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Original Research Article

Management of Postpartum Hemorrhage-Carbetocin Versus Methergin: A Comparative Study

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Abstract

Background: Postpartum haemorrhage (PPH) kills one woman every minute around the world, and it is still the leading cause of maternal death and morbidity. To limit the burden of PPH, early identification of risk factors, as well as effective prevention and management of PPH, are crucial. Carbetocin is a synthetic analogue of oxytocin with a half-life of up to 4 to 10 times that of oxytocin, making it a new medication for the prevention of uterine atony. Unlike oxytocin, it is administered as a single-dose injection rather than an infusion and can be administered intravenously or intramuscularly.

Aim: The aim of our study was to examine the efficacy of carebtocin and combination oxytocin and methergine in avoiding postpartum haemorrhage in high-risk individuals after a normal vaginal delivery.

Materials and Methods: This study was conducted between 01 July 2021 to 01 December 2021. In this study, 150 patients were included between 37 and 40 weeks of gestation with risk factors for developing PPH. In this study, the patients were divided into 2 equal groups namely group I which consisted of 75 pregnant women. These patients received a single dose of carbetocin 100 mg I.M. Group 2 consisted of 75 pregnant women. These pregnant women received oxytocin 5 I.U. I.M. combined with methergine 0.2 I.M.

Results: Carbetocin was significantly more successful in reducing the time of the third stage of labour, reducing the amount of blood loss, and lowering both HB percent and hematocrit levels, all while having a significantly lower incidence of side effects.

Conclusion: A single 100 mg IM dose of carbetocin may be more effective than 5 IU IM oxytocin mixed with 1 mL, 0.2 mg IM methylergonovine maleate (Methergine®) in reducing postpartum blood loss with a smaller drop in haemoglobin levels.

Keywords: Postpartum hemorrhage, vaginal delivery, PPH.

Introduction

Postpartum hemorrhage is defined as after delivery, loss of more than 500 mL of blood and it occurs in upto 18% births[1,2]. Blood loss of 1,000 millilitres or more is considered physiologically severe and can cause hemodynamic instability[3]. Approximately 3% of vaginal deliveries will result in severe postpartum haemorrhage, even with proper treatment. In industrialized countries, it is the most prevalent maternal morbidity, and it is a leading cause of death worldwide. Orthostatic hypotension, anaemia, and exhaustion are all complications of postpartum haemorrhage, and they can make caring for the baby more challenging for the mother[4]. The likelihood of postpartum depression is increased by postpartum anaemia[5]. Blood transfusion may be required, and it comes with its own set of dangers. In the most severe cases, hemorrhagic shock can cause anterior pituitary ischemia, resulting in lactation delay or failure. Myocardial ischemia, dilutional coagulopathy, and mortality are all possibilities. Delayed postpartum haemorrhage, defined as bleeding after 24 hours as a result of placental eschar sloughing or retained placental fragments, can also occur. A lengthy third stage of labour, multiple deliveries, episiotomy, foetal macrosomia, and a history of postpartum bleeding are all risk factors for postpartum haemorrhage. However, postpartum haemorrhage can happen to women who have no risk factors, so doctors must be prepared to treat it at every birth. Identifying and correcting anaemia before birth, being cognizant of the mother's attitudes regarding blood transfusions, and eliminating frequent episiotomy are all strategies for reducing the impact of postpartum haemorrhage. Before leaving the delivery room, recheck the patient's vital signs and vaginal flow to see whether there is any slow, persistent bleeding. Active management of the third stage of labour (number needed to treat [NNT] to prevent one occurrence of postpartum haemorrhage) is the best preventive technique. The incidence of major bleeding has decreased significantly as a result of hospital recommendations advocating this technique. Currently, oxytocin is the uterotonic of choice for WHO-recommended Active Management of Third Stage Labor (AMTSL) to reduce postpartum blood loss. The use of oxytocin as a preventative measure after a baby's birth has been demonstrated to minimise the risk of PPH by roughly 60%. Because oxytocin has a short half-life of 4–10 minutes, it is best given as a continuous intravenous infusion to promote long-term uterotonic action. Carbetocin is a long-acting, synthetic oxytocin analogue with a lengthy half-life. Its prolonged uterine activity may possibly provide advantages over oxytocin in the management of labor's third stage. Carbetocin is more effective than oxytocin in preventing PPH following vaginal delivery in women who have at least two risk factors for developing atonic PPH. Carbetocin's side-effect profile was found to be identical to that of oxytocin[6]. Carbetocin is a long-acting synthetic oxytocin agonistic analogue with a long half-life that prolongs its pharmacological effects. Its longer uterine activity could possibly provide it an edge over oxytocin in the control of the third stage of labour. Carbetocin side-effect profile was found to be similar to that of oxytocin, however it may be favourable when compared to Syntometrine. The aim of our study was to examine the efficacy of carebtocin and combination oxytocin and methergine in avoiding postpartum haemorrhage in high-risk individuals after a normal vaginal delivery.

