Original Article

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Efficacy of Carbetocin and Oxytocin in Reducing Blood Loss during the Third Stage of Labour: A Prospective Observational Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Postpartum Haemorrhage (PPH) remains a leading cause of maternal morbidity and mortality. Prophylactic uterotonics like oxytocin are widely used; however, newer agents such as carbetocin have emerged as potential alternatives with longer half-lives and reduced need for repeated administration.

Aim: To compare the efficacy and safety of carbetocin versus oxytocin in preventing PPH during vaginal delivery.

Materials and Methods: The present prospective observational study was conducted in the Department of Obstetrics and Gynaecology of Amala Institute of Medical Sciences in Kerala, India from December 2022 to December 2023, including 260 women undergoing vaginal delivery. A total of 130 women were administered carbetocin (100 µg) as a single intravenous dose and 130 women were given oxytocin according to Kerala Federation of Obstetrics and Gynaecology (KFOG) guidelines i.e., five units oxytocin diluted in 5 mL Normal Saline (NS) slow Intravenous (i.v.) over five seconds+10 units Intramuscular (IM)+20 units infusion in 500 mL NS at one drop/sec. Primary outcomes included incidence of PPH, estimated blood loss, and the need for additional uterotonics. The Estimated Blood Loss (EBL) was assessed using gravimetric analysis. Haemodynamic parameters were also recorded at five minutes and 30 minutes. Any adverse events and requirement of blood transfusion were also noted. Associations between categorical variables were tested using Chi-square or Fisher's exact test, while associations between continuous variables were evaluated using the independent t-test, with statistical significance set at the 5% level.

Results: In the present study, mean age was 26.08±3.32 years in the oxytocin group and 27.07±3.85 years in the carbetocin group, with predominantly primigravida women (69, 53.1% vs 73, 56.2%) Also, 13 (10%) of the carbetocin patients experienced >500mL blood loss versus 9 (6.9%) in the oxytocin group. Mean estimated blood loss was similar (carbetocin: 316.28 mL; oxytocin: 311.77 mL, p=0.871), as was the need for additional oxytocics (carbetocin: 16 (12.3%); oxytocin: 15 (11.5%), p=0.848). Only one oxytocin patient (0.8%) required transfusion. Vomiting occurred in 2.3% of carbetocin patients, with none in oxytocin. Carbetocin showed a statistically significant slight increase in Systolic Blood Pressure (SBP) at five minutes was +0.892±10.23 mmHg (oxytocin) versus +1.354±6.32 mmHg (carbetocin), p=0.034.

Conclusion: Carbetocin demonstrates comparable efficacy to oxytocin in reducing blood loss and preventing PPH during vaginal delivery.

Keywords: Anaemia, Bleeding, Maternal outcomes, Postpartum haemorrhage, Uterotonic agents

INTRODUCTION

The primary cause of haemorrhage at the time of delivery is uterine atony, therefore there is general agreement that Active Management of the Third Stage of Labour (AMTSL) rather than expectant management is recommended [1]. The third stage of labour is defined as the period that follows delivery and finishes with the delivery of placenta followed by contraction and retraction of uterus and control of haemorrhage [2]. As per World Health Organisation (WHO), AMTSL is one of the most important step in prevention of postpartum haemorrhage [1]. Prophylactic administration of uterotonic agents is one of the most important component of AMTSL [1]. Routine practice of AMTSL has been shown to dramatically reduce blood loss during third stage by up to 50% [3]. And hence it is practised worldwide [1]. Till recently the main uterotonic used for the AMTSL was oxytocin [4].

Carbetocin is a long-acting synthetic analogue of oxytocin that can be administered as a single dose injection in the route of i.v. or IM. In pharmacokinetic studies, i.v. injections of carbetocin produced tetanic contractions within two minutes, followed by rhythmic contractions for a further hour. Intramuscular injection produced tetanic contractions within two minutes, lasting about 11 minutes, and followed by rhythmic contraction for an additional two hours [5]. In comparison with oxytocin, carbetocin produces a prolonged uterine activity when administered postpartum, with respect to both frequency and amplitude of contractions [6]. Additionally, carbetocin is heat stable and does not need cold chain storage [6]. Both carbetocin and oxytocin are used in AMTSL in our Institute.

However, many studies have shown both to be either equally or carbetocin to be more effective [3,7,8]. Therefore, in the present study we are evaluating efficacy and safety of carbetocin in reducing blood loss during third stage of labour in vaginal delivery compared with oxytocin as per the Kerala Federation of Obstetrics and Gynaecology (KFOG) protocol. Most of the literature that shows the supremacy of carbetocin has compared it with the WHO protocol of IM oxytocin [7,8]. In our study, we compared carbetocin with the KFOG protocol of both IM and i.v. oxytocin in reducing blood loss during the third stage of labour in patients undergoing vaginal delivery.

