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A Comparative Randomised Controlled Trial In The Use Of Intra Muscular Carbetocin Vs Intra Muscular Oxytocin In The Prevention Of Postpartum Haemorrhage During Cesarean Section And Blood Loss Estimation

Dr. G. Prema Priya[1], Dr. Karunyaa . M S[2], Dr. Ankitha Srinivas[*3]

[1]Professor and Unit Chief, Department of Obstetrics and Gynaecology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Vinayaka Mission's Research Foundation(DU), Salem

[2]Postgraduate, Department of Obstetrics and Gynaecology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Vinayaka Mission's Research Foundation(DU), Salem.

[3]Postgraduate, Department of Obstetrics and Gynaecology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospitals, Vinayaka Mission's Research Foundation(DU), Salem.

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ABSTRACT

Introduction:

Globally, postpartum hemorrhage (PPH) is a significant factor in maternal mortality and morbidity. It has been demonstrated that actively managing the third stage of labor can effectively prevent PPH. A long-acting oxytocin agonist called carbetocin seems to be a promising treatment for PPH.

AIMS AND OBJECTIVES:

To evaluate the efficacy and safety of intramuscular carbetocin in comparison to oxytocin for prevention of postpartum hemorrhage in women undergoing cesarean delivery.

Materials and Methods:

100 women with singleton pregnancies without any ante-natal complications in the age group 18 to 40years presenting at 34-42 weeks of gestation, consented to participate in this study and were followed up till delivery. Patients and their relatives were explained on the nature of study procedure, benefits and side effects. Written informed consent obtained from patients who were willing to participate in the trial in the prescribed format in the regional language (Tamil) prior to any procedure being performed related to the study. The demographic details of the patients were collected. History recorded from patients, particularly menstrual, marital and obstetric history. Vitals were recorded, General, Systemic, obstetric and vaginal examination were done. Fetal heart rate monitored regularly. Laboratory investigations performed. Patients who fulfil the inclusion and exclusion criteria were enrolled and randomized by simple randomisation to either
test group(carbetocin) or control group(oxytocin). Blood loss was estimated by various methods.

Results:

96% of cases in carbetocin group had blood loss associated with 100-150ml and 96% of cases in oxytocin group had blood loss between 150-200ml.
2% of cases in oxytocin group and none in carbetocin group had blood transfusion which is not statistically significant (p=0.082)
Similarly in both study groups HB levels before and after 2hr and 24hr apart from delivery were similar confirming no significant difference in blood loss level although we found a tendentially lower Hb decrease at 12h from delivery in carbetocin group.
None from carbetocin group vS 6% (3) from oxytocin group needed additional uetrotonics. Hence significantly more women required additional uterotonic agents in oxytocin group (p<0.01).
Difference between mean blood loss between 2 groups was 51ml, statistically significant. (p=0.020)
Conclusion:

We propose that visual estimation of postpartum blood loss be withdrawn from standard obstetric practice and replaced with a more appropriate method, such as objective measurement using a sterile under-buttock drape.
We conclude that a single intra muscular injection of carbetocin appears to be more effective than intramuscular injecton of oxytocin to maintain adequate uterine tone, with a similar safety profile and minor antidiuretic effect.
Keywords: carbetocin, oxytocin, postpartum haemorrhage

A COMPARATIVE RANDOMISED CONTROLLED TRIAL IN THE USE OF INTRA MUSCULAR CARBETOCIN VS INTRA MUSCULAR OXYTOCIN IN THE PREVENTION OF POSTPARTUM HAEMORRHAGE DURING CESAREAN SECTION AND BLOOD LOSS ESTIMATION

INTRODUCTION

Postpartum hemorrhage is any amount of bleeding into or from the vaginal tract after delivery up until the end of the puerperium that has a negative impact on the patient's overall health as seen by a spike in heart rate and a drop in blood pressure(1). Average blood loss in vaginal delivery is 500mL and in cesarean delivery, it is around 1000mL. Depending on the amount of blood loss, it is broadly classified as minor (<1L), major (>1L) and severe (>2L) (2). Types of postpartum haemorrhage are primary haemorrhage which occurs within 24hours following the birth of the baby and secondary haemorrhage which occurs beyond 24hours of delivery and within puerperium.(3)
The posterior pituitary releases oxytocin, a peptide hormone and neuropeptide that is ordinarily synthesized in the hypothalamus.
It is released into the bloodstream as a hormone in response to sexual activity and during labour.

It stimulates uterine contractions to speed up the process of childbirth.(4)

Carbetocin is a long acting synthetic oxytocin agonist. It functions as an agonist at peripheral oxytocin receptors, particularly in the myometrium, with lesser affinity for myoepithelial cells. It is heat tolerant

unlike oxytocin which makes it an advantage for carbetocin use(5).

