Section: Obstetrics and Gynaecology

Original Research Article

EFFECTIVENESS OF CARBETOCIN IN CAESAREAN SECTION FOR PREVENTION OF POST-PARTUM HAEMORRHAGE IN COMPARISON WITH OXYTOCIN AT A TERTIARY INSTITUTE IN NORTH-EAST INDIA: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Post partum haemorrhage is the leading cause of maternal deaths. Newer longer acting synthetic analogue of oxytocin, Carbetocin (1-deamino-1-monocarbo (2-O-Methyltyrosine)-oxytocin) is one of the uterotonic drugs has been approved by drug controller of India (2020). The objective is to compare the amount of blood loss as well as uterine tone following Carbetocin and Oxytocin in caesarean section and to assess the efficacy of the drugs in terms of additional interventions needed as well as drop in haemoglobin. Design is Randomized controlled trials. Setting is tertiary Institute in North-East India. Population Women undergoing Caesarean section. **Materials and Methods:** A Randomized controlled study was conducted in the Department of Obstetrics and Gynaecology, Regional Institute of Medical sciences, Imphal from 1st December 2021 to 31st May, 2023. About 346 pregnant women undergoing caesarean section (CS) who fulfil the inclusion and exclusion criteria after admission, was enrolled by block randomization into Carbetocin group(n=173) and Oxytocin group(n=173). **Result:** Majority of the study population was 18-29 years both Carbetocin and Oxytocin groups (56.6% vs 66.5%) and maximum study population was of 2-4 gravida; 110 (63.6%) vs 114 (65.9%) respectively. Para 0-1 comprised of 143 (82.7%) vs 145 (85.9%). Majority had less blood loss of <500ml in both groups i.e., 154 (89.02%) vs 145 (83.82%) but no statistically significant. Regarding the side-effects, nausea, vomiting was the only side effect which can be compared 5 (2.9%) vs 6 (3.5%) respectively. The Hb fall is from 11.7(10.9-12.5) to 10.4(9.5-11.5) in Carbetocin group and 12 (11-12.8) to 10.5(9.8-11.6) in Oxytocin group whose p-value is 0.129 and 0.218 respectively which was statistically not significant. The Uterine tone comparison was also not statistically significant. **Conclusion:** Carbetocin was equally efficacious as Oxytocin in Caesarean delivery with no adverse side effect. Carbetocin is heat stable and does not require multiple dosing in infusion. Funding: Regional Institute of Medical Sciences, Imphal provided fund for Carbetocin and Oxytocin.

INTRODUCTION

Post-partum haemorrhage (PPH) is a major issue due to its impact on maternal morbidity and mortality. Obstetric haemorrhage, especially postpartum haemorrhage (PPH), is responsible for more than a quarter of all maternal deaths worldwide.[1] In most low-income countries, PPH is the leading cause of maternal deaths. Thus, improving access to safe and effective interventions to prevent PPH is critical to World Health Organization (WHO) strategic priorities (particularly universal health coverage) for achieving the targets of the third Sustainable Development Goal (SDG 3). Postpartum haemorrhage occurs in 5-15% of deliveries.[2] Uterine atony is responsible for more than 50% of

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occurrences of PPH, numerous strategies have been promoted to preserve uterine tone. There are several uterotonic drugs for preventing PPH but it is still debatable which drug is best. Carbetocin is a long-acting synthetic oxytocin analogue, 1- deamino-1-monocarbo-(2-O-Methyltyrosine)-oxytocin, firstly described in 1987. Heat stable Carbetocin, given 100 mcg as an IV bolus over 1 minute, instead of continuous oxytocin infusion, can be administered in elective caesarean section for the prevention of PPH, in the attempt to decrease the need for therapeutic uterotonics. Single dose is more effective than a continuous infusion of oxytocin with a similar safety profile and minor antidiuretic effect, in the third stage of labour and in the first 24 hours. Carbetocin is approved by WHO (2018) and included in the WHO essential medicines drugs list (2019). Storage and cold chain maintenance of Oxytocin is difficult unlike Carbetocin. Recently it has been approved by drug controller of India (2020) for used in prevention of PPH and is now available in India. In Manipur, Carbetocin has not been used and no such study in pregnant women for PPH prevention have been conducted. The majority of PPH related morbidity and mortality are preventable through effective implementation of evidence-based guidelines.[3]