MATERIALS AND METHODS

The present prospective observational study was conducted at the Department of Obstetrics and Gynaecology of Amala Institute of Medical Sciences in Kerala, India from December 2022 to December 2023. Institutional Ethical Committee approval was obtained under Order No.04/EC/23/AIMS-01. Written informed consent

was obtained from all the participants. Convenience sampling was adopted, and a total of 130 participants in each group were included in the study.

Inclusion and Exclusion criteria: For the current study, inclusion was limited to women with singleton pregnancies undergoing vaginal delivery at the tertiary hospital. Exclusion criteria comprised women with heart disease, known coagulation disorders {including HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome or Disseminated Intravascular Coagulation (DIC)}, a history of drug allergies, multiple pregnancies, instrumental deliveries (forceps or vacuum), shoulder dystocia, or existing vaginal or cervical tears.

Study Procedure

Participants were either in spontaneous or induced labour at the time of selection. A detailed history was taken using a standardised proforma, followed by a thorough clinical examination. Labour progress was monitored throughout the first and second stages. During the second stage of labour, patients were transferred to the second stage labour room for delivery.

Patients were alternately allocated to the oxytocin group or the carbetocin group by the principal investigator and outcome assessor was blinded. In the oxytocin group, five units of oxytocin diluted in 5 mL of NS were administered slowly via the i.v. route over five seconds, either immediately after delivery of the anterior shoulder or immediately following delivery of the baby. This was subsequently followed by 10 units of oxytocin administered intramuscularly, along with an i.v. infusion of 20 units of oxytocin diluted in 500 mL of NS over a period of two hours [9]. In the carbetocin group, 100 µg of carbetocin was administered i.v. within one minute of the baby's delivery.

The under pad was changed immediately following delivery, but before placental separation, to prevent any interference from amniotic fluid in blood loss measurement. The vagina and cervix were examined for tears, and any required episiotomy was sutured in layers under local anaesthesia. The weight of all blood-soaked materials (under sheets, mops, pads, cotton balls, and clots) was measured. The dry weight of these materials was subtracted, and the total blood loss was calculated using the gravimetric formula, where one gram of blood corresponds to 1 mL of blood loss [10]. Vital signs were assessed at five minutes and 30 minutes postpartum. Additional uterotonics were administered as needed and recorded. Any patients requiring blood transfusion or blood products were provided the necessary support, with this information being documented. Additionally, any other complications (e.g., nausea, vomiting) were noted.

STATISTICAL ANALYSIS

The data were entered into Microsoft Excel software and analysis performed using Statistical Package for the Social Sciences (SPSS) version 27. Results on continuous measurements are presented as the mean±Standard Deviation (SD) and results on categorical measurements are presented in frequency and percentages. Association between categorical variables was assessed using Chi-square test and Fisher's exact test (when expected cell frequency was <5). Association between continuous variables was assessed using independent t-test. Significance was assessed at 5% level.

RESULTS

Most participants in the oxytocin group were between 18-25 years (46.9%) and in carbetocin group, it was in the age group between 26-30 years (47.7%) [Table/Fig-1]. The most common risk factor was GDM in both groups, with 31.5% in the oxytocin group and 17.69% in the carbetocin group [Table/Fig-2]. There was no statistically significant difference in mode of onset of labour (p=0.700). The mean haemoglobin levels in third trimester were comparable between the two groups [Table/Fig-3].

Variables	Categories	Oxytocin group	Carbetocin group
Age group (in years)	18-25	61 (46.9)	48 (36.9)
	26-30	56 (43.1)	62 (47.7)
	31-35	11 (8.5)	15 (11.5)
	36-40	2 (1.5)	5 (3.8)
	41-45	0	0
	46-50	0	0
Mean maternal age		26.08±3.320 years	27.07±3.847 years
Obstetric score	Primigravida	69 (53.1)	73 (56.2)
	Second gravida	43 (33.1)	45 (34.6)
	Third gravida	16 (12.3)	9 (6.9)
	Fourth gravida	1 (0.8)	3 (2.3)
	Fifth gravida and above	1 (0.8)	0
Gestational age	<28 weeks	1 (0.8)	0
	28-32+6 weeks	0	1 (0.8%)
	33-36+6 weeks	2 (1.5)	9 (6.9%)
	37-39+6 weeks	114 (87.7)	113 (86.9%)
	≥40 weeks	13 (10.0)	7 (5.4%)
Mean gestational age (in weeks)		38.6±1.3	38.4±1.2

[Table/Fig-1]: Sociodemographic data.

