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RESEARCH ARTICLE

Comparison of intravenous carbetocin versus intramuscular oxytocin in management of third stage of labour in vaginal delivery

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ABSTRACT

Background: Post-partum hemorrhage (PPH) and its prevention is a major issue globally due to its impact on maternal morbidity and mortality. Active management of the third stage of labour (AMTSL) should be routinely practiced to prevent the risk of PPH. **Objectives**: Aim of the study was to compare efficacy of intravenous carbetocin and intramuscular oxytocin in management of third stage of labour during vaginal delivery. **Methodology**: A prospective randomized case-control study was conducted in the Department of Obstetrics and Gynaecology, Fakhruddin Ali Ahmed Medical College and Hospital, over a period of 1 year from September 2021 to August 2022. The 200 parturients undergoing vaginal delivery were divided equally into two groups; Group A - women received carbetocin as a bolus of 100 microgram intravenously and group B - women received oxytocin 10 international units (IU) intramuscularly. Outcome measures such as primary PPH, amount of blood loss, need for additional uterotonic drugs, additional blood transfusion and adverse effects were compared postpartum. **Results**: Although, the mean blood loss was lesser in the carbetocin group than that of the oxytocin group with no statistical difference (p value = 0.464), there was a significant statistical difference in incidence of PPH (11% vs 23%; p = 0.037), additional uterotonics requirement (21% vs 35%; p= 0.04) and mean fall in hemoglobin level (p value = 0.0002) between carbetocin and oxytocin groups respectively. Adverse effects of drugs were almost similar in both the groups. **Conclusion**: Carbetocin was found to be an effective new drug over oxytocin for prevention of PPH in vaginal delivery.

Keywords: Uterotonic drugs, postpartum hemorrhage, oxytocin, carbetocin, vaginal delivery.

Postpartum hemorrhage (PPH) accounts for one maternal death in every four minutes worldwide.[1]With a reported incidence of 2-11% globally, PPH is one of the major causes of maternal death.[2 - 4] The incidence is reported to be 2–4% in the North Eastern (NE) region of India following vaginal delivery and 6% following caesarean section, with uterine atony being the primary factor in about 50% of cases.[5]PPH involves blood loss of more than 500 milliliter (ml) during vaginal delivery or 1000 ml during a caesarean section within 24 hours following delivery.[6]

Improving healthcare of women during delivery and administration of an uterotonic drug immediately after childbirth, as a part of AMTSL, are essential steps towards prevention of postpartum hemorrhage. Various strategies have been developed to maintain uterine tone, and uterotonic drugs like oxytocin, carbetocin, ergot alkaloids, etc., are widely used in third stage of labour.

Oxytocin is a widely used uterotonic drug[7,8] and the gold standard[9] for the prevention of PPH, which is administered 10 IU intramuscularly (IM) or 20 to 40 IU intravenous (IV) infusion**.** Carbetocin, a long-acting synthetic oxytocin analogue, is given as a single dose of 100 microgram (mcg)

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IV bolus over 1 minute.[10]

Although great effort has been made to reduce the maternal mortality, PPH still remains the commonest cause of maternal mortality and morbidity. Access to effective uterotonic is the key to prevent PPH caused by atonic uterus. In the prevention and treatment of PPH, uterotonics and minimally invasive procedures are the preferred treatment approaches, with laparotomy being the last resort.

The aim of the present study was to compare the efficacy of intravenous carbetocin and intramuscular oxytocin in management of third stage of labour during vaginal delivery.

Materials and methods

The study was conducted in the department of obstetrics and gynaecology, Fakhruddin Ali Ahmed Medical College and Hospital, Barpeta, from September, 2021 to August, 2022. The study was undertaken after obtaining institutional ethical committee clearance and written informed consent from the parturient. A prospective, randomized case controlled study was done on 200 parturients undergoing normal vaginal delivery. Randomization was done in a 1:1 ratio using a computer generated sequence. Parturients were divided equally into two groups:

1) Carbetocin group (n=100) - women received 100 mcg carbetocin intravenously.
2) Oxytocin group (n=100) - women received 10 IU oxytocin intramuscularly.

Inclusion criteria included all antenatal parturients of age 18 to 35years, singleton pregnancy at term gestation (37-42 weeks) with cephalic presentation at third stage of labour with high risk for PPH (such as multipara, multiple pregnancy, polyhydramnios, augmented labour and past history of PPH).

Exclusion criteria included parturients with history of pregnancy induced hypertension, pre-eclampsia or eclampsia, antepartum hemorrhage and malpresentation, women who had known or suspected coagulopathy, history of heart disease or cardiac arrhythmia, epilepsy, bronchial asthma, history or evidence of chronic liver, renal or endocrine disease and hypersensitivity to carbetocin or oxytocin.

