Section: Obstetrics and Gynecology

Original Research Article

A COMPARATIVE STUDY OF CARDIOVASCULAR EFFECTS OF INTRAVENOUS VERSUS INTRAMUSCULAR CARBETOCIN FOR PREVENTING POSTPARTUM HEMORRHAGE DURING VAGINAL DELIVERY: A RANDOMIZED PARALLEL-GROUP TRIAL

Swati Talwade[1], Rajasri G Yaliwal[2], Neelamma G Patil[3], Aruna. M. Biradar[4]

[1]Junior Resident, Department of Obstetrics and Gynecology, BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India.
[2]Professor, Department of Obstetrics and Gynecology, BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India.
[3]Professor, Department of Obstetrics and Gynecology, BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India
[4]Professor, Department of Obstetrics and Gynecology, BLDE (DU) Shri B M Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India

Received : 21/06/2024
Received in revised form : 12/08/2024
Accepted : 29/08/2024

Keywords:
vaginal delivery , intravenous carbetocin ,intramuscular carbetocin ,post partum hemorrhage(PPH), hemodynamic changes.

Corresponding Author:
Dr. Rajasri G. Yaliwal,
Email: ryaliwal@bldedu.ac.in

DOI: 10.47009/jamp.2024.6.4.201

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (4); 1026-1030

Abstract

Background: The emergence of heat-stable , longer-acting carbetocin presents a promising alternative to Oxytocin, challenging its status as the primary uterotonic agent for PPH.Due to their similar structural makeup, Carbetocin and oxytocin can both lead to similar adverse effects, such as ST-depression on the ECG, elevated heart rate (HR), cardiac output (CO), stroke volume, and systemic vascular resistance, while also causing reduced arterial blood pressure (BP) and systemic vascular resistance.The recommended dosage for Carbetocin is 100 µg which can be administered through intravenous or intramuscular route. The aim of this study was to compare the cardiovascular changes between intramuscular and intravenous route in preventing postpartum hemorrhage during vaginal delivery. **Materials and Methods:** A total of 134 term pregnant women were randomized into two groups .group 1 received 100mcg intravenous injection carbetocin and group 2 received 100mcg iintramuscular injection carbetocIn. Heart rate ,blood pressure,oxygen saturation and electrocardiogram changes were compared between the two groups. **Result:** no statistical significant difference was noted in both the groups with respect to heart rate, blood pressure ,oxygen saturation or electrocardiogram changes($p>0.05$). **Conclusion:** The hemodynamic changes of intravenous versus intramuscular route of injection carbetocin was comparable with no statistical difference in prevention of PPH during vaginal delivery.

INTRODUCTION

One of the most feared obstetric emergencies, postpartum hemorrhage (PPH), is the most common ,potential life threatening and direct cause of maternal mortality (27%).[1] Every year, 1,27,000 women worldwide die from PPH. In India, the current maternal mortality ratio stands at 99 deaths per 100,000 live births.[2] Although certain risk factors are associated with PPH, the precise factors underlying its development remain unclear. Given the unpredictability of atonic PPH, there is a pressing need for proactive strategies to prevent PPH.

The emergence of heat-stable , longer-acting carbetocin presents a promising alternative to Oxytocin, challenging its status as the primary uterotonic agent for PPH.[3] Carbetocin lasts in the body for 40 minutes, which is 4 to 10 times longer than oxytocin. It achieves peak plasma levels within 30 minutes and has an 80% bioavailability.[4]

Acting as an agonist at oxytocin receptors, particularly in the myometrium, Carbetocin exhibits a mechanism akin to oxytocin by engaging G protein-coupled oxytocin receptors. Its action involves second messengers and inositol phosphates production, mirroring the pathway of oxytocin.[5]

Systemic vasodilation occurs following an oxytocin bolus, which results in hypotension, tachycardia, and increased cardiac output and pulmonary artery pressure. These effects occur in a dose-dependent manner and result in transient hypotension and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

tachycardia.[6] Additionally, oxytocin exerts a direct negative chronotropic effect, increases the ejection power of the left ventricle (LV), and modifies the ST segments on the electrocardiogram (ECG). It also causes widespread arterial vasodilation.[7]

Due to their similar structural makeup, Carbetocin and oxytocin can both lead to similar adverse effects, such as ST-depression on the ECG, elevated heart rate (HR), cardiac output (CO), stroke volume, and systemic vascular resistance, while also causing reduced arterial blood pressure (BP) and systemic vascular resistance. Because oxytocin has a short half-life, it is often administered repeatedly, which raises the risk of hypotension, cardiovascular side effects, receptor desensitization, and a decline in uterotonic action.[8]

