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Original Research Article

Comapring a lower dose of carbetocin to the standard dose of carbetocin in the prevention of postpartum hemorrhage during elective cesarean delivery: A randomised parallel group trial

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ABSTRACT

Background: Prophylactic use of uterotonic is a universal practice in vaginal and cesarean delivery. Heat stable carbetocin is a relatively new uterotonic. Lower doses of uterotonics are as effective as standard doses in elective cesarean deliveries. This study aimed to compare the effectiveness and safety of 50 mcg carbetocin (lower dose) to 100mcg carbetocin (standard dose) for the prevention of postpartum hemorrhage during elective cesarean delivery.

Materials and Methods: A total of 212 term pregnant women were randomized to two group. Group I received 50 mcg of carbetocin and Group II received 100 mcg of carbetocin. The blood loss, tone of the uterus, use of additional uterotonics or styptics, requirement of blood transfusions and adverse effects of the drug in both the groups were compared.

Results: There were no statistically significant differences in both the groups with respect to blood loss, uterine tone, blood transfusions or additional use of uterotonics or styptics.($p>0.05$).

Conclusion: A lower dose of 50 mcg is as effective as the standard dose of 100 mcg of carbetocin in elective caesarean delivery in preventing post-partum hemorrhage.

1. Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and maternal mortality globally. The effect it has on the maternal health and its social impact is circumstances of maternal death are devastating. In view of this, universal use of uterotonic drugs during delivery has been advised by the World Health Organization (WHO) as a part of active management of third stage of labor, in the prevention of PPH. The use of 10 IU oxytocin IM or IV has been recommended by the WHO universally within one minute of delivery of the baby during either vaginal delivery or cesarean delivery. Recently carbetocin has been added to the list of essential drugs for PPH prevention by WHO.[1,2]

Carbetocin is a heat stable uterotonic. It is a long acting oxytocin analogue. It has longer duration of action, half -life being 40 minutes. This drug has been used since 1997 in a few countries and has been used in its heat stable form since 2018.[3]

The heat stable nature of carbetocin is useful for its use where refrigeration and electricity supply is a concern which would be needed for the storage of oxytocin.[4] Its longer half - life has an advantage over oxytocin, especially in elective cesearean delivery cases as the need for giving additional oxytocin for a couple of hours after the surgery would be circumvented.[5]

The major drawback of carbetocin is that it is expensive in comparison to oxytocin.

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When the use of prophylactic uterotonics are described, there are no consensus on the dose of uterotonics separately for caesarean delivery vs vaginal delivery. The elective caesarean poses a challenge to the obstetrician as the uterus is not in labour, therefore the oxytocin receptors on the uterus are more sensitive to a smaller dose of uterotonic. Lower doses are said to be as effective as standard dose in elective caesarean delivery. However, there is no consensus on doses of uterotonics for elective vs emergency caesarean delivery.[6,7]

This study aims to compare the effectiveness and safety of 50 mcg carbetocin (lower dose) to 100mcg carbetocin (standard dose) for the prevention of postpartum hemorrhage during elective cesarean delivery.

2. Materials and Methods

This study was conducted at Bijapur Lingayat District Education (Deemed to be University) Shri BM Patil Medical College, Hospital, and Research Center, in the Department of Obstetrics and Gynecology. It was conducted on consenting women with term pregnancies (37-42 weeks of gestation) who were over 18 years undergoing elective LSCS under subarachnoid block (Spinal Anesthesia). Women who were in labor, or those who had coagulopathies, hypertension, cardiovascular disorders, hepatic, renal disorders, epilepsy were excluded. Women with conditions predisposing to uterine atony such as hydramnios, multiple gestation, abruption, placenta previa and severe anemia were also excluded from the study. The study was conducted between July 2022 to December 2023.

2.1. Sample size calculation

The anticipated means of estimated blood loss (ml) with 40 and 100 mg dose of carbetocin 806±310 and 697±453 respectively. (3) the required minimum sample size is 106 per Group (i.e. a total sample size of 212, assuming equal group Sizes) to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in means between two groups. Level of significance = 95%. The power of the study=80%, d = clinically significant difference between two parameters, SD = Common standard deviation.

