RESEARCH ARTICLE

Randomized Parallel Trial of Intramyometrial Injection of Heat-stable Carbetocin vs Intramyometrial Injection of Oxytocin for the Prevention of Postpartum Hemorrhage during Cesarean Delivery

Rajasri G Yaliwal[1], Preeti S Malapure[2]

Received on: 09 May 2024; *Accepted on*: 29 June 2024; *Published on*: 02 September 2024

Abstract

Aim and background: Among various causes of maternal mortality, the leading direct cause of maternal mortality is bleeding. More than half of postpartum hemorrhages are brought on by insufficient uterine contraction following placental delivery [Atonic postpartum hemorrhage (PPH)]. Several uterotonics are available, including oxytocin and carbetocin. This study is the first to use carbetocin via the intramyometrial route for the prophylaxis of postpartum hemorrhage. We aim to contrast the safety and effectiveness of intramyometrial injection of carbetocin vs intramyometrial injection of oxytocin to prevent postpartum bleeding during cesarean delivery.

Materials and methods: In the Obstetrics and Gynecology Department of Shri BM Patil MCH & RC, BLDE (DU), Vijayapura, Karnataka, India, this randomized parallel trial was conducted from August 2021 to July 2022. Women in group I received 100 µg carbetocin intramyometrially immediately after birth of baby but before separation of placenta, injected into the anterior uterine wall. Women in group II received 10 units of oxytocin intramyometrially immediately after birth of baby but before separation of placenta, injected into the anterior uterine wall. The outcomes measured were total blood loss and uterine tone at 1, 3, 5, and 10 minutes after injection, hemodynamic parameters, need for blood and blood products and additional uterotonics and adverse events.

Results: The difference in the preoperative and postoperative hemoglobin was nearly equal in both the groups 0.943 gm/dL in group I and 0.912 gm/dL in group II (p-value < 0.001). The tone of the uterus was well contracted from 5 minutes in both the groups. Additional uterotonics were used for 2 cases in group I and 4 cases in group II. These findings are consistent with non-inferiority as seen in the champion trial. Two patients in group I and one in group II underwent blood transfusions. Group I showed no adverse consequences, whereas group II only showed one case of a statistically insignificant negative event.

Conclusion: Intramyometrial injection of carbetocin is non-inferior to intramyometrial injection of oxytocin in terms of efficacy and safety.

Clinical significance: This study explores an alternative route for the administration of carbetocin for postpartum hemorrhage prophylaxis. This study opens up the prospective of better local action, possible quick action in emergencies and fewer systemic side effects compared to the traditional route.

Keywords: Carbetocin, Cesarean delivery, Intramyometrial, Novel, Postpartum hemorrhage.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2489

Introduction

Worldwide, postpartum hemorrhage, or PPH, is the leading cause of maternal death. Uterine atony has been the commonest cause of PPH. Guidelines for the use of preventive uterotonics in the avoidance of PPH have been provided by the WHO. Carbetocin, oxytocin, methergine, carboprost and misoprostol have been used in the prophylaxis of postpartum haemorrhage.[1] There is, however no mention of any varied dose or route for cesarean delivery. Intramyometrial route has been used to deliver uterotonic drugs such as oxytocin and carboprost by operating obstetricians during cesarean delivery.[2] Studies have shown that the intramyometrial route of uterotonic may cause immediate uterine contractions due to the local action of the absorbed drug. This may be helpful in preventing blood loss. Carbetocin is the synthetic counterpart of oxytocin which is longer acting compared to oxytocin ($t_{1/2}$ 85–100 minutes). Unlike oxytocin, carbetocin does not require cold storage and remains stable for 1.5 years at thirty degrees Celsius temperature and relative humidity of 75%. Heat stable carbetocin was introduced in India in 2021. Carbetocin has been used via intramyometrial route during myomectomy in open and laparoscopic surgeries but not for cesarean sections. Hence, a

[1,2]Department of Obstetrics and Gynecology, Shri BM Patil Medical College, Hospital & Research Center, Vijayapura, Karnataka, India

Corresponding Author: Preeti S Malapure, Department of Obstetrics and Gynecology, Shri BM Patil Medical College, Hospital & Research Center, Vijayapura, Karnataka, India, Phone: +91 9113945722, e-mail: preetimalapure1991@gmail.com

How to cite this article: Yaliwal RG, Malapure PS. Randomized Parallel Trial of Intramyometrial Injection of Heat-stable Carbetocin vs Intramyometrial Injection of Oxytocin for the Prevention of Postpartum Hemorrhage during Cesarean Delivery. J South Asian Feder Obst Gynae 2024;16(Suppl 2):S62–S66.