Higher doses of oxytocin prevent postpartum hemorrhage (PPH), but we have to take in to consideration that it can also induce hypotension, ST-depression, tachycardia, arrhythmias, and prolong the QTc interval, which can be fatal for patients with underlying myocardial disease. Despite these risks, oxytocin can offer cardio protection at biochemical levels. Given the significant risks to vulnerable patients, it is essential to characterize the circulatory changes caused by oxytocin and its widely used analog, carbetocin, during PPH treatment.[9] However, Clinical trials have identified similar side effects when comparing the contractile effects of oxytocin and carbetocin.[10-12]

The recommended dosage for Carbetocin is 100 µg which can be administered through intravenous or intramuscular route. The aim of this study was to compare the cardiovascular changes between intramuscular and intravenous route in preventing postpartum hemorrhage during vaginal delivery.

MATERIALS AND METHODS

We conducted this study in the Department of Obstetrics and Gynecology, Shri B M Patil Medical College, Hospital and Research Centre, BLDE (DEEMED TO BE UNIVERSITY) Vijayapura, Karnataka, India. Ethical clearance was obtained from institutional ethics committee (reference no. BLDE [DU]/IEC/774/2022-23) per the Declaration of Helsinki. This study was registered with Clinical Trials of India (CTRI/2023/03/050468).

Inclusion Criteria

Women with term pregnancy (37 - 42 weeks of gestation) expected to be delivered vaginally, be above 18 years and have consented to take part in the study.

Women having known conditions predisposing to atonic PPH, like Multiple gestations, polyhydramnios, severe anemia and prolonged labor were excluded. We also excluded women who were planned for an elective caesarean section and had cardiovascular disorders, hypertensive disorders, hepatic or renal disease, or epilepsy.

Sample Size

Using G*Power version 3.1.9.4 software for sample size calculation, the study examined blood loss and cardiovascular effects in Carbetocin administered intravenously (IV) with a mean of 292.2 ml and a standard deviation (SD) of 32.8 ml, and intramuscularly (IM) with a mean of 337.73 ml and an SD of 118.77 ml. The study required a total sample size of 134 participants, with 67 in each group, assuming equal group sizes. This setup aimed to achieve 85% power for detecting differences between the two means with a 5% level of significance using a t-test for independent samples.

Statistical Analysis

The data were input into a Microsoft Excel spreadsheet and analyzed using SPSS version 21 (IBM Corp., Chicago, IL). Results are displayed as means, counts, percentages, and charts. For comparing normally distributed continuous variables between groups, independent t-tests were used, while the Mann-Whitney U test was employed for non-normally distributed variables. Categorical variables between two groups were compared using the chi-square test. A p-value of <0.05 was deemed statistically significant. All statistical tests were conducted with a two-tailed approach.

Study Design

The research was a randomized, parallel-group, single-blinded trial. A computerized randomization chart was used for the randomization process.

Data Collection

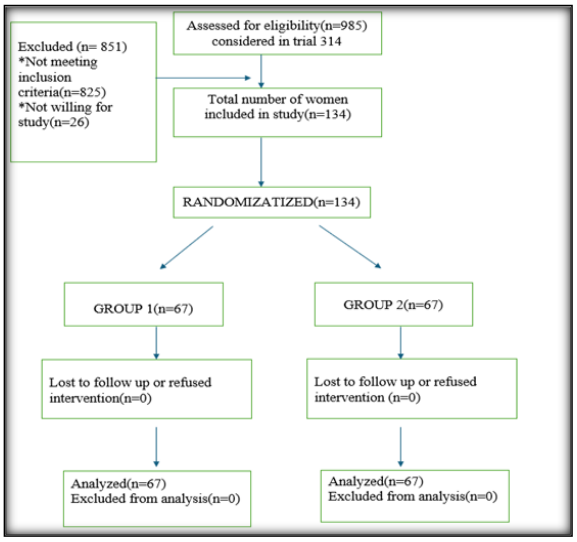
During the study period at BLDE(Deemed to be University) Shri B. M. Patil Medical College, Hospital, and Research Centre, 985 pregnant women underwent vaginal delivery. Among them, 851 were excluded because they did not meet the inclusion criteria. The study included 134 consenting women, who were randomly assigned to Group 1 or Group 2 using a computer-generated randomization sequence. Upon admission, the researchers recorded their heart rate (HR), blood pressure (BP), oxygen saturation (SpO2), and electrocardiogram (ECG). The women were unaware of the drug administration route when they consented to the study. Group 1 received a 100 mcg (1 ml) injection of carbetocin diluted with 9 ml of normal saline, administered slowly over one minute within one minute of delivery. Group 2 received a 100 mcg intramuscular injection of carbetocin within one minute of delivery. The study used the uterotonic drug to actively manage the third stage of labor, and controlled cord traction was applied to deliver the placenta. Researchers recorded HR, BP, and SpO2 at 1, 5, and 10 minutes after carbetocin administration and again at the end of one hour. An ECG was performed one hour after delivery.