Methods and Materials:

This study was conducted between 01 July 2021 to 01 December 2021. In this study, 150 patients were included between 37 and 40 weeks of gestation with risk factors for developing PPH. In this study, the patients were divided into 2 equal groups namely group I which consisted of 75 pregnant

women. These patients received a single dose of carbetocin 100 mg I.M. Group 2 consisted of 75 pregnant women. These pregnant women received oxytocin 5 I.U. I.M. combined with methergine 0.2 I.M. Women who were planning on giving delivery vaginally, women who had gestational age of 37 to 40 weeks, women who had previous PPH, primipara of greater than 40 years, grandmultipara of greater than 5 previous vaginal deliveries, BMI greater than 35, multiple pregnancies, prolonged labor, ultrasound estimated fetal weight was greater than 4 kg were included in the study. Gestational age of less than 37 weeks and more than 40 weeks, women who have no risk factors for atonic PPH, women are too upset to provide informed consent, women who had known allergies to carbetocin, oxytocin homologues or methylergometrine, women who had a serious cardiovascular disorder, serious hepatic or renal disease, epilepsy or coagulopathy,

causes of antepartum hemorrhage such as placenta previa, abruptio placenta are excluded from the study. Complete history taking; personal history, including name, age, and address; menstrual history, obstetric history, drug history, past history of diabetes, hypertension, previous operation, blood transfusion, and drug allergy; history of postpartum haemorrhage; and family history of congenital anomalies, twins, diabetes, and hypertension are all part of the clinical evaluation. Vital signs such as pulse, blood pressure, body temperature was recorded, head, neck, chest and heart examination was done. Many other examinations such as lower limb and abdominal examination such as fundal level assessment, fetal lie, fetal heart sounds, uterine contractions and previous surgeries scars. To rule out traumatic postpartum haemorrhage, extend the episiotomy, and evaluate the placenta and membrane after separation after delivery. During vaginal delivery, blood loss quantification was conducted by following methods; A list of dry weights for delivering items that might get bloody was prepared, along with instructions on how to calculate blood loss. Blood loss was measured shortly after the baby's birth (before the placenta was delivered), and the volume of fluid collected was measured and recorded in a calibrated under-buttocks drape. Keep in mind that amniotic fluid, urine, and faeces make up the majority of the fluid collected before the placenta is delivered. Subtract the amount of irrigation from the total fluid that calibrated under-buttocks drape, if irrigation is employed. Keep in mind that amniotic fluid, urine, and faeces make up the majority of the fluid collected before the placenta is delivered. Subtract the amount of irrigation from the total fluid collected if irrigation was used. The total volume of fluid gathered in the drape under the buttocks was measured. To determine the actual blood loss, the preplacental fluid volume was deducted from the postplacental fluid volume. Keep in mind that the majority of the fluid collected following the placenta's birth is blood. To estimate the cumulative amount of blood loss or quantification of blood loss, the fluid volume collected in the draperies was added to the blood volume obtained by weighing soaked items. To establish cumulative volume, all blood-soaked materials and clots were weighed. J milli-litre blood loss volume equals 7 gram weight. When estimating blood loss from a blood-soaked item, the following equation was used: wet item gram weight - dry item gram weight=milliliters of blood within the item. Despite the fact that a gram is a unit of mass and a millilitre is a unit of volume, the conversion from one to the other is straightforward. Maternal age, weight, height, BMI, and haematological parameters were all equivalent at the start of the study, as were parity, gestational age, and the use of cervical ripening, forceps delivery, or epidural analgesia. Throughout the trial, all episiotomies were performed