Oxytocin, which has a short half-life and duration of action, is the current standard therapy for the prevention of postpartum haemorrhage. However, as it is susceptible to heat, its efficacy cannot be assured in many developing countries. Carbetocin has been widely used in preventing postpartum haemorrhage since 1997, and has been shown to maintain active for more than 36 months at 30 °C and 75% relative humidity. (6)

METHODOLOGY

STUDY PERIOD: AUGUST 2022- AUGUST 2023

STUDY DESIGN: comparative randomised controlled trial IEC
NO: VMKVMC&H/IEC/22/142

STUDY POPULATION: Pregnant women with singleton pregnancies in age group of 18-40 years presenting at 34- 42 weeks gestation attending Outpatient Department of Obstetrics and Gynaecology and getting admitted at Vinayaka Mission's Kirupananda Variyar Medical College Hospital, Salem.

Randomized controlled trials with outcome measure of blood loss ≥500 ml were eligible if they compared carbetocin with oxytocin to prevent postpartum hemorrhage in women undergoing caesarean delivery.

SAMPLE SIZE: 100 cases.

Inclusion Criteria

Pregnant women with singleton pregnancies in age group of 18-40 years presenting at 34-42 weeks gestation attending Outpatient Department of Obstetrics and Gynaecology and getting admitted at Vinayaka Mission's Kirupananda Variyar Medical College Hospital, Salem.

Women giving consent for participating in the study, with two or more previous caesarean section, presence of uterine fibroids, previous myomectomy, *placenta previa*, past history of PPH, fetal macrosomia and fetal malformations associated with polyhydramnios.

Exclusion Criteria

1. Women not willing to participate in the study
2. Women with multiple pregnancies.
3. Women delivering by vaginal delivery.
4. Women with history of pre-existing medical conditions (hypertension, diabetes, congenital heart diseases, renal or liver disease, thyroid, bronchial asthma, epilepsy)
5. Women below 18years and above 40years.
6. women with hypersensitivity to carbetocin.

METHODOLOGY

It is a hospital based study which included patients from the department of Obstetrics and Gynaecology, Vinayaka Mission's Kirupananda Variyar medical College Hospital,100 women with singleton

pregnancies without any ante-natal complications in the age group 18 to 40years presenting at 34-42 weeks of gestation, consented to participate in this study and were followed up till delivery.

Patients and their relatives were explained on the nature of study procedure, benefits and side effects. Written informed consent obtained from patients who were willing to participate in the trial in the prescribed format in the regional language (Tamil) prior to any procedure being performed related to the study. In patients who were illiterate, left thumb impression was obtained

after explaining the study in detail with the birth companion nearby who serve as an impartial witness. The demographic details of the patients were collected. History recorded from patients, particularly menstrual, marital and obstetric history. Vitals were recorded, General, Systemic, obstetric and vaginal examination were done. Fetal heart rate monitored regularly. Laboratory investigations performed. Patients who fulfil the inclusion and exclusion criteria were enrolled and randomized by simple randomisation to either test group(carbetocin) or control group(oxytocin).

Vitals recorded

Height Weight
Body mass index Pulse rate
Blood Pressure
Respiratory rate
Axillary Temperature

Investigations done during antenatal visits

- Urine pregnancy test
- Ultrasound obstetrics
- Complete Hemogram
- Urine Routine
- Blood grouping and typing
- Fasting and Postprandial blood sugar
- VDRL
- HIV-ELISA
- HBsAg
- Liver Function Test
- Renal Function Test

Investigations done on the day of delivery

- Complete Hemogram
- Urine Routine
- Random Blood Sugar

Investigations done 24hours after delivery

- Complete hemogram

METHODS OF BLOOD LOSS ESTIMATION

1. Visual estimation of blood loss with uncalibrated drapes
2. Quantitative measurement of blood loss by gravimetric measurement
3. Haematocrit values before and after caesarean section
4. Blood Loss in Relation to 3rd Stage Complications
5. Additional Oxytocics Used in Third Stage of Labor
6. Need for Blood Transfusion.

Blood soaked materials were weighed, dry weight was subtracted and the net blood loss volume was obtained. Measurement of blood loss began when the amniotic membranes ruptured or after the infant was born. All the fluids in the suction canister before delivery of placenta were quantified. After delivery of the placenta all fluids in the suction canister and the drapes was measured. All blood soaked materials and clots were weighed. The amount of blood on the floor, clothes, and delivery table was roughly measured. At the end of the surgery all these were totalled up to get the complete blood loss estimation.

Soaked mop pads and gauze pieces were quantitated. A calibrated suction canister was used during cesarean birth. The volume of fluid collected before delivery of the placenta was largely composed of amniotic fluid and was subtracted from the total volume of fluid collected after completion of birth to determine the volume of blood lost during birth. Additionally, the amount of any fluid used for irrigation is subtracted from this volume. Finally, at the end of 1hour total cumulative blood loss in milliliters is determined by adding the weight in grams of blood-soaked materials (eg, sponges, bedsheets, underpads) minus the dry weight of those materials.