RESULTS

A total of 985 pregnant women underwent vaginal delivery during the study period. Out of these,851 were excluded from the study and did not meet the

ISSN (O): 2687-5365; ISSN (P): 2753-6556

inclusion criteria. A total of 134 consenting women were included in the study and were randomized into group 1 and group 2 by computer- generated randomized sequence. There were no dropouts from the study as described in [Figure 1].



The mean heart rate before intervention was 103.58±13.02 bpm, while the mean heart rate after 5 minutes of intervention was 105.88±12.47 bpm. Overall, there was a statistically significant correlation between the heart rate before and after intervention. However, on comparison of heart rate at 5, 10 and 15 minutes after intervention amongst the two groups, did not show a statistically significant correlation as shown in [Table 1 & 2].

The analysis revealed no statistically significant differences in systolic or diastolic blood pressure between the groups before, during, or after the procedure. Additionally, neither group showed significant increases or decreases in systolic or diastolic blood pressure during the procedure, as detailed in [Table 3 and 4].

There was no significant correlation between the two groups on comparing SpO2 at 5, 10 and 15 minutes after intervention. The means of SpO2 at 5,10 and 15 minutes showed the presence of matching population between both the groups as shown in [Table 5].

The ECG traces recorded preoperatively and one hour postoperatively showed no differences between the groups. Neither group exhibited any ST segment changes, as detailed in [Table 6].

Table 1: Comparison of heart rate before intervention and heart rate after 5 minutes.

Heart rate	Mean	Standard deviation	t value	P value
Heart rate before intervention	103.58	13.02	-5.47	0.00
Heart rate after 5 min	105.88	12.47		

Paired t test

Table 2: heart rate data for groups I and II

Heart rate (beats per minute)	Intervention	N	Mean rank	Mann Whitney U test	P value
At 5 min	IV	67	70.54	2041	0.11
	IM	67	64.46		
At 10 min	IV	67	62.32	1897.5	0.51
	IM	67	72.68		
At 15 min	IV	67	65.33	2099	0.72
	IM	67	69.67		
At one hour	IV	67	70.98	2089	0.56

Table 3: Systolic blood pressure data for groups I and II

Systolic blood) pressure(mmhg)	Intervention	N	Mean rank	Mann Whitney U test	P value
Before intervention	IV	67	68.49	2250	0.89
	IM	67	67.89		
At 5 min	IV	67	67.52	2243	0.99
	IM	67	67.48		
At 10 min	IV	67	66.23	2159.5	0.70
	IM	67	68.77		
At 15 min	IV	67	66.34	2167	0.72
	IM	67	68.66		
At one hour	IV	67	70.26	2189	0.78
	IM	67	69.82		

Table 4: Diastolic blood pressure data for groups I and II

Diastolic blood) pressure(mmhg)	Intervention	N	Mean rank	Mann Whitney U test	P value
Before intervention	IV	67	68.49	2120	0.36
	IM	67	67.89		
At 5 min	IV	67	70.54	2041	0.11
	IM	67	64.46		
At 10 min	IV	67	62.32	1897.5	0.51
	IM	67	72.68		

ISSN (O): 2687-5365; ISSN (P): 2753-6556

At 15 min	IV	67	65.33	2099	0.72
	IM	67	69.67		
At one hour	IV	67	70.98	2089	0.56
	IM	67	69.12		

Table 5: Oxygen saturation data for groups I and II

SPO2	Intervention	N	Mean rank	Mann Whitney U test	P value
Before intervention	IV	67	68.12	2120	0.36
	IM	67	69.59		
At 5 min	IV	67	64.55	2047	0.33
	IM	67	70.45		
At 10 min	IV	67	69.63	2102	0.46
	IM	67	65.37		
At 15 min	IV	67	64.99	2076	0.34
	IM	67	70.01		
At one hour	IV	67	70.98	2030	0.52
	IM	67	69.12		

