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RESEARCH ARTICLE

ROLE OF OXYTOCIN VERSUS CARBETOCIN IN ACTIVE MANAGEMENT OF THIRD STAGE OF LABOR

Dr. Simran Tyagi (JR3)[1], Dr. Shashi Bala Arya[2], Dr. Jyoti Baghel[3] and Dr. Shubhangi Gupta[4]

1. Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences Bareilly.
2. Professor and Head of Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences Bareilly.
3. Assistant Professor Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences Bareilly.
4. Assistant Professor Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences Bareilly.

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Abstract

Background and aims: Post partum haemmohrage is the most common cause of direct maternal death globally. Most of these deaths can be prevented by Active Management of Third Stage of Labour (AMTSL). This prophylactic use of uterotonic agents in the AMTSL aids in preventing life threatening haemorrhage. This study compares Oxytocin and its newer analogue Carbetocin in AMTSL in terms of blood loss, haemodynamic changes, side effects and need for use of additional uterotonics.

Methodology: A prospective observational study was conducted in the Department of Obstetrics and Gynecology, Shri Ram Murti Smarak Institue of Medical Sciences over a period of from 1st September ,2022 to 28th February 2024. Hundred patients undergoing vaginal delivery at term were randomized into two groups receiving either 10IU oxytocin or 100 µg carbetocin. Outcomes were measured such as haemoglobin, amount of blood loss, change in general condition and need for additional uterotonic agents/ any other measure to control PPH.

Results: In this study, massive blood loss did not occur in either groups. The incidence of atonic post-partum haemorrhage was 10% in oxytocin group while in the Carbetocin group, none had atonic PPH. Moreover, none of the women in carbetocin group had blood loss exceeding 500ml. Haemoglobin drop at 24 hours post delivery was observed more in oxytocin group. There was no difference in neonatal outcome in terms of NICU admission in both the groups.

Conclusion: Carbetocin is an effective and heat stable analogue that has potential to be used as first line drug in AMTSL.

Corresponding Author:- Dr. Simran Tyagi (JR3)
Address:- Department of Obstetrics and Gynaecology, Sri Ram Murti Smarak Institute of Medical Sciences Bareilly.

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Introduction:-

Postpartum haemorrhage is the loss of ≥500 ml blood following vaginal delivery and ≥1000 ml following cesarean section; from or into the genital tract after childbirth. Primary PPH occurs due to atonicity, genital tract injuries, retention of placental bits or blood clots and coagulation dysfunction. The volume of blood loss depends on how long it takes the placenta to separate from its bed and how effectively the uterine muscle (living ligatures) contracts in the immediate postpartum period. Principle of active management of third stage is to initiate potent uterine contractions within one minute of delivery of the baby by giving parenteral oxytocics. This prophylactic intervention minimizes blood loss in third stage by one-fifth and shortens the duration of third stage to half.

Oxytocin is a synthetic form of the natural nonapeptide. The plasma half-life of oxytocin is 3-4 minutes and duration of action is approximately 20 minutes, with a clinical response lasting about 2-3 hours. Oxytocin is not heat stable and loses its effectiveness unless preserved at 2˚ C - 8˚C, hence compromising its effectiveness in low-cost setups. Oxytocin leads to physiological uterine contraction.

Carbetocin is a long-acting heat stable stuructural analogue of oxytocin that can be administered as a single dose (100 µg) injection in the route of intravenous or intramuscular. The amino group (NH_2) in cysteine has been replaced with a hydrogen atom, the disulphide bond has been changed to a thio-ether bond (CH_2S) and the hydroxyl group (OH) of tyrosine has been substituted by methyl ether group. These modifications in the original molecule of oxytocin make it resistant to enzymatic degradation by amino peptidase extending its pharmacological action. Intramuscular injection produces tetanic contractions within two minutes, lasting about 11 minutes, and followed by rhythmic contraction for an additional two hours.

With the availability of spectrum of uterotonic drugs it is important to delineate the use and side effects to establish better protocols for PPH management to reduce maternal mortality and morbidity associated with it. This study compares the efficacy of Oxytocin and Carbetocin in preventing overt blood loss in third stage and subsequently PPH.