Source of support: Nil

Conflict of interest: None

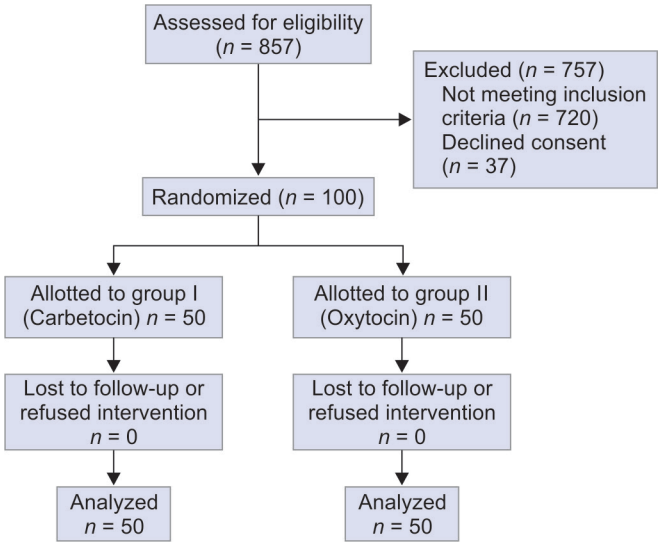

Fig. 1: CONSORT flowchart

Novel study was designed for intramyometrial injection of heat stable carbetocin vs intramyometrial injection of oxytocin for the prevention of postpartum bleeding during cesarean delivery.

Materials and Methods

This 1 year study, a randomized parallel trial, was conducted in the Obstetrics and Gynecology Department at the Shri BM Patil Medical College, Hospital and Research Centre, BLDE (DU), in Vijayapura, Karnataka, India. The Institutional Ethics Committee (IEC) has granted the study ethical clearance. BLDE(DU)/IEC/562/2021-2022. Clinical Trials of India CTRI/2021/09/036792 has the trial registered.

Sample Size: 100

A total of 95 patients were required to have a 90% chance of detecting, as significant at the 5% level, which was rounded off to 100 patients, 50 cases in each group.

Calculation based on the formula:

$$n = f(\alpha/2, \beta) \times 2 \times \sigma^2/(\mu_1-\mu_2)^2$$

Where μ1 and μ_2 are the mean outcome in the study groups respectively and σ is the standard deviation.

All consenting pregnant women ≥18 years old not in active labor (defined as cervical dilation less than 6 cm) undergoing a cesarean section were included in the study (low-risk cases). Cases perceived as high risk for PPH were excluded, i.e., active labor with cervical dilation ≥6 cm, mothers with antepartum and intrapartum hypertensive disorders of pregnancy, antepartum hemorrhage, bleeding disorders and coagulation abnormalities, intrauterine fetal death in the present pregnancy, women with vascular disorders, cardiac or hepatic disease, seizure disorder, women who refuse blood and blood products transfusion, and women with sensitivity to any of the study drugs. This was a single-blinded study and the study population of 100 patients was randomly divided (Fig. 1) by computer-generated randomized list into two groups, each including fifty patients (1:1 allocation ratio). Group I received a 100 μg heat-stable carbetocin intramyometrial injection immediately after the birth of the baby but before placental separation. 1 mL heat stable carbetocin was taken in a 2 mL disposable syringe and injected into the anterior uterine wall toward the uterine fundus by single shot. The uterus was closed in a single layer using round-body polyglactin 910 No.1. One OBG Junior resident, who did not scrub in for the case, was assigned as the timekeeper/record-keeper. The uterine tone was simultaneously assessed while closing the uterus by the operating surgeon at the defined time intervals as prompted by the timekeeper. Similarly, group II received 2 mL (10 units) of oxytocin taken in a 2 mL syringe and injected into the anterior uterine wall toward the uterine fundus immediately after the birth of the baby but before placental separation. The uterine tone was measured at 1, 3, 5 and 10 minutes after the intramyometrial injection on a scale of 1–5 after extraction of the baby.

1 = Atonic.
2 = Partial, inadequate uterine contractions.
3 = Adequate contractions.
4 = Well contracted.
5 = Very well contracted.