2.2. Statistical analysis

The data obtained was entered in a Microsoft Excel Sheet, and statistical analysis was performed using statistical package for the social sciences (Version 21). Results will be presented as means, counts and percentages. For normally distributed continuous variables between two groups Independent t test was used. For not normally distributed variables Mann Whitney U test was used. Categorical variables between two groups were compared using Chi square test.

A $p < 0.05$ was considered statistically significant.

2.3. Study design

The study was a randomized parallel single blinded group trial.

The study was conducted in accordance with the Declaration of Helsinki. It had obtained the Ethical clearance from the Institute Ethical committee, bearing Reference No. BLDE (DU)/IEC/575/2021-22 and was registered at Clinical Trials Registry of India CTRI/2022/03/041222.

The primary outcome of the study was to assess the blood loss in both groups by assessing intraoperative blood loss and the difference in preoperative and post-operative hemoglobin levels.

The secondary outcome was to assess the tone of the uterus, use of additional uterotonics or styptics, requirement of blood transfusions and adverse effects of the drug.

2.4. Method

A total of 2465 women were screened for inclusion into the study. After meeting the inclusion criteria and obtaining written and informed consent, the participants were assigned to either Group I or Group II as per predetermined randomization chart. Randomization was done by computerized randomization chart obtained from www.randomizer.org. Pre-operative pulse, blood pressure (BP) and complete blood count was obtained. Spinal anesthesia was given using bupivacaine 0.5% and cesarean delivery was performed. Group I was administered 50 mcg of carbetocin as a bolus dose IV within one minute of the delivery of the neonate. The drug was administered over 1 minute. Group II was administered 100mcg of carbetocin IV within one minute after the delivery of the baby. The drug was administered over one minute. The uterine one was recorded at one, five and ten minutes. It was assessed on a scale of one to five, where in the uterine tone corresponded to the following 1. Atonic, 2. Partial, inadequate uterine contractions, 3.Adequate contractions of the uterus 4. Well contracted uterus, 5.Very well contracted uterus. Blood loss was assessed by collection of blood in the suction bottle and weighing the wet mops. Mops were weighed pre-operatively and post operatively and the difference was calculated. The estimated blood loss was calculated using the formula 1 gm = 1ml of blood. The total blood loss was calculated by adding the blood in the suction apparatus and the blood from the mops. Pulse rate and blood pressure of the participants were recorded at beginning of the procedure and at one, five, ten minutes and at end of procedure. In case of use of any additional uterotonic or tranexamic acid or blood transfusion, it was recorded. The Complete Blood Count (CBC) was repeated between 48-72 hours after the

Table 1: Showing basic variables

Variable	Group I(N=108)		Group II (N=104)		Man WhitneyU Test	Significant Value (P)
	Mean	±SD	Mean	±SD		
Age (years)	25.72	4.394	25.45	4.065	5537.500	0.860
Period of gestation	38.41	1.059	38.55	1.198	5253.500	0.399
Prior gestation LSCS	0.93	0.821	0.78	0.682	5109.500	0.266
Prior vaginal delivery	0.19	0.552	0.17	0.445	5455.000	0.828

Note: p value <0.05 is significant

Table 2: Showing clinical parameters on enrolment to the study

Basic Variables	Group (N=108)		Group II (N=104)		Man WhitneyU test	Significant Value (P)
	Mean	±SD	Mean	±SD		
Pulse on Admission	86.88	8.504	86.38	7.252	5546.000	0.875
SBP	114.91	7.460	115.01s	8.695	5503.000	0.786
DBP	73.87	5.311	74.10	6.638	5466.500	0.712
WT IN KG	65.78	8.718	65.63	10.952	5606.000	0.982
Uterine Size	37.98	1.111	38.05	1.127	5559.500	0.892
FHR	141.34	5.586	141.52	5.902	5317.000	0.49