The ongoing blood loss assessment should continue as long as active bleeding is present, or as long as the patient is unstable after a blood loss of more than 1,000 mL, including the postpartum care setting.

ASSESSMENT :

a. Efficacy parameters

b. Safety parameters

a. Efficacy parameters:-

Parameters evaluated soon after delivery

1. Volume of blood loss: Volume of blood collected in the blood collecting drape was measured against the calibrated markings in the drape for each group. Data compared and analysed between each group. The drape was disposed as per biomedical waste management.
2. Need for additional uterotonic agents: In both groups apart from allotted uterotonic drugs, data on need for additional uterotonic agent was noted.
3. Number of units of blood transfused: Need for blood transfusions and the number of units of blood transfused despite the use of additional uterotonic agents in both groups were recorded.

Parameters measured 24 hours after delivery

1. Comparison of Haemoglobin: Haemoglobin as gram percent was measured by standard automated flow cytometer before surgery and compared with values measured 24 hours post- delivery evaluated by the same flow cytometer method. Haemoglobin percent drop between these two values were statistically compared between the two groups.
2. Comparison of Haematocrit value: Haematocrit as percentage is measured by standard automated flow cytometer before surgery and compared with that of 24 hours post-delivery evaluated by the same flow cytometer method. Haematocrit percentage drop between these two values were statistically compared between both the study groups.

b. Safety parameters:-

Carbetocin is known to cause nausea, vomiting, headache and flushing as side effects

1. Number of patients developing nausea and vomiting: Subjects who developed postpartum nausea and vomiting in both groups after intervention were assessed
2. Number of patients developing headache and flushing: Subjects who developed headache and flushing post-delivery were assessed.

Adverse events: Any other adverse events reported by the patient or observed by the obstetrician during the study were recorded. The time of onset of the adverse events, causal relationship to the study drug and action taken was recorded. Appropriate medical care was provided.

Withdrawal: At the decision of the investigator, the subjects were withdrawn from the study if any adverse event was observed or reported by the patients. During the study period, the subject was also allowed to withdraw her voluntary consent and opt out of study.

RESULTS

The data obtained was manually entered into Microsoft Excel, coded, and recoded. Analysis was done using Statistical Package for the Social Sciences (SPSS) v23. Hence the data of 100 patients, 50 patients in control group(oxytocin) and 50 patients in test group(carbetocin) who completed the study were analysed.

- Mean age distribution, mean body weight, mean birth weight of delivered babies of all participants in both groups were analysed by Student independent t test.
- Volume of blood loss between both control and test groups analysed by independent 2 sample t test and within the sub groups compared by trend chi square test.
- Need of blood transfusions was analyzed by chi square test.
- Comparison of haemoglobin percentage and haematocrit before and after delivery in both control and test groups were analyzed by paired t test.
- Incidence of adverse events were analyzed by paired t test.

Probability of <0.05 considered as statistically significant P< 0.01
considered as highly significant
P<0.001 considered as very highly significant.

TABLE 1-Distribution of Age among study population

Group	No. of Patients	Mean age (in years)	Standard Deviation	P value
Oxytocin group	50	22.5	4.1	0.7
Carbetocin group	50	22.9	3.8	

Mean age in oxytocin group was 22.5 years and mean age in carbetocin group was 22.9 years. There was no significant statistical difference between control and study groups. Using student independent t-test p value is found to be 0.7.

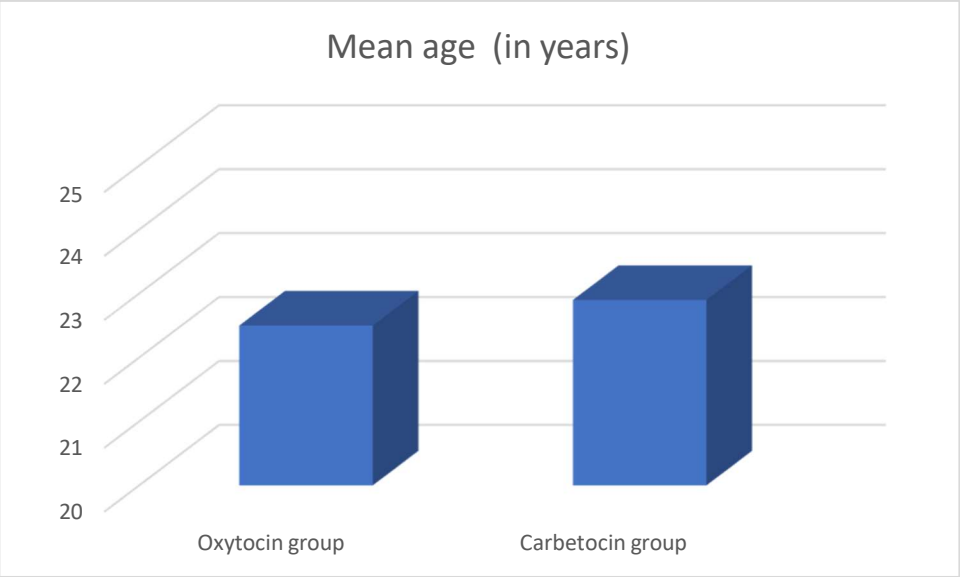


Figure 1-Distribution of Age among study population

Table 2- Distribution of Mean Body Weight among study population

Group	No. of Patients	Mean weight (in kgs)	Standard Deviation	P value
Carbetocin group	50	69	12.2	0.07
oxytocin group	50	65.5	12	