Table 6: ECG readings for groups I and II

ECG	Intravenous carbetocin				Intramuscular carbetocin			
	Mean	Standard deviation	95% CI		Mean	Standard deviation	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
PRE ECG PR	0.18	0.21	0.13	0.23	0.16	0.01	0.15	0.16
PRE ECG QRS	0.08	0.10	0.05	0.10	0.07	0.02	0.06	0.07
PRE ECG QTC	0.39	0.03	0.38	0.40	0.39	0.04	0.38	0.40
PRE ECG RV5+SV1	2.94	0.36	2.85	3.03	2.87	0.37	2.78	2.97
POST ECG PR	0.16	0.01	0.15	0.16	0.15	0.01	0.15	0.16
POST ECG QRS	0.08	0.10	0.05	0.10	0.08	0.10	0.05	0.10
POST ECG QTC	0.39	0.04	0.38	0.40	0.39	0.05	0.37	0.40
POST ECG RV5+SV1	2.93	0.36	2.84	3.02	2.89	0.39	2.80	2.99

DISCUSSION

This study was conducted to compare the cardiovascular changes of intravenous versus intramuscular route. The emergence of heat-stable, longer-acting carbetocin presents a promising alternative to oxytocin, challenging its status as the primary uterotonic agent for PPH.[3] Currently, there is insufficient evidence to ascertain the comparative effectiveness of IV versus IM carbetocin in preventing PPH during vaginal deliveries; none of the literature found and examined for this study compares the efficacy of carbetocin administered via these routes.

Our study found increase in heart rate (HR)with mean of 103.58±13.02 bpm before intervention, while the mean heart rate after 5 minutes of intervention was 105.88±12.47 bpm which was statistically significant (p=0.00). However, on comparison of heart rate at 5, 10 and 15 minutes after one hour after intervention amongst the two groups, did not show a statistically significant correlation. Rabow et al. who studied the cardiovascular changes in women receiving 100 mcg of carbetocin compared to 5 international units of oxytocin during elective cesarean delivery concluded that there were no significant differences between the groups in terms of SpO2, heart rate (HR), blood pressure (BP), or ECG.[8]

In a study conducted by Bahr et al. which was a double-blind, randomized, controlled trial, compared the effects of intravenous oxytocin and carbetocin administered to total of 80 women. Both groups showed a significant increase in heart rate (HR) and a decrease in blood pressure (BP) from baseline at all intervals (i.e., 1, 5, 10, and 15 minutes after administration). However, the oxytocin group had a significantly greater increase in HR and a more evident decrease in BP and SpO2 compared to the carbetocin group. This finding suggests that carbetocin may be preferably used safely for women with hypertensive disorders of pregnancy.[15]

In a study conducted by Basma.A.Mohamed and et al conducted that postpartum pulse in both carbetocin and oxytocin group was considerably greater than before administrating drug which is complementary to our study.[16] However we would like to conclude that in spite of tachycardia after administration of the study drug, the tachycardia decreased within 60minutes after injection without any treatment. This may complicate the monitoring of women with bleeding and lead to missed diagnosis.

The time interval between the peak and end of the T wave measures myocardial repolarization dispersion. Our study found no ECG changes in either group, which aligns with the findings of M. Bruyère and colleagues. They concluded that while carbetocin has not been associated with symptomatic arrhythmias, it is prudent to avoid this drug in patients with a prolonged QT interval, as it may increase the risk of Torsade de Pointes.[17]

CONCLUSION

The hemodynamic changes of intravenous versus intramuscular route of injection carbetocin was

ISSN (O): 2687-5365; ISSN (P): 2753-6556

comparable with no statistical difference in prevention of PPH during vaginal delivery.

Limitations

Limited sample size and exclusion of high-risk populations affect generalizability. Additionally, the lack of blinding for the treating doctor could be a potential limitation of this study.