Table 3: Showing the uterine tone at various time after delivery of the drug

Firmness of Uterus	Group I (N=108)		Group II (N=104)		95% Confidence Interval of the Difference		Man Whitney U test	Significant value
	MEAN	±SD	MEAN	±SD	Lower	Upper		
At 1 min	3.21	0.627	3.33	0.660	3.18	3.36	5138.500	P = 0.226
At 3 min	3.53	0.676	3.59	0.617	3.47	3.64	5492.000	P = 0.753
At 5 min	3.73	0.692	3.77	0.672	3.66	3.84	5427.000	P = 0.642
At 10 min	4.04	0.610	4.02	0.653	3.94	4.11	5540.000	P = 0.846

Table 4: Comparison of blood loss between the groups

	Group I (N=108)		Group II (N=104)		95% Confidence Interval of the Difference		Man Whitney U Test	Significant Value
	MEAN	±SD	MEAN	±SD	Lower	Upper		
Estimated Blood Loss	340.65	135.188	337.21	120.665	321.64	356.29	5605.000	0.980
Pre OP HB	11.578	1.0967	11.600	1.1775	11.435	11.742	5504.000	0.802
Post OP HB	10.919	1.0259	10.909	1.3393	10.753	11.074	5523.500	0.836

caesarean delivery.

3. Result

A total of 2456 women were screened. A were excluded due to unwillingness to participate in the study or not meeting the inclusion criteria. 108 participants were in Group I (carbetocin 50 mcg) and 104 in Group II (carbetocin 100mcg).

There was no significant difference between both the groups with respect to age of the participant (p=0.860), gestational period (p = 0.399), prior history of vaginal or cesarean delivery. (p=0.828, 0.266 respectively) (Table 1).

There were no statistically significant differences between both the groups with respect to pulse rate, systolic and diastolic blood pressure on admission, weight of the patient, uterine size and fetal heart rate (p>0.05). (Table 2)

Comparing the two groups with respect to the tone of the uterus after administering the carbetocin in the specified dose, there was no statistical significance. Most of the participants had a good tone by 1 minute. The mean tone was 4 at 10 minutes in both the groups. (Table 3)

Adverse effects of the drugs like nausea, vomiting, headache, chills, back pain, hypotension, flushing, dyspnea, and chest pain were not seen in any patient in both the groups

There was no statistical difference in blood loss, (Table 4) need for uterotonics, and additional procedures blood transfusion in both the groups. The average blood loss in both the groups was less than 350 ml.

There was no need for surgical intervention like brace sutures, revascularization, uterine artery ligation, internal iliac ligation, per partum hysterectomy in both the groups.

None of the patients required any blood transfusion or additional drugs.

4. Discussion

This study aimed to study the effectiveness of a lower dose of carbetocin during elective cesarean delivery. The study showed that the blood loss in both the 50mcg carbetocin and 100mcg carbetocin were similar. Various studies have used lower doses of carbetocin in the elective cesarean. Doses as low as 20mcg have shown to be as effective in maintaining the uterine tone, use of additional uterotonics and blood transfusion in comparison to the standard dose of 100 mcg.[8] Even a dose of carbetocin as low as 14.8 mcg was considered non inferior to the standard dose.[9] In comparison, lower doses of oxytocin have shown to be as effective as the standard dose of oxytocin in elective cesarean section. As carbetocin has a longer duration of action, it would not require the additional infusion after the bolus dose during elective cesarean delivery as in comparison to oxytocin.[10]

Other studies show that a dose of 62.9mcg of carbetocin was required for women with a BMI of more than 40 kg/m^2.[11]

In a study conducted in Canada a total of 120 women were randomly allocated to groups receiving carbetocin doses of 20 μg, 40 μg, 60 μg, 80 μg and 100 μg. There was no difference in uterine tone among all dose groups and there still appeared to be an unacceptably high incidence of hypotension.[12] Study did not find any significant difference in both the groups with respect to hemodynamic circulation or was there any significant hypotension. Carbetocin could be made as a choice in resource limited conditions.[13] The cost of the drug is the main hinderence to its use. WHO has signed a memorandum with the manufacturers to reduce its price.[14] Adverse effects of carbetocin are low and are similar to those of oxytocin.[15]

Carbetocin has been recently introduced in the India, in the year 2021, hence the studies conducted on carbetocin during cesarean delivery are less in number. This study shows that the 50mcg dose of carbetocin is non inferior to the standard dose of carbetocin.