mediolaterally if necessary. If an oxytocin infusion was started during labour, it was stopped as soon as the second stage was completed. The weight of the foetus at birth was recorded. At the time of admittance to the labour room, the patient's blood pressure and pulse rate were taken. On admission to the labour room, blood samples were collected to evaluate haemoglobin levels, and they were repeated 2 hours and 12 hours later. An extra oxytocic medication was given if the uterine tone was not firm or the amount of bleeding was unsatisfactory after the medicine was given. The time between the initial administration of the chosen medicine and the type of additional oxytocic intervention was recorded. The umbilical cord was clamped as soon as the infant was delivered. For the detection of delayed placental separation, retained placenta or retained sections of placenta, or membranes, the duration of the third stage was measured. Following the delivery of the baby, a new plastic sheet was placed beneath the patient's thighs to limit the error of incorporating amniotic fluid and blood soaked into drapes, and blood loss was measured shortly after medicine administration. Controlled cord traction was used to deliver the placenta. For the first hour after the placenta was delivered, all gauzes, tampons, and pads that were later used were collected. We utilised a computerised weighing scale. The weight difference between before and after the hour was computed. A 100-gram increase in weight was equated to a 100-milliliter rise in blood volume. In the labour ward, the uterine fundal height was measured after medication administration, and vital signs were observed at 0, 30, and 60 minutes. Significant increases in systolic and diastolic pressures of 30 and 20 mmHg, respectively, were regarded significant. The mean blood pressure levels across the three post-injection assessments, as well as the mean pulse rate for both groups, were computed for each set. During the first 12 hours after delivery, the patients were followed for side effects of the chosen medicine. After drug administration, in the recovery area, and in the post-natal ward, patients were questioned about adverse effects. Signs of flushing, sweating, tremor, and vomiting were also observed in the individuals. Any other symptoms mentioned by the patient or signals witnessed by the doctor or nurse were also noted. In the first 12 hours after delivery, any blood transfusions or iron sucrose injections were noted, as well as any cases of PPH. SPSS software was used to conduct the analysis (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The Shapiro-Wilk Test was used to determine the data's normality. If numerical data was regularly distributed, it was described as mean + SD. For categorical variables, frequency tables with percentages were employed. To compare parametric quantitative variables, the independent Student t-test is utilised. The categorical variables were analysed using the Chi-square test. A statistically significant p-value of 0.05 was used.

Results:

In terms of demographics, the patients in the study (n=150) ranged in age from 18 to 39 years old. Calculated from the first day of LMP, the gestational age ranged from 37 to 41 weeks. Gravidity levels ranged from 1 to 6. In terms of mother age, gestational age, gravidity, and parity, there was no statistically significant difference between the two groups. However, there was a significantly significant difference between the two groups in terms of BMI ($P < 0.05$)

Table 1: Distribution based on demographics of patients

Characteristics	Group	Mean	P value
Age (Years)	Group 1	26.95	>0.05
	Group 2	27.38	
Gravidity	Group 1	2.84	0.47
	Group 2	2.99	
Gestational Age (Weeks)	Group 1	40.56	>0.05
	Group 2	40.19	
Parity	Group 1	1.36	0.59
	Group 2	1.64	
BMI	Group 1	30.22	<0.001
	Group 2	30.18	

Table 1 shows that mean age in years in group 1 was 26.95 and in group 2, it was 27.38 and P value was >0.05, group 1 had a gravidity of 2.84 and in group 2, it was 2.99. Gestational age in weeks was 40.56 in group 1 and it was 40.19 in group 2, parity was 1.36 in group 1 and 1.64 in group 2, basal metabolic index was 30.22 in group 1 and it was 30.18 in group 2.

Table 2: Distribution based on risk factors of PPH

PPH Risks	Group 1 (n, %)		Group 2 (n, %)		P value
Primipara (>40 years)	33	44%	29	38.6%	>0.05
Grand Multipara	36	48%	37	49.4%	
Prolonged labour	6	8%	9	12%	

Table 2 shows that PPH risk factors were 44% and 38.6% for primipara (>40 years) in group 1 and 2 respectively. Grand multipara was 48% and 49.4% respectively, prolonged labour was 8% and 12% respectively in group 1 and 2.