Risk factors	Oxytocin group n (%)	Carbetocin group n (%)
GDM	41 (31.5)	23 (17.6)
Gestational hypertension	4 (3.0)	3 (2.3)
Pre-eclampsia	0	1 (0.7)
Anaemia	17 (13)	17 (13)
Seizure disorder	1 (0.7)	2 (1.5)
Thyroid disorders	15 (11.5)	15 (11.5)

[Table/Fig-2]: Risk factors of the participants.
GDM-Gestational Diabetes Mellitus

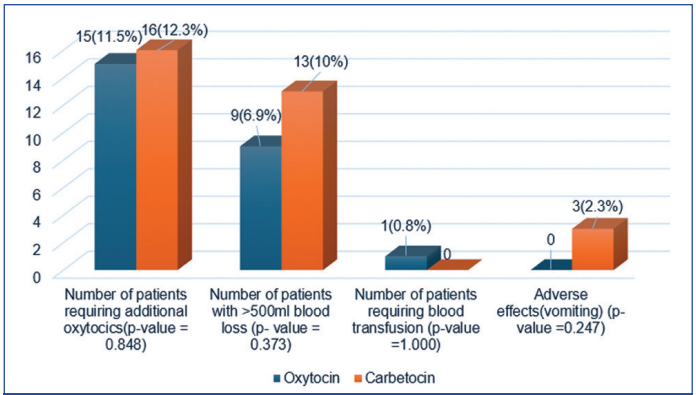
Variables	Oxytocin group	Carbetocin group	p-value
Induced	83 (50.9)	80 (49.1)	0.700#
Spontaneous	47 (48.5)	50 (51.5)	
Mean Hb	11.939±1.237 g/dL	11.971±1.092 g/dL	0.872*
Mean duration of labour	3.52±1.93	4.03±1.82	0.214*

[Table/Fig-3]: Comparison of Hb and delivery details of the study participants.
#- Chi-square test, *- Independent t-test
Hb-Haemoglobin

The mean estimated blood loss was similar between the two groups, with 311.77±247.62 mL in the oxytocin group and 316.28±196.38 mL in the carbetocin group (p=0.871). The number of patients requiring additional oxytocics was also similar, with 11.5% (15 patients) in the oxytocin group and 12.3% (16 patients) in the carbetocin group (p=0.848). Adverse effects were reported in three patients (2.3%) in the carbetocin group, while no adverse effects were observed in the oxytocin group (p=0.247) [Table/Fig-4].

Although the change in systolic blood pressure at five minutes was statistically significant between the oxytocin and carbetocin groups (p=0.034), the actual numerical difference was minimal (+0.892±10.23 mmHg vs. +1.354±6.32 mmHg) [Table/Fig-5,6].

At 30 minutes, no statistically significant differences were observed between the oxytocin and carbetocin groups in terms of mean changes in pulse rate, SBP, or Diastolic Blood Pressure (DBP) [Table/Fig-7].



[Table/Fig-4]: Bar chart comparing clinical outcomes between oxytocin and carbetocin groups.
Chi-square test

Variables	Oxytocin group	Carbetocin group	p-value
Mean baseline PR	81.59±1.36	78.48±8.28	0.002
Mean PR at 5 minutes	82.25±9.25	79.65±10.87	0.038
Mean PR at 30 minutes	81.39±8.29	79.78±7.60	0.105
Mean BP			
SBP	112.94±7.92	112.94±9.53	1.00
DBP	70.25±7.40	71.56±7.05	0.143
Mean BP at 5 minutes			
SBP	113.83±10.56	114.29±9.64	0.713
DBP	70.28±7.89	72.75±7.19	0.009
Mean BP at 30 minutes			
SBP	112.60±9.59	113.41±8.96	0.484
DBP	69.63±7.33	72.05±6.65	0.006

[Table/Fig-5]: Comparison of haemodynamic variables - baseline, at 5 minutes and at 30 minutes between oxytocin and carbetocin groups.
PR: Pulse rate; Values expressed as SBP/DBP (mmHg)

Comparison	Oxytocin group	Carbetocin group	p-value
Mean change in PR at 5 minutes	+0.662±7.48	+1.162±9.47	0.086
Mean change in SBP at 5 minutes	+0.892±10.23	+1.354±6.32	0.034
Mean change in DBP at 5 minutes	+0.031±8.20	+1.192±6.73	0.190

[Table/Fig-6]: Comparison of mean changes in pulse rate and blood pressure at 5 minutes post-delivery between oxytocin and carbetocin groups.
Independent t-test