Mean body weight in oxytocin group was 65.5kg and in carbetocin group was 69 kg. Mean body weight in carbetocin group was 3.5kg higher than oxytocin group. Intergroup analysis showed p value of 0.07 using student independent t-test illustrating there is no statistically significant difference in both groups.

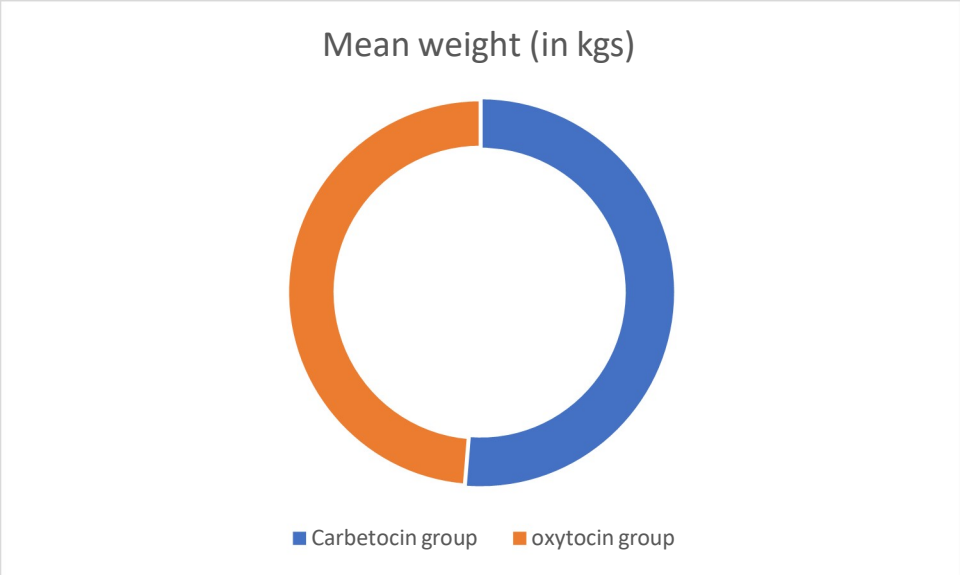


Figure 2- Distribution of Mean Body Weight among study population

Table 3-Distribution Of Mean Birth Weight Among Delivered Babies

Group	No. of Patients	Mean weight (in kgs)	Standard Deviation	P value
Carbetocin group	50	2.78	0.43	0.48
oxytocin group	50	2.82	0.43	

In Oxytocin group mean birth weight was 2.82kgs and mean birth weight in carbetocin group was 2.78kgs. Intergroup analysis show p value of 0.48 by using student independent t-test which illustrates no statistical difference in between both groups.

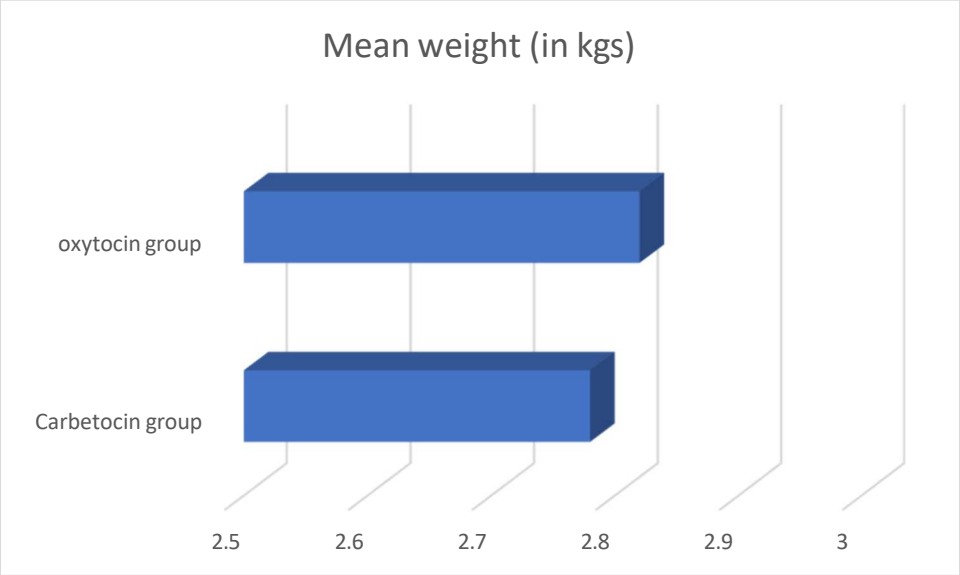


Figure 3-Distribution Of Mean Birth Weight Among Delivered Babies

Table 4-Distribution of Contraceptive History

Usage of contraceptive	Used	Not used	P value
Carbetocin group	9	41	0.69
oxytocin group	10	40	

Table 4 shows contraceptive usage in both the study groups which were comparable with p value of 0.69 which illustrates statistically no significant difference in between oxytocin and carbetocin groups.