Table 3: Distribution based on % Hb, predelivery hematocrit value, 2 hours and 12 hours post-delivery, predelivery pulse rate, blood loss, fetal birth weight, 3rd stage time in studied groups

Characteristics	**Group**	**Mean**	**P value**
Pre-labour Pulse	Group 1	79.65	>0.05
	Group 2	78.88	
Pre-labour %Hb (mg/dL)	Group 1	11.24	>0.05
	Group 2	10.48	
Pre-labour HCT	Group 1	35.11	0.017
	Group 2	36.50	
3rd stage of labor time (hr)	Group 1	2.74	0.012
	Group 2	2.94	
Blood Loss (mL)	Group 1	298.36	<0.001
	Group 2	420.87	
2hr Post labor Hb% (mg/dl)	Group 1	11.289	>0.05
	Group 2	11.784	
2 hr Post labor HCT	Group 1	32.589	0.028
	Group 2	33.694	
12hr Post labor Hb% (mg/dl)	Group 1	11.892	>0.05
	Group 2	11.907	
12 hr Post labor HCT	Group 1	32.281	0.069
	Group 2	32.728	
Birth Weight (g)	Group 1	3456.88	>0.05
	Group 2	3469.17	

Table 3 shows that Pre-labor HCT, 2hr post-labor HCT, 12hr post-labor HCT, time of 3rd stage of labour (P<0.05) have shown statistically significant difference was observed, extremely significant difference in blood loss (P<0.01), and non-significant difference in other parameters was observed.

Table 4: Distribution based on %Hb difference and HCT fall pre and post-delivery in both groups

Characteristics	Group 1 (mean±SD)	Group 2 (mean±SD)	P value
Hb difference	0.46±0.057	0.84±0.29	<0.01
HCT difference	0.125±0.04	0.33±0.02	0.06

Table 4 shows that in group (1) and group (2), the mean difference in haemoglobin level before and after delivery was 0.46±0.057 and 0.84±0.29, respectively, with a large statistically significant difference between the two groups. Furthermore, there was a statistically significant difference in hematocrit levels between the two groups.

Table 5: Distribution based on postpartum hemorrhage history.

Previous PPH	Group 1 (n, %)	Group 2 (n, %)	P value
Positive	63 (84%)	59 (78.6%)	>0.05
Negative	12 (16%)	16 (21.4%)	

Table 5 shows that there was no statistically significant difference between the two groups when it came to past postpartum haemorrhage.

Table 6: Side Effects

Side effects	Group 1 (n, %)	Group 2 (n, %)	P value
Facial flushing	4 (5.3%)	5 (6.6%)	>0.05
Headache	5 (6.6%)	10 (13.3%)	>0.05
Nausea	5 (6.6%)	10 (13.3%)	>0.05
Shivering	4(5.3%)	12 (16%)	>0.05
Vomiting	3 (4%)	5 (6.6%)	>0.05

Table 6 shows that the various types of adverse effects observed in the various study groups. Each sort of adverse effect did not have a statistically significant difference. However, across the two groups, there was a highly significant difference in the total number of instances reported as having side effects.

Discussion

The patients in the study (n=150) ranged in age from 18 to 39 years old in terms of demographics. The gestational age ranged from 37 to 41 weeks when calculated from the first day of LMP. The amounts of gravity ranged from 1 to 6. There was no statistically significant difference between the two groups in terms of mother age, gestational age, gravidity, or parity. In terms of BMI, however, there was a significant difference between the two groups (P<0.05). There was a statistically significant difference in pre-labor HCT, 2hr post-labor HCT, 12hr post-labor HCT, and time of 3rd stage of labour (P<0.05), as well as an extremely significant difference in blood loss (P<0.01) and a non-significant difference in other parameters. Maged et al. (2016)[7] found no significant differences in age, gravidity, parity, body mass index, gestational age, or foetal birth weight between the groups when comparing the efficacy of Carbetocin against oxytocin for the prevention of postpartum haemorrhage following vaginal delivery in high-risk