There are several uterotonic drugs for preventing PPH but it is still debatable which drug is best. Oxytocin is the most widely used uterotonic agent. Oxytocin (10 IU), administered intramuscular is used for the prevention of PPH in low-risk vaginal and caesarean deliveries. Intravenous infusion of Oxytocin (20 to 40 IU in 1000 mL, 150 mL/ hour) is an acceptable alternative for the active management. Ergonovine can be used but it may be considered a second choice to Oxytocin due to the greater risk of maternal adverse effects. Carbetocin is a long-acting synthetic Oxytocin analogue, 1- deamino-1-monocarbo-(2-O-Methyltyrosine)-Oxytocin is now included in the 21st essential medicines list of WHO.[4] Carbetocin, given 100 mcg as an IV bolus over 1 minute, instead of continuous Oxytocin infusion, can be administered in elective caesarean section for the prevention of PPH, in the attempt to decrease the need for therapeutic uterotonics. Single dose is more effective than a continuous infusion of Oxytocin with a similar safety profile and minor antidiuretic effect, in the third stage of labour and in the first 24 hours.[5-10]

Considering the effects and side effects, Carbetocin should be a good choice at caesarean delivery, particularly in intravenously use.[11] Cochrane meta-analysis included 140 randomised trials with data from 88,947 women. Ergometrine plus oxytocin combination, Carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH ≥ 500 mL than the current standard oxytocin. Carbetocin had the most favourable side-effect profile amongst the top three options.[12] Carbetocin is solely efficient in controlling PPH and is associated with less need for further uterotonics agents or surgical haemostatic measures in comparison to Oxytocin and Misoprostol groups.[13] The medicine is approved by Drug Controller General of India (2020) and for used in health care facilities.

MATERIALS AND METHODS

A Randomised controlled study was conducted in the Department of Obstetrics and Gynaecology, Regional Institute of Medical sciences, Imphal, Manipur from 1st December 2021 to 31st May, 2023.All pregnant women undergoing caesarean section who fulfil the inclusion and exclusion criteria after admission, was enrolled by block randomisation into group A and group B after informed consent. . This study was registered with CTRI No. : CTRI/2022/04/041583.

Participants: Inclusion criteria: All pregnant women who were undergoing caesarean section who gave informed consent was consecutively enrolled. The exclusion criteria include the presence of hypertension, cardiac, renal or liver diseases, epilepsy, general anaesthesia, bleeding disorders as well as women with history of hypersensitivity to any drugs. We recruited 346 pregnant women undergoing caesarean section and blocked randomisation with single binding into two groups was done. A total of 173 women was randomised to Carbetocin arm (Group A), and another 173 women to Oxytocin arm (Group B). Women in the group A received a bolus of 100 µg IV immediately after the delivery of the baby; women in the group B received 20 IU of Oxytocin in 500 ml of Ringer Lactate solution infusion. Sample Size: 346 with 173 in each Carbetocin arm and Oxytocin arm was calculated using appropriate statistical formula.

Sampling/Recruitment/Collection: Patient demographics, medical history and information on the current pregnancy, co-morbidities and co-medication were collected in a patient proforma sheet along with written informed consent to be taken from eligible women on admission. All routine tests were sent as usual. Data collection procedures were adopted and followed standard operating procedures (SOP) like measurement blood loss estimation, and standard monitoring as applicable. The study focuses on the amount of blood loss estimation (and primary PPH) after injection. During this time span, information on additional uterotonic medication, blood transfusion, operative interventions related to PPH, haemoglobin (Hb) and haematocrit were collected. Any side effects were noted.

Study tools: Carbetocin vials, Oxytocin ampoules, Syringes, Visual Blood loss estimation and Performa sheet.

Outcome variables: Independent variables: age in years, parity, high risk for PPH and maternal medical/ obstetric conditions. Dependent variables: amount of blood loss, uterine tone, additional interventions like need of mixed uterotonics, drop in Hb, blood transfusion, any surgical intervention, and side effects including tachycardia, hypotension & others.