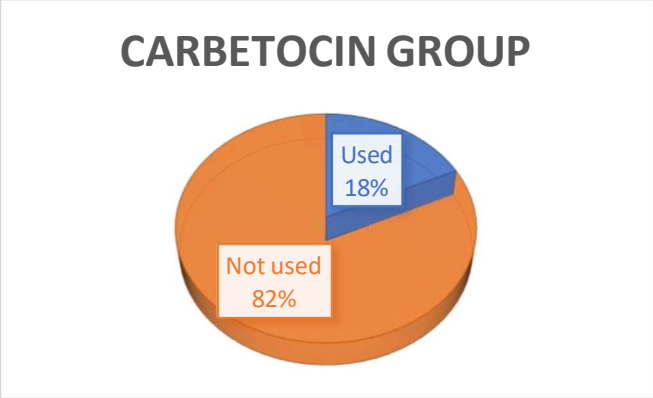


Figure 4-Distribution of Contraceptive History in Carbetocin Group

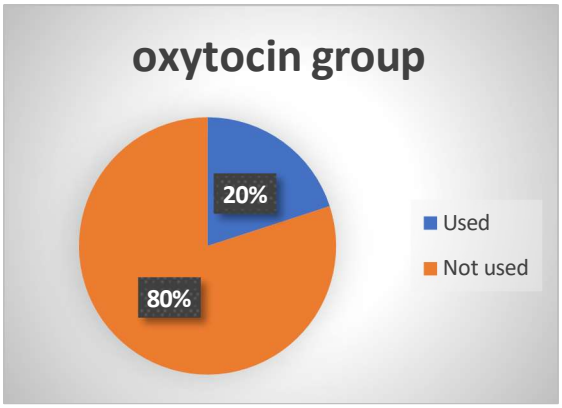


Figure 5-Distribution of Contraceptive History in Oxytocin Group Table 5-Distribution of Obstetric score among the study population

Parity	Carbetocin	Oxytocin	P value
Primigravida	24	23	0.198
Multigravida	26	27	

Table 5 shows parity comparison between control and study groups expressed in %. Number of primipara and multipara in oxytocin group was 23(46%) and 27(54%) respectively whereas number of primipara and multipara in carbetocin group was 24(48%) and 26(42%) respectively. Intergroup analysis showed p value of 0.198 using chi square test of independence which illustrates no significant statistical difference between both groups and are comparable.

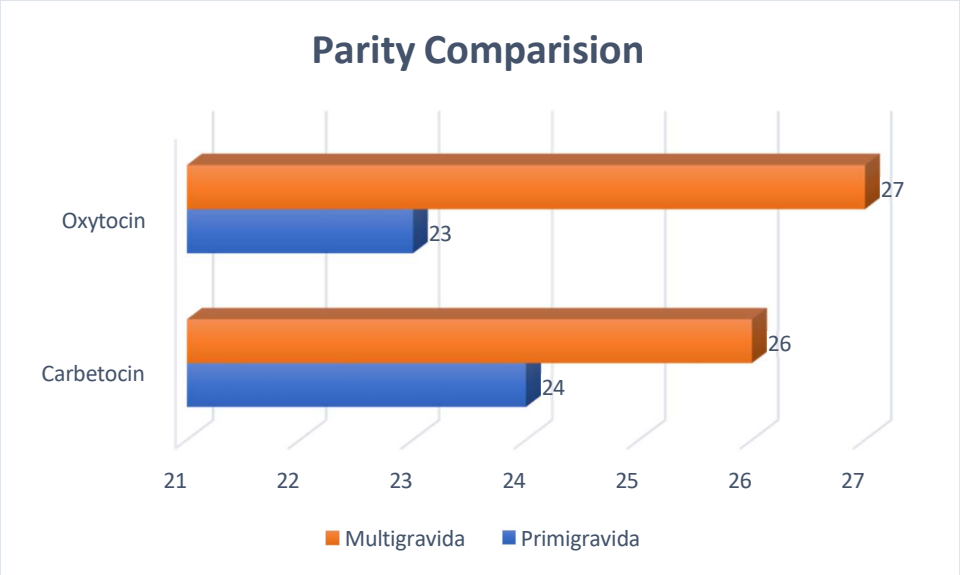


Figure 6- Distribution of Obstetric score among the study population

Table 6 - Distribution of Blood Loss among the study population

	CARBETOCIN		OXYTOCIN		TOTAL
	FREQUENCY	PERCENTAGE	FREQUENCY	PERCENTAGE	
<100ml	1	2	0	0	1
100-150ml	48	96	1	2	49
150-200ml	1	2	48	96	49
>200ml	0	0	1	2	1
TOTAL	50	100	50	100	100

96% of cases in carbetocin group had blood loss associated with 100-150ml and 96% of cases in oxytocin group had blood loss between 150-200ml.