Material and Methods:-

This is a prospective observational study conducted in Department of Obstetrics and Gynaecology Shri Ram Murti Smarak Institue of Medical Sciences, Bareilly (1st September, 2022 to 28th February 2024) which is a tertiary care teaching cum referral centre, after the institute ethical committee clearance. A total of 100 patients meeting the inclusion and exclusion criteria were divided into two groups, each group consisted of 50 subjects based on computer generated randomization software(Randomizer- Random number generator).

The study included all term, singleton pregnant women admitted for vaginal delivery in labor room of our centre. Women refusing consent, patients with antenatal complications like severe anemia, multifetal pregnancy, polyhydromnios, hypertenisive disorders of pregnancy , medical disorders as severe heart disease, liver disease, renal disorders, history of any coagulation disorder or history of use of any anti-coagulant medication and who delivered by cesarean section were excluded.

Methodology:-

After obtaining written informed consent, detailed medical and obstetrical history was taken. A through general and systemic physical examination was done and recorded . Complete blood counts including hemoglobin, total leukocyte count, differential leucocyte count, and platelet count, blood group and Rh-type were sent to record baseline haemoglobin and to rule out thrombocytopenia. Progress of labor was monitored and fetal heart rate, color of liquor, cervical dilatation, descent of head, frequency and strength of uterine contractions, maternal vitals were observed and charted in partograph and pre-designed proforma. In third stage of labor V-Drape was placed under patients buttocks. Both groups were given uterotonic agent following delivery of fetus for Active Management of Third Stage of Labor . Group A received 10IU of oxytocin intra-muscular and group B received 100 microgram of carbetocin intra-muscular following delivery of fetus.

Following expulsion of placenta, placenta was examined for completeness and local examination of genital tract done to rule out any laceration or trauma. Patient was monitored uptill 30 minutes; any post partum hemorrhage, retained placenta, cervical and genital tract trauma, use of additional uterotonic drugs like prostaglandins, methergin

was managed according to standard protocol of labor room. Patient vitals , uterine tone, and amount of bleeding (volume of blood in V-Drape) was documented. Following first 30 minutes, patient was monitored at first hour, second hour, sixth hour, 12th hour and 24th hour of delivery. To observe the amount of bleeding patient was asked to preserve all pads used in first 24 hours. Haemoglobin was repeated after 24 hrs.

Primary outcome was measured on the basis of amount of blood loss, need for additional uterotonic agents, other measure taken to control PPH, change in general condition, fall in hemoglobin levels and need for blood transfusions . Secondary outcome was based on side effects observed.

Results:-

Table 1:- Distribution of cases according to blood loss in 3rd stage of labour.1

Blood loss	**Carbetocin**		**Oxytocin**	
	N	**%**	**N**	**%**
≤500ml	50	100.0%	43	86.0%
>500ml	0	.0%	7	14.0%
Total	50	100.0%	50	100.0%

Table 2:- Distribution of cases according to use of additional uterotonics in both the groups.

Additional uterotonic	**Groups**						**p value**
	Carbetocin		**Oxytocin**		**Total**		
	N=50	**%**	**N=50**	**%**	**N**	**%**	
No	50	0%	28	56.0%	78	78.0%	<0.001
Yes	0	0%	22	44.0%	22	22.0%	

Table 3:- Comparison of hemoglobin between carbetocin and oxytocin groups at different time points.

Hemoglobin (mg/dL)	**Groups**						**p-value**
	Carbetocin		**Oxytocin**		**Total**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Before delivery	9.94	1.76	10.54	1.39	10.24	1.60	0.062
At 24 hour (after delivery)	8.77	1.56	9.20	1.46	8.99	1.52	0.162

Table 4:- Distribution of cases according to need for blood transfusion in both groups.

Need for blood transfusion	**Carbetocin**		**Oxytocin**	
	N	**%**	**N**	**%**
No Blood Transfusion required	50	100.0%	47	94.0%
Blood Transfusion required	0	0.0%	3	6.0%
Total	50	100.0%	50	100.0%

Graph 1:- Chart showing **c**omparison of hemoglobin between carbetocin and oxytocin groups at different time points.