women. Risk factors for atonic and traumatic PPH were not substantially different across the groups, and there were no significant changes in the duration of the first, second, and third stages of labour, which was contrary to our findings. The carbetocin group had much less haemorrhage, PPH, the need for further uterotonics, and the difference between blood haemoglobin levels before delivery and 24 hours after delivery. In terms of the occurrence of serious PPH and the requirement for blood transfusion, however, there was no significant difference between the two groups, which is consistent with our findings. Carbetocin was found to be a better alternative to standard oxytocin in preventing PPH following vaginal delivery, with identical side effects and minor hemodynamic alterations. Zein El Abdeen (2018)[8] conducted a prospective randomised observational study to examine the effects of carbetocin versus oxytocin and ergometrine for the prevention of postpartum haemorrhage following caesarean section. There were no significant variations in age, gravidity, parity, gestational age, or BMI across the study groups. It was discovered that there was a significant association between carbetocin and vaginal bleeding in both groups when compared to the mean in the oxytocin group. It was also discovered that uterine atony occurred more frequently in women in the oxytocin with ergometrine group (39 percent) than in the carbetocin group (21 percent). The oxytocin group required much more oxytocics than the carbetocin group. These findings were in line with our findings, which compared the quantity of PPH. This study was conducted on women who had C.S, which was associated with a higher risk of PPH, and it demonstrated that carbetocin was superior to oxytocin mixed with ergometrine in preventing PPH. In women with at least two risk factors for developing atonic PPH, carbetocin is superior to oxytocin in preventing PPH and Hb decrease following vaginal delivery. This can be explained by the fact that carbetocin has a longer half-life than oxytocin, resulting in a greater uterine response in terms of frequency and amplitude of uterine contractions (Reyes and Gonzalez, 2011)[9]. In our research, there was a statistically significant difference between the two groups in terms of Hb percent difference and Hct decline before and after delivery. In terms of mean Hct fall, there was a statistically significant difference between the two groups. The difference between blood haemoglobin levels before delivery and 24 hours after delivery was significantly lower in the carbetocin group, according to Maged et al. (2016)[7]. In terms of the occurrence of serious PPH and the requirement for blood transfusion, however, there was no significant difference between the two groups. These findings corroborate our findings. Two comprehensive trials comparing active third-stage treatment to expectant management have convincingly demonstrated the benefits of active management. The Bristol trial, in which active management was the norm, and the Hinchingbrooke trial, in which expectant management was the norm, both showed significant reductions in the incidence of PPH with active management compared to expectant management (5.9% versus 17.9% and 6.8% versus 16.5 percent, respectively). Because the disparity in PPH rate was so great, both studies were halted after interim analysis (Maged et al., 2016)[7]. Reyes and Gonzalez (2011)[9] discovered that carbetocin was more effective than oxytocin in preventing PPH in their investigation. Carbetocin had a similar safety profile to oxytocin and was not linked to the development of oliguria or hypertension. They came to the conclusion that carbetocin, rather than oxytocin, is a good alternative for preventing PPH in women with severe preeclampsia. Concerns about the need for more uterotonic medicines. The authors

compared the need for extra uterotonic medications between carbetocin and oxytocin. They discovered a strong link between the two groups. However, when they used carbetocin and oxytocin to investigate the requirement for extra uterotonic drugs after vaginal deliveries, they observed no statistical significance between the two groups. Despite the differing route of distribution, this was consistent with our thesis. The mode of delivery can have a significant impact on the therapeutic outcome. Askar et al., 2011[10], Westhoff et al., 2013[11], and Kansouh & El Naggar, 2019)[12], propose that more research be done with patients who have varied means of delivery and risk factors for PPH. Kansouh and El Naggar (2019)[12] examined the effects of carbetocin against oxytocin in the prevention of postpartum haemorrhage in late preterm twin pregnancy after caesarean section. The carbetocin group did not have a substantially smaller difference in blood haemoglobin levels 24 hours after birth. 2 hours after CS, women in the oxytocin group had statistically substantially higher SBP and DBP than women in the carbetocin group. This study backed up our findings since, as previously stated, twin pregnancy is a risk factor for PPH, and carbetocin was found to be more effective than oxytocin in avoiding PPH. There was no statistically significant difference between either category of side effect in our investigation. However, between the two groups, there was a significantly significant difference in the total number of cases of side effects.

Conclusion

In lowering postpartum blood loss with a smaller decline in haemoglobin levels, a single 100 mg IM dosage of carbetocin may be more effective than 5 IU IM oxytocin mixed with 1 mL, 0.2 mg IM methylergonovine maleate (Methergine®). Carbetocin was paired with oxytocin's safety and ergot preparations' greater duration of action.

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Ethical Approval

Approved by Institutional ethical Committee, CAIMS, Karimnagar

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