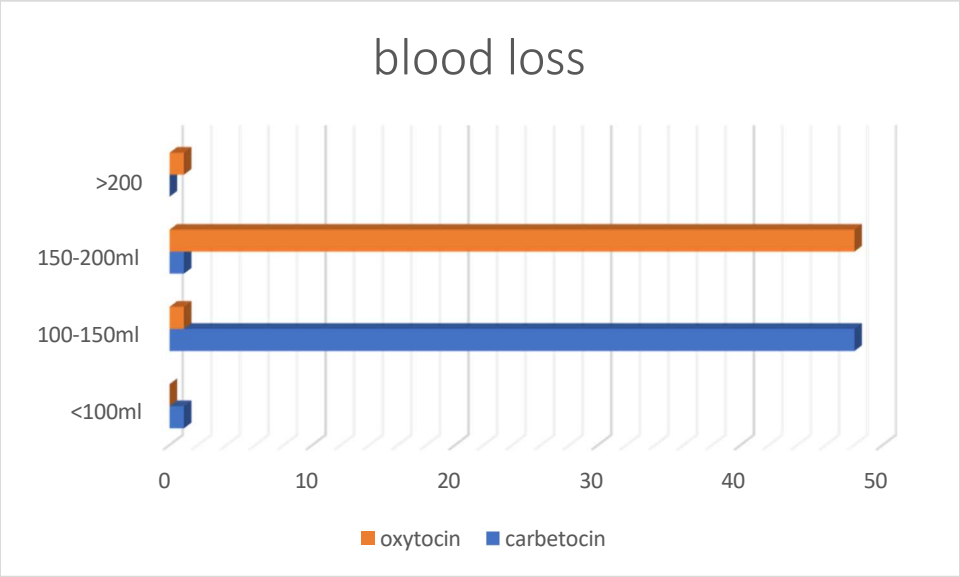
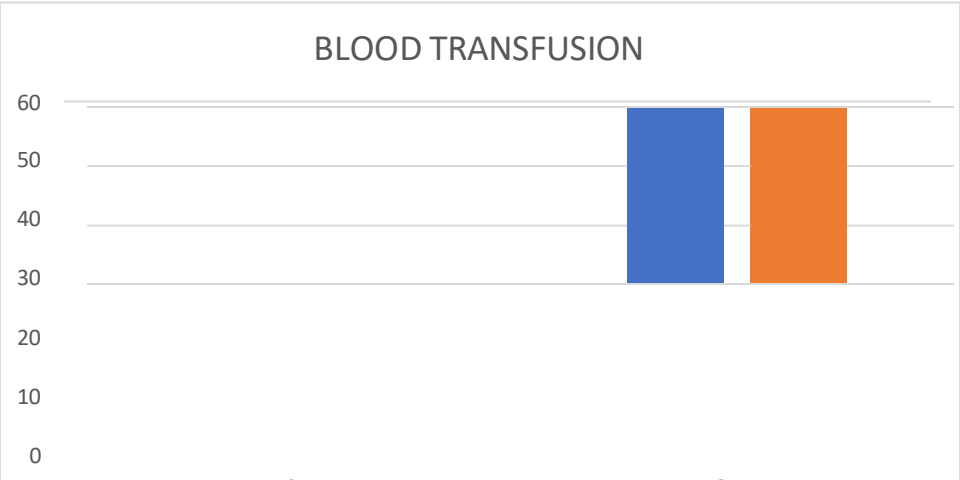


Figure 7 - Distribution of Blood Loss among the study population

Table 7 - Distribution of blood transfusion among the study population

BLOOD TRANSFUSION	CARBETOCIN		OXYTOCIN	
	FREQUENCY	PERCENTAGE%	FREQUENCY	PERCENTAGE%
YES	0	0	1	2
NO	50	100	49	98

2% of cases in oxytocin group and none in carbetocin group had blood transfusion which is not statistically significant (p=0.082)