In order to create a standard interpretation, every surgeon taking part in the trial received training in uterine tone assessment. Hemodynamic data such as heart rate, systolic and diastolic blood pressure, and oxygen saturation were recorded by the record-keeper at 1, 5 and 10 minutes intervals after the extraction of the baby, and the adverse events such as nausea, PPH, tachysystole, uneasiness in chest/chest pain, any other uterotonic used via any other route and use of blood and blood product transfusions. Postoperatively total of 5 pints of iv fluids (2 pints ringer lactate, 2 pints 0.9% normal saline and 1 pint DNS) were given at 100 mL/hr over 24 hours along with antibiotics and analgesics. The difference between the levels of hemoglobin before and after surgery was used to compute the total blood loss. The preoperative hemoglobin level was measured within 24 hours of posting the patient for LSCS, and the post-operative hemoglobin level was measured 48 hours following the cesarean delivery.

Statistical Analysis

All attributes were summarized descriptively. The summary statistics of N, mean, and standard deviation (SD) were applied to continuous variables. When it came to categorical data, the summaries and analyses employed percentages and numbers, as well as the Chi-square test for association, the *t*-test for mean comparison, ANOVA, and diagrammatic presentation.

Results

A total of 857 pregnant women underwent cesarean sections during the study period. The first 100 pregnant women who fit the study requirements were included in the study. Informed written consent was obtained and randomized into group I (Carbetocin group) and group II (Oxytocin group). There were no drop-outs after inclusion in the study. Group I and group II were homogeneous with respect to patient characteristics. There was no statistically significant difference across the two groups in the women's age, parity, obstetric score, or weight (Table 1). This study excluded women in active labor. We included the women in early labor defined as less than 6 cm cervical dilation. In both study groups, the proportion of these women was comparable (*p*-value 0.335 - not significant). Hemoglobin levels prior to operation and the postoperative hemoglobin levels on day 2 of surgery were measured. The drop in the hemoglobin levels was measured and found to be similar, and although there was a statistically significant difference between the two groups, the difference is not substantial in terms of clinical

Table 1: Demographic characteristics

					95% of confidence interval	
Parameters	*Group*	*Mean*	*SD*	*p-value*	*Lower class limit*	*Upper class limit*
Age (years)[$]	Group I	26.12	4.374	0.143	–0.425	2.905
	Group II	24.88	4.008			
Obstetric score (gravida)	Group I	2.36	1.258	0.450	–0.0232	1
	Group II	2.1	0.909			
Parity	Group I	1.04	0.925	0.152	–0.0222	1
	Group II	0.76	0.744			
Period of gestation (in weeks)	Group I	37.86	1.99	0.311	0.02356	1
	Group II	37.38	2.398			
Weight (in kgs)	Group I	71.571	7.176	0.015	0.0682	6.181
	Group II	68.14	6.599			

$, independent sample *t*-test; Others Mann–Whitney *U* test; Group I carbetocin arm; Group II oxytocin arm

Table 2: Blood loss

					95% of confidence interval	
Variables	*Group*	*Mean*	*SD*	*p-value*	*Lower class limit*	*Upper class limit*
Postoperative Hb	Group I	10.172	1.066	0.013	–0.962	–0.118
	Group II	10.712	1.062			
Preoperative Hb	Group I	11.115	1.056	0.044	–1.02	–0.014
	Group II	11.632	1.45			
Difference in hemoglobin levels in gm/dL	Difference in group I mean and SD	0.943	0.01	<0.001	0.729	1.134
	Difference in group II mean and SD	0.912	0.388			

p-value <0.05 is significant

Table 3: Tone of the uterus

					95% of confidence interval	
Uterine tone	*Group*	*Mean*	*SD*	*p-value*	*Lower class limit*	*Upper class limit*
1 minute	Group I	2.82	0.8	0.586	–0.0091	0.00817
	Group II	2.9	0.678			
3 minutes	Group I	3.48	0.886	0.286	–0.0332	0.02246
	Group II	3.3	0.735			
5 minutes	Group I	4.04	0.727	0.298	–0.0144	0.02457
	Group II	3.94	0.55			
10 minutes	Group I	4.78	0.648	0.073	–0.036	0.00858
	Group II	4.68	0.513			

Mann–Whitney *U* test

outcomes (Table 2). The uterine tone was assessed at 1, 3, 5, and 10 minutes in both the groups after administration of the drug on a scale of 1–5. It was found to be similar in the both the groups over the time intervals (*p*-value > 0.05) (Table 3). The variations in vital parameters heart rate, systolic BP, diastolic BP and SpO_2 were recorded at 1, 5, and 10 minutes. No significant variability was noted in both the groups (Table 4). The adverse events following the administration of drugs, such as nausea, PPH, tachysystole, uneasiness in chest/chest pain, were looked out for. One case in group II had nausea. No other cases in both the groups reported any adverse reactions (*p*-value 0.315) (Table 5). In two cases in group I and four cases in group II, additional uterotonics were delivered. Two cases in group I and one case in group II involved the transfusion of blood and blood components.

