=65)	P- value
Haemoglobin (mg/dl)	Pre	Mean ± SD	11.7± 1.0	11.5± 0.9	0.1
	Post	Mean ± SD	10.4±1.0	9.8±1.3	0.03
HCT	Pre	Mean ± SD	34.4 ± 2.0	33.8 ± 1.8	0.07
	Post	Mean ± SD	31.97±1.2	31.4±1.5	0.04

Table 4.1 Estimated blood loss

Category	Group 1 (n=65)		Group 2 (n=65)		χ^2 -value	P-value
	No.	%	No.	%		
0-500(ml)	58	89.2	45	69.2	12.8	0.001
500-1000(ml)	7	10.7	16	24.6		
1000-1500(ml)	0	0	4	6.15		



Graph 1. Estimated blood loss

Table 4.2 -Estimated blood loss

Blood loss(ml)	Group 1(n=65)	Group 2(n=65)
0-500	58	45
500-1000	7	16
1000-1500	0	4

Table 5: Blood transfusion and utilization of the additional uterotonics

Variable	Group 1 (n=65)		Group 2 (n =65)		χ^2 - value	P-value
	No.	%	No.	%		
Additional drugs:						
Yes	6	9.2	25	38.5	23.46	<0.001
No	59	90.8	40	61.5		
Blood transfusion:						
Yes	5	7.69	12	18.5	5.07	0.025
No	60	92.3	53	81.5		

Table 6: Pain perception and Pruritus

Variable	Group 1 (n=65)		Group 2 (n=65)		χ^2 value	P-value
	No.	%	No.	%		
Pain perception:						
Heavy	19	29.2	31	47.7		
Moderate	29	44.6	22	33.8	8.9	0.01
Minimum	17	26.1	12	18.5		
Pruritus:						
Present	25	38.5	3	4.6	8.9	<0.001
Absent	40	61.5	62	95.4		

Table 7: Comparison of side effects in both drugs

Side effects	Group 1 (n=65)		Group 2 (n=65)		χ^2 value	P-value
	No.	%	No.	%		
Nausea:						
Present	9	13.8	17	26.2	5.1	0.02
Absent	56	86.2	48	73.8		
Vomiting:						
Present	12	18.5	20	30.8	4.6	0.03
Absent	53	81.5	45	69.2		
Increased Temperature:						
Present	10	15.4	5	7.7	5.4	0.02
Absent	55	84.6	60	92.3		
Sweating:						
Present	4	6.2	13	20	7.7	0.005
Absent	61	93.8	52	80		

- The current prospective cohort study on the comparison of outcomes of carbetocin and the oxytocin in PPH included total of 130 samples, out of 130 samples – 65 samples are the recipients of carbetocin-100ug-IM in vaginal delivery and 100ug-IV in caesarean delivery and 65 samples are the oxytocin- 10IU-IV, infused in 500(ml) of Nacl solution and 10IU- IM were enrolled and the results are estimated.

- There are no statistically significant differences in the demographic data in relation of both the groups and in conventional criteria which included the age greater than 18 years, gestational age greater than 28 weeks, gravidity did not show the statistically significant difference in between group 1 of carbetocin and group 2 of the oxytocin.
- In the vital sign, the blood pressure is recorded. The systolic and diastolic blood pressure prior to delivery and postdelivery has no statistically significant difference in both the groups, however we noticed the gradual decrease of blood pressure in carbetocin group and there was fluctuation of Bp in oxytocin group especially in the criteria of gestational hypertension.
- The haemoglobin (Hb) and haematocrit (hct) values are noted where the pre delivery readings has no apparent differences in both the groups, in regarding of postdelivery, there is apparently significant differences showing the p- value = 0.03 for Hb and 0.04 for hct between the both study groups states significant decrease in haemoglobin and haematocrit values in oxytocin recipients (group 2) in regarding of carbetocin recipients (group1).
- In this study the estimated blood loss is noted in between the group 1 and group 2 and there was highly statistically significant reduced blood loss with the p-value = 0.001 and reduced occurrence of PPH in the recipients of carbetocin group than in the recipients of oxytocin group.
- There was significant decrease in induction of blood transfusions with p =0.025 in carbetocin recipients and requirement of the additional uterotonic drugs in carbetocin group is highly statistically decreased with the p value = < 0.001 compared to oxytocin group where the oxytocin group patients received 38.5% additional drugs such as misoprostol in the form of rectal suppository and patients who had prone to excess blood loss received the carbetocin- IM to prevent the PPH.
- The pain perception is studied in both the groups p value = 0.01 shows apparently different where the group 1 is having reduced pain in regarding of group 2.

- The current study showed that there is statistically significant increased frequency of incidence of pruritus with p value = <0.001 and 38.5% in carbetocin recipients compared to oxytocin recipients.
- In the current study there is significant reduction of side effects notably nausea and vomiting in carbetocin group than the oxytocin group stated by p value – 0.02, 0.03 respectively.
- There is highly statistically significant increase of sweating stated by p-value = 0.005 and 20% in oxytocin group than the carbetocin group.
- In the current study increased temperature is included p-value of 0.02 shows significantly increased in carbetocin recipients than the oxytocin group.
- In conclusion the present study showed carbetocin the non- inferiority effect on oxytocin for prevention of PPH.

4. Conclusion

The current study on comparison of outcomes of carbetocin and the oxytocin in PPH included total of 130 samples, 65 samples are the recipients of carbetocin and 65 samples are the oxytocin were enrolled and the results are estimated. Regarding predelivery haemoglobin and HCT, there was no statistically significant difference and postdelivery there was statistically significant differences between the two study groups. There was significant increase in frequency of blood transfusion and need of additional uterotonic drugs in oxytocin group regard to carbetocin group. There was statistically significant increase pain perception in oxytocin group than carbetocin group. There was statistically significant increased incidence of pruritus in carbetocin group than oxytocin group. There was statistically significant increase in frequency of nausea, vomiting, sweating in oxytocin group compared to carbetocin group. There was significant increase in frequency of elevated temperature in carbetocin group compared to oxytocin group.

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