Discussion:-

A total of 100 nulliparaous women within age group of 18 to 35 years with mean age of 26.43±4.13 years were enrolled. In the Carbetocin group, mean age is 26.62 years (SD=4.63), slightly higher than the Oxytocin group's mean age of 26.24 years (SD=3.61).The present study had a relatively older age profile of women with mean age 26.43 years compared to the study done by Ashraf et al. in which the mean age of women was 23.9 ± 3.2 in carbetocin versus 23.3 ± 3.2 in oxytocin group.[2] Widmer M et al. conducted a similar study in which the mean age was higher in both the groups when compared to our study.[3] In carbetocin group mean age was 33.8±4.7 years while in oxytocin group it was noted to be 33.5 ±4.7 years.

Among participants administered Carbetocin, none of the subjects had blood loss >500ml which is the cut off for PPH in this study. On the contrary, we observed 7 women who were administered 10 IU of intramuscular oxytocin had blood >500ml collected in V-Drape (Table 1).These patients were managed with additional uterotonics and

uterine massage. None of the patients had traumatic PPH. None of the recruited patients had massive PPH. The comparison of collection in the V drape showed no statistically significant difference, with a p-value of 0.215 between both groups. In the Carbetocin group, the mean collection was 325.00 ± 84.67ml whereas in the Oxytocin group, it was slightly higher at 352.60 ±131.36ml. Cetin C et al. perfomed a similar study in 300 patients and reported, in the Carbetocin group, the mean collection was 277.19±208.10 ml whereas in the Oxytocin group, it was slightly higher at 294.13±198.64ml however, this study demonstrated a loss of >500ml of blood in both the groups[4] in contrary to our observations. Ahmed Mohamed et al. in a study population of 200 showed the occurrence of PPH were 4% in carbetocin group versus 16% in oxytocin group , with a mean blood loss of 337.73 ± 118.77ml in carbetocin recipients versus 378 ± 143.2ml in oxytocin recipients, which was found to be statistically significant.[5]

In this study, In the Carbetocin group, no additional uterotonic interventions were needed. However, in the Oxytocin group, additional uterotonic interventions were recorded 22 patients (44%). This was found to be statistically significant with a p-value of<0.001.(Table 2) Single dose of carbetocin provided better uterine tone when compared to intramuscular 10 IU of oxytocin which explains the over-enthusiastic use of oxytocics.

In a similar study conducted by Patil et al. 8% patients in carbetocin group required additional uterotonic agents, whereas in the oxytocin group, 15% of patients needed such supplementation.[7] Attilakos et al. too demonstrated that more women needed additional oxytocics in the oxytocin group (45.5%) when compared to women in carbetocin group(33.5%) in non-complicated cesarean deliveries.[8]

We further evaluated the clinical parameters of both the groups in respect to pulse rate, blood pressure, respiratory rate and temperature. In our study, at baseline, the mean pulse rate was slightly lower in the Carbetocin group i.e. 82.16 ± 6.56 beats per minute compared to the Oxytocin group which was 84.72 ± 6.24 beats per minute. At 1 hour, and 24 hours post-administration, the mean pulse rates were consistently higher in the Oxytocin group compared to the Carbetocin group, with significant differences observed at first hour (Carbetocin: 86.12 ± 5.35 beats per minute, Oxytocin: 89.92 ± 4.22 beats per minute, $p < 0.001$) and 24 hours (Carbetocin: 81.68 ± 3.64 beats per minute, Oxytocin: 85.20 ± 3.90 beats per minute, $p < 0.001$).

Tachycardia and hypotension are reported side effects of both the drugs. In our study tachycardia was recorded in both the groups at first hour and 24 hours but was more in oxytocin recipients. This can be due to slightly more blood loss due to atonicity in oxytocin group versus carbetocin recipients.

Hypotension is a major and most commonly reported side effect of carbetocin therefore meticulous BP monitoring is recommended. In the Carbetocin group, significant decrease in systolic blood pressure (SBP) were observed from baseline to 30 minutes, first hour, and 24 hours, with mean differences of 6.56 mm Hg, 3.60 mm Hg, and 2.32 mm Hg, respectively ($p < 0.001$ for all). These findings suggest an initial rise in SBP at baseline, followed by a gradual decline in carbetocin group.