Immediately after normal vaginal delivery of the baby, the study drug was administered and management of third stage of labour was conducted. Soon after the umbilical cord was clamped and cut, the study drug was injected and time was noted. Blood was collected for 1 hour in a kidney tray that was placed beneath the women's buttock and then the amount of blood was measured in a calibrated glass container (in milliliter). However, in case of a right mediolateral episiotomy wound (RMLE), the assistant firmly pressed over the wound to prevent oozing of blood without disturbing the position of tray, thereby avoiding blood loss from episiotomy wound.

Estimated blood loss, maternal haemoglobin at the time of admission and 24 hours post-partum, duration of third stage of labour, use of any additional uterotonics, need for blood transfusion and any side effects were noted.

The primary outcomes of this study were mean blood loss, development of postpartum hemorrhage and the fall in hemoglobin concentration after delivery. The secondary outcomes included any additional uterotonics required, need for blood transfusion and adverse effects (if any).

Statistical analysis - All data were presented as mean ± SD (standard deviation). All quantitative data were assessed using student's t - test to analyze changes over a period of time. Qualitative data were assessed using fisher exact test or chi- square test. P-value < 0.05 was considered as statistically significant. The statistical software GRAPHPAD INSAT-3 was used for the analysis of data and Microsoft word and Microsoft Excel have been used to generate graphs, tables, etc.

Results

All parturients were observed for duration of third stage of labour, estimated blood loss, development of PPH, need for additional uterotonics and blood transfusion, and haemoglobin level at both before and after delivery of the baby. The side effects (if any) associated with the study drugs in the present study was also recorded.

The demographic profile (table 1) such as mean age group, mean gestational age, antenatal checkup (ANC) status, parity, mode of delivery, events in labour pain [either spontaneous vaginal delivery (SVD)] or augmentation [artificial rupture of membrane (ARM) with or without oxytocin)] and mean duration of third stage of labour were comparable in both the groups with no significant difference (p-value > 0.05).

The mean blood loss was lesser in the carbetocin group than that of the oxytocin group (405.10 ± 133.77 ml and 420.50 ± 161.42 ml respectively, p-value = 0.464) with no significant difference. 89% of women in carbetocin group and 77% in oxytocin group did not develop PPH (blood loss < 500 ml). However, 11% in carbetocin group and 23% in oxytocin group had developed PPH (blood loss > 500ml) following the delivery of baby with statistically significant difference (p-value = 0.037) (table 2).

Table 1: Demographic characteristics

Characteristics		Carbetocin		Oxytocin		P-value
		Mean	SD	Mean	SD	
Mean age (in years)		23.07	4.69	22.80	4.48	0.678
Mean gestational age (in weeks)		38.63	1.44	38.74	1.43	0.588
Mean duration of third stage of labour (in minutes)		7.28	2.90	7.56	2.52	0.467
		Number	Percentage	Number	Percentage	
ANC Status	Booked	89	89 %	87	87 %	
	Unbooked	11	11 %	13	13 %	0.663
Parity	Primi gravida (G_1)	67	67 %	61	61 %	
	Gravida 2 (G_2)	22	22 %	24	24 %	
	Gravida 3 (G_3)	8	8 %	10	10 %	
	Gravida 4 (G_4)	3	3 %	5	5 %	0.462
Events in labour pain	Spontaneous labour progress	86	86 %	88	88 %	
	Labour augmentation (ARM + Oxytocin)	14	14 %	12	12 %	0.674
Mode of delivery	SVD with RMLE	73	73 %	80	80 %	
	SVD without RMLE	27	27 %	20	20 %	0.243

ARM – artificial rupture of membrane, SVD – spontaneous vaginal delivery, RMLE – right mediolateral episiotomy

Table 2: Postpartum hemorrhage in both groups

Categories	Carbetocin		Oxytocin		P-value
	Number	Percentage	Number	Percentage	
No PPH (Blood Loss < 500 ml)	89	89 %	77	77 %	0.037
PPH (Blood loss > 500 ml)	11	11 %	23	23 %	

Table 3: Hemoglobin level profile in both groups

Characteristics		Carbetocin		Oxytocin		P-value
		Mean	SD	Mean	SD	
Mean hemoglobin level (gm/dl)	Before delivery	10.94	1.69	11.17	1.77	0.346
	After delivery	10.24	1.42	10.12	1.39	0.557
Mean fall in hemoglobin level (gm/dl)		0.70	0.58	1.05	0.78	0.0002

Table 4: Side effects in both groups

Parameters		Carbetocin		Oxytocin		P-value
		Number	Percentage	Number	Percentage	
Side effects	Nausea	7	7 %	10	10 %	
	Vomiting	5	5 %	6	6 %	
	Shivering	4	4 %	4	4 %	0.619
	Pyrexia	4	4 %	3	3 %	
	Diarrhoea	2	2 %	3	3 %	
No side effects		78	78 %	74	74 %	

There was no significant difference in the mean hemoglobin level at before (10.94 ± 1.69 gm/dl and 11.17 ± 1.77 gm/dl, p-value = 0.346) and after delivery of the baby (10.24 ± 1.42 gm/dl and 10.12 ± 1.39 gm/dl, p-value = 0.557) in carbetocin and oxytocin group respectively. However, there was a very significant difference in the mean fall in hemoglobin level of the women (0.70 ± 0.58 gm/dl and 1.05 ± 0.78 gm/dl, p-value = 0.0002) in both carbetocin and oxytocin group respectively (table 3).