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Primary outcome was the evaluation of intraoperative blood loss and early primary PPH following carbetocin versus oxytocin injection. The blood loss was checked immediately during and after caesarean, defining as haemorrhage a blood loss more than 1000 ml. Blood loss was estimated by the surgeon in the usual standard way (visual estimation, number of used swabs and amount of aspirated blood). Uterine tone (standardized as Very good (4), Good (3), Sufficient (2), Atony (1), were monitored immediately, 2 hours, and 24 hours after delivery. All patients underwent the same spinal anaesthesia. The second outcome was the need for additional interventions like need of uterotonic agents, blood transfusion, surgical interventions and the evaluation of the drop in haemoglobin level by comparing the haemoglobin concentration on admission and 24 hours after delivery. A complete blood count was to be taken upon their admission, and again 24 hours postpartum. Clinical assessments were collected and vital signs monitored at regular intervals following study drug administration up to 24 hours postpartum. Any uterine massage that was started after placental delivery because of excessive bleeding or inadequate uterine tone was recorded as an additional uterotonic intervention. Massage performed as part of active management of the third stage of labour was not recorded as an additional uterotonic intervention. The number of additional uterotonic agent doses and the time interval between initial study drug administration and additional uterotonic interventions were recorded. All subjects were monitored as per standard operating guidelines. The occurrence of nausea, vomiting, tachycardia, hypotension, flushing, headache, dyspnoea or any other side effects were recorded. Clinical safety assessment was performed by recording vital signs and adverse events at all study time points.

Statistical analysis: Collected data was checked for consistency and completeness. Data was entered in SPSS 21 version.

RESULTS

Majority of the study population was in 18-29 years age group i.e., 98(56.6%) in Carbetocin and 115(66.5%) in Oxytocin group as shown in table1. The study population belongs to gravida 2-4 i.e., 110(63.6%) in Carbetocin group and 114(65.9%) in Oxytocin group. Parity 1-0 comprises of 143(82.7%) in Carbetocin group and 145(83.8%) in Oxytocin group. Risk factor is maximum in post caesarean group in both cases i.e., 62(35.8%) and 58(33.5%) in Carbetocin and Oxytocin group respectively.

Hypotension was observed in two cases of oxytocin group but none in Carbetocin. The commonest side effect observed in both the group was nausea and vomiting found in 5(five) cases of Carbetocin and 6(six) cases of oxytocin group. Tachycardia was also another side effect seen as in [Table 1].

Table 1: Characteristics of the study population and side-effects of both groups.

Variables		**Group**		**Total (%) N=346**
		Carbetocin (%) N=173	**Oxytocin (%) N=173**	
Age (in years)	18-24	44(25.4%)	56(32.4%)	100(28.9%)
	25-29	54(31.2%)	59(34.1%)	113(32.7%)
	30-34	41(23.7%)	26(15.0%)	67(19.4%)
	35-39	29(16.8%)	26(15.0%)	55(15.9%)
	≥ 40	5(2.9%)	6(3.5%)	11(3.2%)
Gravida category	1	57(32.9%)	53(30.6%)	110(31.8%)
	2-4	110(63.6%)	114(65.9%)	224(64.7%)
	>4	6(3.5%)	6(3.5%)	12(3.5%)
parity category	0-1	143(82.7%)	145(83.8%)	288(83.2%)
	2-3	29(16.8%)	27(15.6%)	56(16.2%)
	>3	1(0.6%)	1(0.6%)	2(0.6%)
Risk Factors of PPH	Big Baby	3(1.7%)	7(4.05%)	10(2.9%)
	Poly Hydramnios	1(0.6%)	4(2.31%)	5(1.4%)
	Post CS	62(35.8%)	58(33.53%)	120(34.7%)
	Past H/O PPH	00.0	1(0.58%)	1(0.3%)
	PROM	15(8.7%)	20(11.56%)	35(10.1%)
	Prolonged Labour	2(1.2%)	4(2.31%)	6(1.7%)

Side effects of Carbetocin and oxytocin			
Side Effect	**Types of drugs**		**Total (%)**
	Carbetocin (%)	**Oxytocin (%)**	
Nausea/Vomiting	5(2.9%)	6(3.5%)	11(3.2%)
Tachycardia	3(1.7%)	4(2.3%)	7(2.0%)
Chills	1(0.6%)	2(1.2%)	3(0.9%)
Hypotension	-	2(1.2%)	2(0.6%)
Dizziness	1(0.6%)	-	1(0.3%)

There was no significant statistical difference in the amount of estimated blood loss and in the incidence of primary post-partum haemorrhage (>1000 mL) in Carbetocin and Oxytocin group as shown in table 2 below. There was requirement of additional uterotonic drugs in 24 cases of Carbetocin group and 27 cases in Oxytocin group. In addition, 3 cases in Oxytocin group required surgical intervention i.e.,

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compression suture, devascularisation and haemostatic suture as in [Table 2].