Comparison	Oxytocin group	Carbetocin group	p-value
Mean change in PR at 30minutes	-0.200±7.19	+1.300±6.28	0.192
Mean change in SBP at 30 minutes	-0.338±8.71	+0.469±6.62	0.892
Mean change in DBP at 30 minutes	-0.615±7.26	+0.485±6.88	0.880

[Table/Fig-7]: Comparison of mean changes in pulse rate and blood pressure at 30 minutes post-delivery between oxytocin and carbetocin groups.
Independent t-test

DISCUSSION

In the present study, 10% of patients in the carbetocin group experienced >500 mL blood loss, compared to 6.9% in the oxytocin group. However, this difference was not statistically significant. This trend is consistent with the Community Health Promotion and Medical Provision for Neonatal Health (CHAMPION) trial [11] and the Boucher M et al., study where blood loss rates between the two groups were similar [12]. But we can also see that blood loss with oxytocin is much less than in the CHAMPION trial, which might be due to KFOG protocol. Wohling J et al., reported a significantly higher incidence of blood loss >500 mL in the oxytocin group (39.4%) compared to the carbetocin group (27.3%), suggesting a different trend in that population [13].

The mean estimated blood loss in the present study was comparable between oxytocin (311.77 mL) and carbetocin (316.28 mL). This EBL is lower than the values reported in previous studies including Boucher M et al., (413.3±197.5 mL in the carbetocin group and 410.4±194.1 mL in the oxytocin group) and Wohling J et al., (503±312 mL in the carbetocin group and 573±315 mL in the oxytocin group), where mean blood loss exceeded 400 mL [12,13]. Blood transfusion was rare in the present study. Only one patient (0.8%) in the oxytocin group required transfusion, while none in the carbetocin group required it. This contrasts with the Widmer M et al., (CHAMPION trial) in which the transfusion was required among 1.6% of the patients in the carbetocin group and 1.3% in the Oxytocin group [11]. In the Wohling J et al., study, transfusion rates were 1.2% in the carbetocin group and 1.6% in the Oxytocin group [13]. The lesser blood loss and lesser need for blood transfusion as compared to international studies could be due to the better mechanical measures we have in Kerala for control of PPH including the transvaginal uterine artery clamp and the suction cannula.

No maternal deaths or major complications occurred in the present study. Vomiting was the only adverse effect, observed in three patients (2.3%) in the carbetocin group. This rate is lower than the reported adverse effects in other studies. For instance, Boucher M et al., reported that at least one adverse effect was present in 51.8% and 54.5% of the participants in the carbetocin and oxytocin group respectively [12]. Widmer M et al., reported that, the percentages of women with at least one unanticipated adverse event were 4.9% in the carbetocin group and 4.7% in the oxytocin group [11]. No adverse effects were reported in the oxytocin group in this study.

In the present study, both oxytocin and carbetocin induced minimal changes in pulse rate, SBP, and DBP. However, carbetocin demonstrated a statistically significant (though numerically minimal and clinically insignificant) increase in SBP at five minutes, while oxytocin showed no significant changes. A similar effect was observed in the studies by Larciprete G et al., and Maheshwari B et al., where, while using carbetocin, BP either remained the same, the fall in BP was minimal, or there was a slight increase at five and 30 minutes [14,15]. In contrast, Moertl M et al., observed significant hypotension and tachycardia within 30-40 seconds of administering oxytocin and carbetocin, followed by a rebound phenomenon: rebound bradycardia and hypertension at 200 seconds in the oxytocin group and 270 seconds in the carbetocin group [16].

The slight BP increase with carbetocin at five and 30 minutes in the present study likely reflects this rebound effect. However, since pulse rate and BP measurements began at five minutes, the initial hypotension and tachycardia reported by Moertl M et al., might have been missed [16]. The results suggest that carbetocin may mitigate oxytocin-induced hypotension, offering hemodynamic stability. However, it may cause a transient increase in BP, which appears to be clinically insignificant but statistically notable.

Limitation(s)

The present study has several limitations that should be considered. First, the prospective observational design, rather than a randomised controlled trial, may introduce selection bias despite the alternate allocation of participants. As the study was conducted at a single tertiary care centre in Kerala, the findings may not be generalisable to other populations or healthcare settings. Blood loss estimation relied on gravimetric analysis, which, although objective, may be subject to inaccuracies due to potential contamination with amniotic fluid or other fluids despite precautions. The exclusion of certain high-risk groups, including women with instrumental deliveries or multiple pregnancies, limits the applicability of the results to these populations.

CONCLUSION(S)

Carbetocin, with its prolonged uterine activity and single-dose administration, offers a practical advantage making it a valuable

alternative to oxytocin, particularly in resource-limited settings. Further large-scale studies could provide additional insights into the cost-effectiveness and long-term benefits of integrating carbetocin into routine obstetric practice.

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