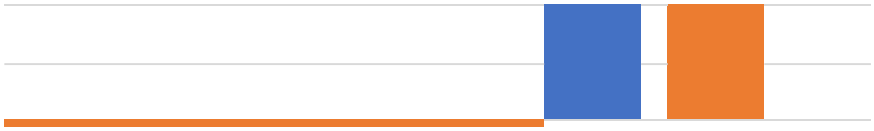


Figure 8 - Distribution of blood transfusion among the study population

Table 8 – Distribution of Maternal blood loss during different time periods among study population

	carbetocin		oxytocin		P value
During cs	frequency	percentage	frequency	percentage	
<500ml	38	76	34	68	0.18
500-1000ml	12	24	14	28	
>1000ml	0	0	2	4	
2hr after cs					
<500ml	49	98	49	98	1
500-1000ml	1	2	1	2	
>1000ml	0	0	0	0	
12hr after cs					
<500ml	50	100	50	100	1
500-1000ml	0	0	0	0	
>1000ml	0	0	0	0	
24h after cs					
<500	50	100	50	100	1

500-1000ml	0	0	0	0	
>1000ml	0	0	0	0	

Similarly in both study groups Hb levels before and after 2hr and 24hr apart from delivery were similar confirming no significant difference in blood loss level although we found a tendentially lower Hb decrease at 12h from delivery in carbetocin group.

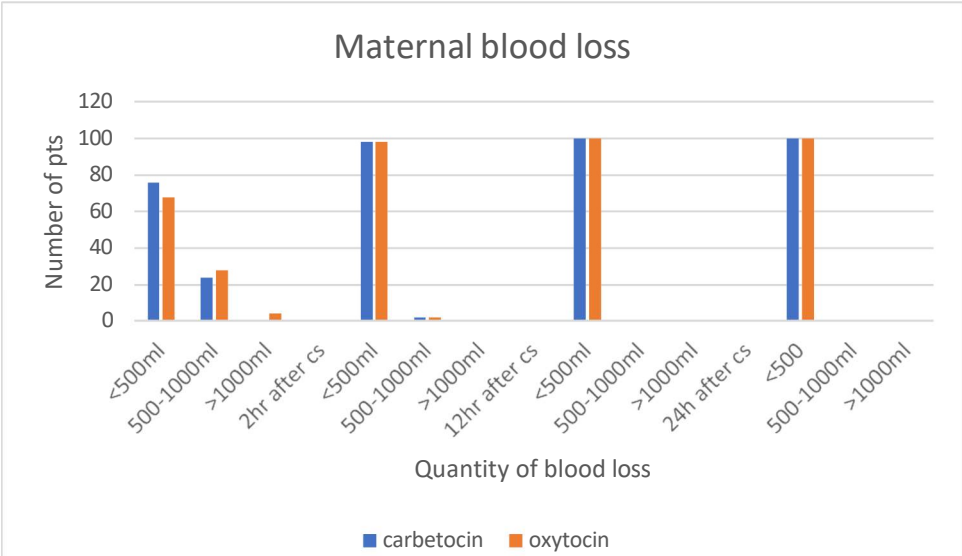


Figure 9 – Distribution of Maternal blood loss during different time periods among study population

Table 9 - Distribution of pre op blood counts among the study population

Pre op values	CARBETOCIN	OXYTOCIN	P VALUE
Hb	11.4	11.8	0.33
HCT	34.6	34	0.80

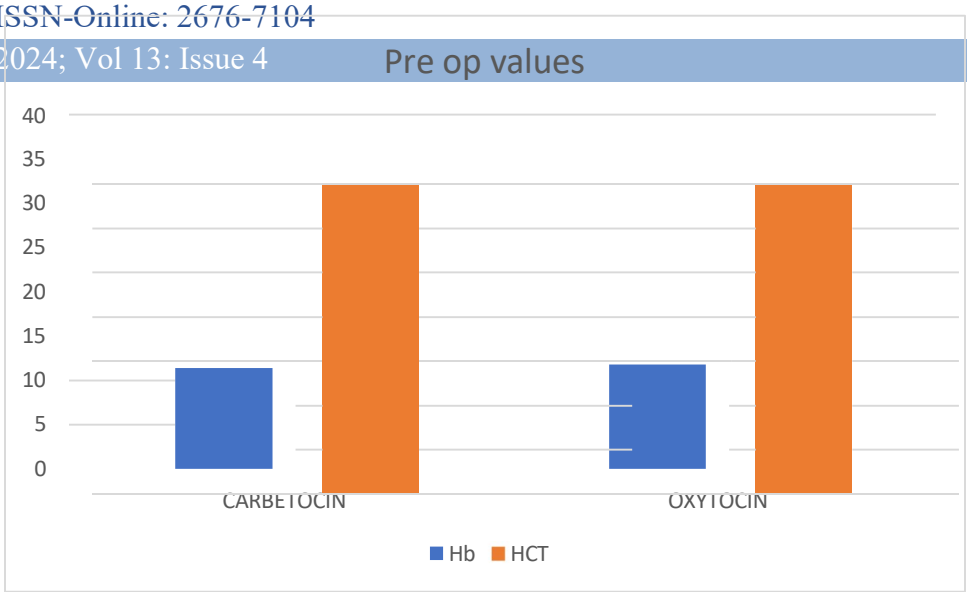


Figure 10 - Distribution of pre op blood counts among the study population

Table 10- Distribution of post op drop in Hb values among the study population

Post op Hb drop	Carbetocin	Oxytocin	P value
2h after cs	-0.6	-0.7	0.463
12h after cs	-0.7	-1.1	0.074