The Hb fall was not significant in both Carbetocin group from 11.7g/dl to 10.4g/dl (P-value: 0.129) and Oxytocin group from 12g/dl to 10.5g/dl (P-value: 0.218) as in [Table 2].

Table 2: Visual estimated blood loss and fall of hemoglobin in both the groups

Blood loss visual estimation category	**Group**		**Total (%)**	**P-value**
	Carbetocin (%)	**Oxytocin (%)**		
<500ml	154(89.02%)	145(83.82%)	299(86.4%)	0.181
500-1000ml	17(9.83%)	25(14.45%)	42(12.1%)	
1000ml-2000ml	1(0.58%)	2(1.16%)	3(0.9%)	
>2000ml	1(0.58%)	1(0.58%)	2(0.6%)	
* Average blood loss: Median(IQR) 300(280-400) in Carbetocin group and 320(272.5-410)				
Hb level before and 24 hours after caesarean section				

	Hb level, Mean (SD)				**P-value**
	Carbetocin group $\underline{X}_M(IQR)$N=158		**Oxytocin group $\underline{X}_M(IQR)$N=159**		
Pre-Op Hb	11.7	(10.9-2.5)	12.0	(11.0-12.8)	0.129
Post-Op Hb	10.4	(9.5-11.5)	10.5	10.5(9.8-11.6)	0.218

$\underline{X}_M = Median$, IQR = Interquartile Range

*29 cases from 346 were excluded as there was laboratory error of rise in Hb after 24 hours from pre-op Hb

The uterine tone measured at 2 hours of skin incision of caesarean section, end of CS and after 24 hours designated as atony(1), sufficient(2), good(3), very good(4) in both groups are represented in [Figure 1]

The haemodynamic effects following administration of Carbetocin and Oxytocin had hypotensive effects but the comparative effects showed no statistical significance as in [Table 3].

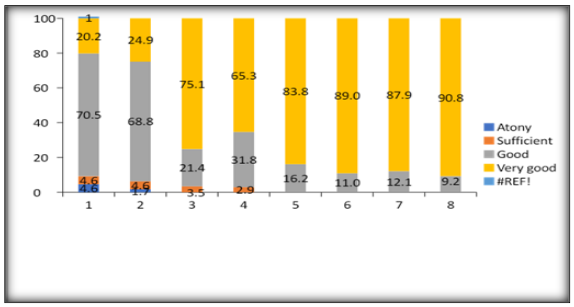

Figure 1: Showing different uterine tones at different hours after uterotonic administration (Not statistically significant)

Table 3: Vitals in both the groups during and after caesarean section

Vitals		**Carbetocin $\underline{X}$±SD or $\underline{X}_M(IQR)$**	**Oxytocin $\underline{X}$±SD or $\underline{X}_M(IQR)$**	**P-Value**
Systolic BP	Time of measurement			
	pre-operative	116(110-120)	120(110-121)	0.104
	5mins of skin incision	110(108-120)	110(110-120)	0.851
	at the end of CS	110(110-120)	110(110-120)	0.703
	Post-Operative			
	at 2 hours after CS	110(100-120)	110(100-120)	0.771
	at 24 hours after CS	112(110-120)	112(110-120)	0.635
Diastolic BP	(Median, Interquartile range)			
	pre-operative	80(70-80)	80(70-80)	0.621
	5mins of skin incision	70(64-77)	70(66-79)	0.145
	at the end of CS	70(62-80)	70(68-80)	0.110
	Post Operative			
	at 2 hours after CS	70(70-80)	70(70-80)	0.461
	at 24 hours after CS	78(70-80)	74(70-80)	0.954
	Pre-Operative	90±10	88±11	.135
	at 5 min of Skin Incision	90(83-97)	90(84-98)	.576
Pulse Rate	at the end of CS	87(80-93)	87(80-96)	.496
	at 2 hours after CS	82(76-90)	84(75-90)	.772
	at 24 hours after CS	84±9	82±10	.088

_X = Mean, SD = Standard Deviation, _X_M=Median, IQR = Interquartile Range

Urine output was also monitored at 2 hours, end of CS and 24 hours after CS as shown in [Table 4].