Majority of the women in both the groups (79% in carbetocin group and 65% in oxytocin group) did not require additional uterotonics. However, 21% in carbetocin group and 35% in oxytocin group had requirement for additional uterotonics with significant difference (p value = 0.040). Also, only 9% in carbetocin group and 14% in oxytocin group had needed for blood transfusion which on comparison has no significant difference (p value = 0.376).

Side effects were seen in 22% and 26% of the women in both Carbetocin and Oxytocin group, respectively, with no significant difference (p-value = 0.619) (table 4).

In the present study, carbetocin IV bolus was demonstrated to be as effective as oxytocin IM in preventing postpartum hemorrhage after vaginal delivery. Therefore, carbetocin can be considered as an effective alternative uterotonic drug to oxytocin to prevent post partum hemorrhage following delivery.

Discussion

The third stage of labour is a period of great potential hazard because of many life threatening events that can occur without any predisposing factors and may results in mortality of parturient if not managed promptly. Both oxytocin and carbetocin acts by binding to oxytocin receptors present in the uterine myometrium resulting in rhythmic contractions of uterus.[11] Oxytocin when administered by IM route, responds within 3-5 minutes and the effect subsides within 2-3 hours approximately. It takes approximately 40 minutes to reach a steady-state concentration in the plasma following parenteral

administration.[12] Oxytocin has a half-life ranging from 1-6 minutes, requiring a continuous intravenous infusion.[12] Oxytocin is available as an aqueous solution in an ampoule and requires cold chain for storage and trained healthcare professionals for administration.

In contrary, the bioavailability of carbetocin is around 80%.[13] It has an elimination half-life of 40 minutes (4-10 times longer than oxytocin).[10] A single intravenous bolus of carbetocin produces uterine contraction within 2 minutes and it persists for 60 mins approximately.[14]

The mean blood loss in those women receiving carbetocin was lesser that those receiving oxytocin as an uterotonic drug to preserve the uterine tone during the active management of the third stage of labour. In the present study, the estimated mean blood loss was 405.1 ± 133.77 ml in carbetocin group and 420.5 ± 161.42 ml in oxytocin group which was similar to the study like Boucher M, et al.[15] Even the incidence of PPH was lesser in carbetocin group than that of the oxytocin group. Similar results in relation to incidence of PPH were also observed in the studies of Askar AA et al,[16] Amornpetchakul P et al[17] and Baruah HR et al.[18] The requirement for additional uterotonic drug and blood transfusion was also lesser in those women receiving carbetocin drug than those receiving oxytocin drug. Such results were also observed in other studies like Maged AM et al,[19] Kang S et al[20] and Boucher M et al.[15] Although, both carbetocin and oxytocin drugs were effective in preventing the uterine atony. Carbetocin was seen more effective in management of third stage of labour to prevent PPH. This effectiveness may be attributed to the heat stability of the carbetocin, as it is a heat stable drug lasting at 30ºC for 3 years, 40ºC for 6 months, 50ºC for 3 months and 60ºC for 1 month.[21]

The fall in mean hemoglobin following delivery of the baby was higher in those women receiving oxytocin than that of carbetocin during the active management of third stage of labour. Such similar results were seen in the other studies like Aksar AA et al[16] and Sotillo L et al.[22] More women in oxytocin group needed blood transfusion after delivery as compared to carbetocin group and similar results were seen in other studies like Jin XH et al[23] and Maged AM et al.[19]

Side effects such as nausea, vomiting, pyrexia, diarrhea and shivering were seen in both the groups with no statistically significant difference. They were promptly identified and treated during the postpartum period. The studies of Kansouh AM et al[24] and Nirmala K et al,[25] had shown similar adverse effect profiles in either group in their study with no significant differences.

In the present study, carbetocin IV bolus is demonstrated to be as effective as oxytocin IM in preventing postpartum hemorrhage after vaginal delivery. Therefore, carbetocin can be considered as an effective alternative uterotonic drug to oxytocin to prevent post partum hemorrhage following delivery.

Conclusion

Postpartum hemorrhage is an extremely challenging obstetric emergency associated with significant maternal morbidity and mortality. Early recognition and treatment are essential to ensure the best outcome from this life threatening condition. Although both the drugs, carbetocin and oxytocin, are effective in preserving uterine tone and preventing PPH, the carbetocin is found to be more efficacious over the oxytocin because of its safety and heat stability and does not require cold chain transport and storage. Therefore, carbetocin can be considered as an effective alternative uterotonic drug to oxytocin for prevention of post partum hemorrhage following vaginal delivery.

Conflict of interest: None. **Disclaimer:** Nil.

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