5. Conclusion

Low dose carbetocin is as efficacious and safe as standard dose of carbetocin for the prevention of postpartum hemorrhage in elective cesarean delivery. This inference could reduce the cost of the drug used. It could lead to smaller packaging of the drug. It could potentially prevent cardiovascular adverse effects, though this study did not reveal any untoward cardiovascular effects of carbetocin.

6. Limitation

This study is limited to Indian ethnicity. The study did not blind the operating obstetrician or anesthesiologist. The study did not differentiate between primary or repeat cesarean deliveries.

7. Sources of Funding

This study was internally funded by the Bijapur Lingayat District Education (Deemed to be University) Shri BM Patil Medical college, Hospital and Research Centre, Vijayapura, Karnataka, India.

8. Conflict of Interest

None.

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References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):323–33.
2. WHO recommendations: uterotonics for the prevention of postpartum haemorrhage. Geneva: World Health Organization; 2018. Available from: https://iris.who.int/bitstream/handle/10665/277276/9789241550420-eng.pdf.
3. Malm M, Madsen I, Kjellström J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. *J Pept Sci*. 2018;24(6):e3082.
4. Tran NT, Bar-Zeev S, Zeck W, Schulte-Hillen C. 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.
5. Zubaidi SA, and TA. Heat stable carbetocin vs. oxytocin for the prevention of post-partum hemorrhage in emergency caesarean delivery: a randomized controlled trial. *J Perinat Med*. 2021;50(2):150–6.
6. Elbourne DR, Prendiville WJ, Carroli G, Wood J, Mcdonald S. Prophylactic use of oxytocin in the third stage of labour. *Cochrane Database Syst Rev*. 2001;(4):CD001808. doi:10.1002/14651858.CD001808.
7. Lokugamage AU, Paine M, Bassaw-Balroop K, Sullivan KR, Refaey HE, Rodeck CH. Active management of the third stage at caesarean section: a randomised controlled trial of misoprostol versus syntocinon. *Aust N Z J Obstet Gynaecol*. 2001;41(4):411–4.
8. Mcdonagh F, Carvalho JCA, Abdulla S, Cordovani D, Downey K, Ye XY, et al. Carbetocin vs. oxytocin at elective caesarean delivery: a double-blind, randomised, controlled, non-inferiority trial of low- and high-dose regimens. *Anaesthesia*. 2022;77(8):892–900.
9. Khan M, Balki M, Ahmed I, Farine D, Seaward G, Carvalho JC. Carbetocin at elective Cesarean delivery: a sequential allocation trial to determine the minimum effective dose. *Can J Anaesth*. 2013;61(3):242–8.

10. Heesen M, Carvalho B, Carvalho JCA, Duvekot JJ, Dyer RA, Lucas DN, et al. International consensus statement on the use of uterotonic agents during caesarean section. *Anaesthesia*. 2019;74(10):1305–19.
11. Drew T, Balki M, Farine D, Ye XY, Downey K, Carvalho JCA. Carbetocin at elective caesarean section: a sequential allocation trial to determine the minimum effective dose in obese women. *Anaesthesia*. 2020;75(3):331–7.
12. Anandakrishnan S, Balki M, Farine D, Seaward G, Carvalho JCA. A Carbetocin at elective Caesarean delivery: a randomized controlled trial to determine the effective dose. *Can J Anesth*. 2013;60(2):1054–60.
13. Heesen M, Orbach-Zinger S. Optimal uterotonic management. *Best Pract Res Clin Anaesthesiol*. 2022;36(1):135–55.
14. Gallos ID, Coomarasamy A. Carbetocin: Worth the extra expense? *Best Pract Res Clin Obstet Gynaecol*. 2019;61:55–65.
15. Jin B, Du Y, Zhang F, Zhang K, Wang L, Cui L. Carbetocin for the prevention of postpartum hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *J Matern Fetal Neonatal Med*. 2016;29(3):400–7.

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