Table 4. Urine output in both the study population

Urine output (ml)	**Group**		**P-value**
	Carbetocin $\underline{X}_M(IQR)$ N=173	**Oxytocin $\underline{X}_M(IQR)$ N=173**	
at 5 min	30(20-50)	30(20-50)	0.186
at CS end	100(80-100)	100(70-100)	0.059
after 2 hrs of CS	200(150-275)	200(127-250)	0.158

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after 24 hrs of CS	1700(1400-2000)	1600(1275-2000)	0.385

_X_M=Median, IQR = Interquartile Range

DISCUSSION

PPH happens in 5-15% of all deliveries in the general population in absence of preventive measures without regard to maternal or foetal risk factors.[14] The incidence increased to 16-58% for women at risk receiving prophylaxis. So, this is one of the few studies to compare efficacy of Carbetocin and oxytocin in caesarean section concerning both the haemodynamic effects of these drugs and prevention of PPH.[15-19]

The primary outcome of the study is the evaluation of intraoperative blood loss and uterine. Giovanni et al,[5] concluded blood loss in the first 24 hours and drop in haemoglobin shows no difference in both the study groups and it is agreeable to the findings in our study. The uterine contraction and tonicity were noted that Carbetocin group shows no statistically significant with Oxytocin unlike Giovanni et al study.[5]

Out of 173, 2(two) cases of Carbetocin and 3(three) cases of Oxytocin develop PPH even after medication. However, the difference is not statistically significant as their P-value is 0.181. The haemodynamic effects were comparable in both the study population in both blood loss and uterine tonicity. There was almost equal requirement of additional uterotonic medication in the two-study population (24 cases in Carbetocin and 27 cases in Oxytocin) which is in contrast to the findings of a large multicentre trial done by Dansereau et al,[20] and Borruto et al,[22] but in agreement with a double-blind randomized trial comparing Carbetocin 100mcg IM and Oxytocin 10 IU in 500ml 5% Dextrose, 0.45% Normal saline by Marc Boucher et al.[21] Oxytocin group showed requirement of surgical intervention in 3(three) cases (01-Anteroposterior compression suturing;01-Bilateral uterine artery ligation;01-haemostatic suture), which might require further research as the difference might be due to sampling error.

Carbetocin and Oxytocin have similar safety profile when vitals, side effects were compared. It is a known fact that oxytocin bolus cause hypotension due to systemic vasodilation, tachycardia and increase in cardiac output. The hypotension and tachycardia are dose-dependent.[15-17] Giovanni et al concluded hypotension is more prominent with oxytocin group at 5 mines of oxytocin administration and during uterine repair and also in post-operative period whereas in our study, there was no such difference5. In hypovolaemia and cardiac disease, these haemodynamic effects of Oxytocin can cause myocardial ischaemia.[18] Moertl et al Oxytocin cause more pronounced hypotension and haemodynamic rebound than Carbetocin with comparable effects on the cardiovascular system.[19]

Carbetocin shows a moderate antidiuretic effect without statistically significant difference in urine output between Carbetocin and Oxytocin.[23] This finding was also found in our study. Giovanni et al,[5] found Carbetocin group have a significant higher diuresis than Oxytocin group, especially 12 hours after caesarean section. The antidiuretic effect was statistically not significant.

CONCLUSION

The study concluded that all pregnant women undergoing caesarean section with or without risk factors have comparable effect with regard to blood loss and uterine tone. So, Carbetocin is a better alternative to Oxytocin in clinical settings where an IV line is not easily available or is unsafe as it has the advantage of a single parenteral administration over a continuous IV infusion. It should also be the uterotonic drug of choice in pregnant women with high risk factor for PPH in peripheral set up in developing countries where cold chain cannot be maintained as it is heat stable.

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