REFERENCES

1. Gallos I, Devall A, Martin J,et.al: Randomized trial of early detection and treatment of postpartum hemorrhage. New England Journal of Medicine. 2023, 6:11-21. 10.1056/NEJMoa2303966
2. Meh C, Sharma A, Ram U : Trends in maternal mortality in India over two decades in nationally representative surveys. BJOG. 2022, 129:550-561. 10.1111/1471-0528.16888
3. Rath W: Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin . European Journal of Obstetrics & Gynecology and Reproductive Biology. 2009, 1:15-20. 10.1016/j.ejogrb.2009.06.018
4. Khan M, Balki M, Ahmed I, et.al: Carbetocin at elective cesarean delivery: a sequential allocation trial to determine the minimum effective dose. Canadian Journal of Anesthesia. 20141, 61:242-8. 10.1007/s12630- 013-0082-9
5. Zingg HH, Laporte SA. The oxytocin receptor. Trends in Endocrinology & Metabolism. 2003 Jul 1;14(5):222-7.
6. Moertl MG, Friedrich S, Kraschl J, Wadsack C, Lang U, Schlembach DJ. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2011 Oct;118(11):1349-56.
7. Rabow S, Hjorth U, Schönbeck S, Olofsson P. Effects of oxytocin and anaesthesia on vascular tone in pregnant women: a randomised double-blind placebo-controlled study using non-invasive pulse wave analysis. BMC pregnancy and childbirth. 2018 Dec;18:1-2.
8. Rabow, S., Jonsson, H., Bro, E., & Olofsson, P. (2023). Cardiovascular effects of oxytocin and carbetocin at cesarean section. A prospective double-blind randomized study using noninvasive pulse wave analysis. The Journal of Maternal-Fetal & Neonatal Medicine, 36(1). https://doi.org/10.1080/14767058.2023.2208252
9. Bekkenes ME, Fagerland MW, Solberg OG, Aaberge L, Klingenberg O, Norseth J, Rosseland LA. Exploring Cardiac Effects After Oxytocin 2.5 I U or Carbetocin 100 µg: A Randomised Controlled Trial in Women Undergoing Planned Caesarean Delivery. Obstetric Anesthesia Digest. 2023 Sep 1;43(3):124-5.
10. Yaliwal RG, Patil NG, Bidri S. A Comparative Study of the Cardiovascular Effects of a Lower Dose of Heat-Stable Carbetocin Versus the Standard Dose in the Prevention of Postpartum Hemorrhage During Elective Cesarean Delivery: A Single-Blinded, Randomized, Parallel-Group Trial. Cureus. 2024 Jul 21;16(7):e65049. doi: 10.7759/cureus.65049. PMID: 39165461; PMCID: PMC11335180.
11. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesaeter E. Changes in blood pressure and cardiac output during cesarean delivery: the effects of oxytocin and carbetocin compared with placebo. Anesthesiology. 2013 Sep 1;119(3):541-51.
12. Pisani I, Tiralongo GM, Gagliardi G, Scala RL, Todde C, Frigo MG, Valensise H. The maternal cardiovascular effect of carbetocin compared to oxytocin in women undergoing caesarean section. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2012 Apr 1;2(2):139-42.
13. Widmer M, Piaggio G, Abdel-Aleem H: Room temperature stable carbetocin for the prevention of postpartum haemorrhage during the third stage of labour in women delivering vaginally: study protocol for a randomized controlled trial. Trials. 2016, 17:19.10.1186/s13063-016-1271-y
14. Maged AM, Waly M, Fahmy RM, et.al.: Carbetocin versus rectal misoprostol for management of third stage of labor among women with low risk of postpartum hemorrhage. Int J Gynaecol Obstet. 2020, 148:238–42.10.1002/ijgo.13056
15. Bahr MH, Abdelaal Ahmed Mahmoud M Alkhatip A, Ahmed AG, Elgamel AF, Abdelkader M, Hussein HA: Hemodynamic effects of oxytocin and carbetocin during elective cesarean section in preeclamptic patients under spinal anesthesia: a randomized double-blind controlled study. Anesth Pain Med. 2023, 13:e128782. 10.5812/aapm-128782
16. Mohamed, B., Mohamed, M., Sharaf Eldeen, A., Sakr, B. (2023). Effect of Carbetocin on Blood Loss after Cesarean Section or Vaginal Delivery. Benha Journal of Applied Sciences, 8(6), 1-7. doi: 10.21608/bjas.2023.221160.1200
17. Bruyere M, Hamou NA, Benhamou D, Chousterman B, Boulard V, Charbit B. QT interval prolongation following carbetocin in prevention of post-cesarean delivery hemorrhage. International Journal of Obstetric Anesthesia. 2014 Feb 1;23(1):88-9.

ISSN (O): 2687-5365; ISSN (P): 2753-6556