Discussion

Studies have been conducted on the dosage and delivery method of uterotonics during elective cesarean sections. Though the use of intramyometrial route has not been licensed for oxytocin, the use has been advocated for over 30 years. Intramyometrial route is said to be faster in action in comparison to the intramuscular

Table 4: Variation in hemodynamic parameters

						95% of confidence interval	
Parameters	*Variables*	*Group*	*Mean*	*SD*	*p-value*	*Lower class limit*	*Upper class limit*
Heart rate	1 minute	Group I	90.16	11.559	0.961	–4.000	4
		Group II	89.54	10.79			
	5 minutes	Group I	90.52	12.616	0.653	–3.815	6.05
		Group II	89.4	12.247			
	10 minutes	Group I	89.76	11.122	0.569	–2.000	6
		Group II	87.78	10.691			
Systolic blood pressure	1 minute	Group I	120.36	12.96	0.131	–0.0155	
		Group II	116.94	12.764			
	5 minutes	Group I	121.22	12.848	0.460	–4.00	8
		Group II	118.14	14.213			
	10 minutes$	Group I	119.18	11.982	0.163	–1.314	7.674
		Group II	116	10.622			
Diastolic blood pressure	1 minute	Group I	76.96	12.224	0.337	–2.00	6
		Group II	75.9	10.725			
	5 minutes	Group I	77.88	11.403	0.557	–2.00	6
		Group II	75.74	12.409			
	10 minutes	Group I	77.06	10.318	0.612	–3.000	4
		Group II	76.96	10.254			
SpO_2	1 minute	Group I	99.58	0.81	0.179	–0.0227	0.01604
		Group II	99.66	1.042			
	5 minutes$	Group I	99.56	0.884	0.275	–0.009	0.05974
		Group II	99.76	0.625			
	10 minutes	Group I	99.68	0.683	0.37	–0.014	0.05101
		Group II	99.66	0.895			

$, independent sample *t*-test; Others Mann–Whitney *U* test

Table 5: Adverse events and others

Parameters	*Group I*	*Group II*	*p-value*
Adverse effects			
Nausea	0	1	0.315
PPH	0	0	
Tachysystole	0	0	
Uneasiness in chest/Chest pain	0	0	
Use of additional uterotonics			
No	48	46	0.678
Yes	2	4	
Blood and components transfusion			
No	48	49	0.500
Yes	2	1	

route due to local action of the drug. However, the comparison of intramyometrial route to the intravenous route in the use of oxytocin has not shown to have any benefits other than reducing nausea and vomiting.[5] This is the first study to assess the use of carbetocin intramyometrially during a cesarean surgery. Compared to oxytocin, carbetocin has a longer half-life, which results in a longer duration of effect. The intramyometrial route of carbetocin has been less studied. This study highlights that when administered intramyometrially, carbetocin is just as efficient as oxytocin in preventing postpartum hemorrhage. The blood loss was nearly equal in both the study groups, 0.943 gm/dL in group I vs 0.912 gm/dL in group II. A large multicentric trial showed that the amount of blood loss of at least 500 mL or additional uterotonic agents used were similar in both the carbetocin group, and oxytocin group.[4] The tone of the uterus was well contracted for 5 minutes in both the groups. Just 4% of cases in group I and 8% of cases in group II warranted the administration of additional uterotonics. These findings are consistent with non-inferiority, as seen in the Champion trial.[4] Blood transfusion was done for 4 percent of cases in group I and 2 percent of cases in group II. About the dosage of carbetocin, one study that used 100 micrograms of the drug intravenously during a cesarean section right after the baby was delivered reported that only 3.3% of patients experienced significant bleeding. The usefulness of carbetocin in preventing postpartum hemorrhage during cesarean sections was highlighted in this study.[6] No adverse effects were observed in group I, and only one case in group II had an adverse event, which is statistically not significant. Studies on the intramyometrial route suggest that this route would deliver an immediate effect on the uterus, with lesser systemic effects. Our study did not show any significant variations among the