Conversely, in the Oxytocin group, SBP displayed a distinct trajectory, with significant decrease observed from baseline to 30 minutes, first hour and 24 hours, featuring mean differences of 2.64 mm Hg, 2.72 mm Hg and 1.56 mm Hg, respectively ($p = 0.003$, 0.001 and 0.020). Notably, at later intervals, no significant changes were observed within the Oxytocin group.

Comparison of diastolic blood pressure (DBP) between the Carbetocin and Oxytocin groups revealed no significant difference at baseline (Carbetocin: 75.80 ± 5.75 mm Hg, Oxytocin: 77.00 ± 6.14 mm Hg, $p = 0.316$). Similarly, at 30 minutes, first hour, and 24 hours post-administration, no significant differences in DBP were observed between the two groups ($p > 0.05$ for all time points). Moertl J et al. studied the haemodynamic effects of carbetocin and oxytocin and found out pulse rate increased 17.98 ± 2.53 bpm for oxytocin and 14.20 ± 2.45 bpm for carbetocin which is consistent with our findings. Systolic blood pressure (SBP) decreased by 26.80 ± 2.82 mmHg in oxytocin group versus 22.98 ± 2.75 mmHg in carbetocin group. [9] Rabow S,et al. studied cardiovascular effects of both the drugs and found out that both carbetocin and oxytocin have equal hypotensive and tachycardic effects.[10] Although significant the mentioned studies were conducted in patients undergoing caesarean section where the patients were monitored in controlled fashion which is different from our study.

In our study, the statistics reveal changes in Hemoglobin levels in both the Carbetocin and Oxytocin groups over 24 hours. In the Carbetocin group, the mean Hemoglobin drop was 1.2 gm/dl from baseline at 24 hours. Similarly, in

the Oxytocin group, there the mean Hemoglobin drop was observed to be 1.3gm/dl at 24 hours which was not statistically significant. (Table 3,Graph 1).Cetin C et al. in their study demonstrated demonstrated fall in haemoglobin levels from baseline in their study groups. However fall in oxytocin group (1.3±0.85gm/dl) was higher when compared to carbetocin group(1.03±1.04gm/dl). [4] In concordance to our study, A.M.Maged et al. reported hemoglobin 24 h after delivery to be higher in carbetocin group however, there was no significant difference between the two study groups regarding occurrence of major PPH.[5]

Despite fall in haemogloin levels in both study groups, in our study, Carbetocin recipients (100%) did not require blood transfusion, while in the Oxytocin group 3 (6%) patients had haemoglobin levels <7gm/dl(severe anemia) twenty-four hours after delivery and needed blood transfusion but refused. A similar study by Ashraf,et al. reported that five patients (10.6%) in oxytocin group underwent blood transfusions however no patient in carbetocin group required blood transfusion after delivery which is consistent with our study.[2] In contrary to our observations, Ahmed Mohamed et al. reported fall in haemoglobin levels and blood transfusions more in carbetocin group.[5] In their study 9 (1.4%) patients in carbetocin group were transfused blood versus 2(0.3%) patients in oxytocin group.

Neonatal outcome was observed in terms of baby weight, APGAR score, birth injuries and NICU admission. Only one neonate of carbetocin group was admitted in NICU in view of respiratory distress.

Conclusion and Recommendation:-

The present study investigates carbetocin as a potential altenative to oxytocin in active management of third stage of labour. Oxytocin and carbetocin had similar outcomes in terms of blood loss in women aged between 18-35yrs of age with varying gravidity and parity; however carbetocin helped in achieving better uterine tone with single injection. Injudicious use of oxytocics is more in oxytocin group. Side effects are similar in both the drugs. Moreover carbetocin is an effective and heat stable analogue that has potential to be used as first line drug in AMTSL. The outcome of the present study may recommend carbetocin to be included as a safe option for the prevention and treatment of PPH. However further studies on larger sample size with inclusion of a diversified profile of pregnant women is required to make any recommendation.

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