two groups with respect to hemodynamics after administering the drug. In a study using 20 IU oxytocin intramyometrially, they observed that there was more hypotension in comparison to the intravenous route.[7] Other studies have not shown significant hypotension after administering intramyometrial oxytocin. However, the study could not conclude any advantage of the intramyometrial route. The tone of the uterus was similar after administering intramyometrial carbetocin or oxytocin. Studies conducted in Japan have observed a delay in the tone in the intramyometrial group.[8] Studies on the use of intramyometrial carbetocin are few. One study has used the intramyometrial carbetocin during myomectomy and concluded that the blood loss was less in comparison to rectal misoprostol or the use of nothing.[9] A literature review was done on the implementation of heat-stable carbetocin for PPH prophylaxis in poor-resource countries. They observed that heat stable carbetocin can be affordably used in low-income economies for public sector use and that it has demonstrated efficacy in reducing postpartum bleeding in vaginal and cesarean sections in tertiary level hospitals.[10]

Limitations

A larger sample size will be more helpful in getting clinically significant differences in blood loss estimates.

Conclusion

In terms of effectiveness and safety in preventing postpartum hemorrhage during cesarean sections, intramyometrial injection of carbetocin is comparable to intramyometrial injection of oxytocin. Heat stable carbetocin has the advantage of a long half-life along with not requiring cold transportation and storage. With competitive pricing, carbetocin could be projected as an appropriate replacement for oxytocin in the prophylaxis of PPH.

Ethical Approval

The Institutional Ethics Committee (IEC) has granted the study ethical clearance. BLDE(DU)/IEC/562/2021–2022 and the trial is listed as CTRI/2021/09/036792 with Clinical Trials of India.

Clinical Significance

Intramyometrial route for injection of carbetocin in the prophylaxis of PPH has been explored in this study. Our study data suggests it is safe and effective. Further studies can be done to compare it with different drugs for PPH, as well as other routes of administration.

Orcid

Rajasri G Yaliwal https://orcid.org/0000-0002-9740-6300
Preeti S Malapure https://orcid.org/0000-0002-9214-1147

References

1. WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
2. Gallos ID, Williams HM, Price MJ, et al. Uterotonic agents for preventing postpartum haemorrhage: A network meta-analysis. Cochrane Database Syst Rev 2018;4(4):CD011689. DOI: 10.1002/14651858.CD011689.pub2.
3. Van der Nelson H, O'Brien S, Lenguerrand E, et al. Intramuscular oxytocin versus oxytocin/ergometrine versus carbetocin for prevention of primary postpartum hemorrhage after vaginal birth: Study protocol for a randomized controlled trial (the IMox study). Trials 2019;20(1):4. DOI: 10.1186/s13063-018-3109-2.
4. Widmer M, Piaggio G, Nguyen TMH, et al. Heat-stable carbetocin versus oxytocin to prevent haemorrhage after vaginal birth. N Engl J Med 2018;379(8):743–752. DOI: 10.1056/NEJMoa1805489.
5. Torloni MR, Siaulys M, Riera R, et al. Route of oxytocin administration for preventing blood loss at caesarean section: A systematic review with meta-analysis. BMJ Open 2021;11(9):e051793. DOI: 10.1136/bmjopen-2021-051793.
6. Razzaque SM, Khan AM. Efficacy and safety of carbetocin for the prevention of primary PPH during caesarean section: An open label single arm study. Bangladesh Journal of Obstetrics & Gynaecology 2020;33(2):119–124. DOI: 10.3329/bjog.v33i2.43563.
7. Dennehy KC, Rosaeg OP, Cicutti NJ, et al. Oxytocin injection after caesarean delivery: Intravenous or intramyometrial? Can J Anaesth 1998;45(7):635–639. DOI: 10.1007/BF03012092.
8. Akinaga C, Uchizaki S, Kurita T, et al. Randomized double-blind comparison of the effects of intramyometrial and intravenous oxytocin during elective cesarean section. J Obstet Gynaecol Res 2016;42(4):404–409. DOI: 10.1111/jog.12926.
9. Ashraf MH, Ahmed SM, Mohamed TF. Comparative study of the effect of intramyometrial carbetocin injection and rectal misoprostol on blood loss during myomectomy operations. Al-Azhar Assiut Medical Journal 2021;19(4):539–547. DOI: 10.4103/azmj.azmj_63_21.
10. Tran NT, Bar-Zeev S, Zeck W, et al. Implementing heat-stable carbetocin for postpartum haemorrhage prevention in low-resource settings: A rapid scoping review. Int J Environ Res Public Health 2022;19(7):3765. DOI: 10.3390/ijerph19073765.