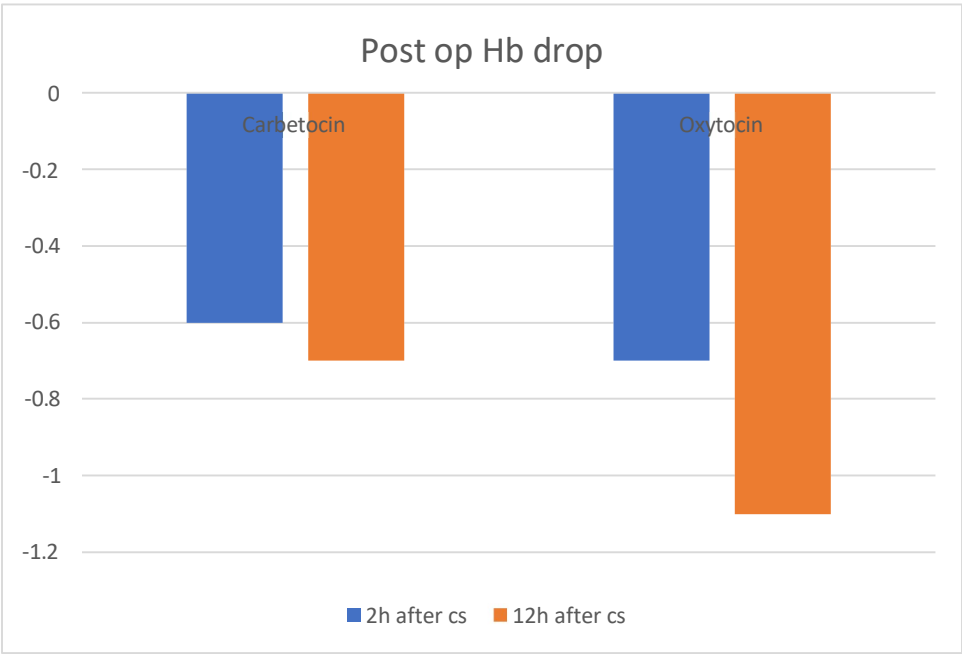


Figure 11- Distribution of post op drop in Hb values among the study population

Table 11- Distribution of post op drop in HCT values among the study population

Post op HCT drop	Carbetocin	Oxytocin	P value
2h after cs	-1.4	-1.8	0.074
12h after cs	-1.4	-1.9	0.205

None from carbetocin group vS 6% (3) from oxytocin group needed additional uetrotonics. Hence significantly more women required additional uterotonic agents in oxytocin group ($p<0.01$).

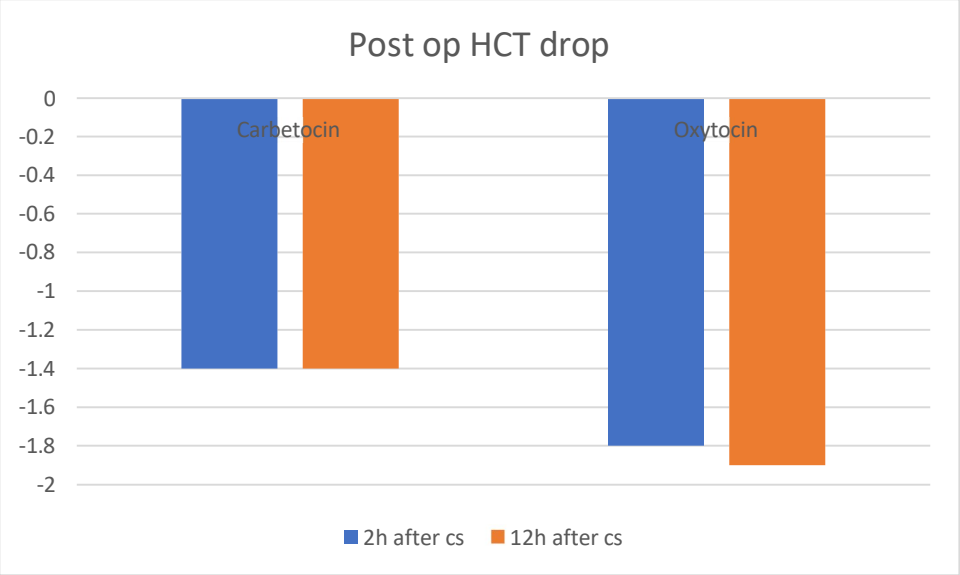


Figure 12- Distribution of post op drop in HCT values among the study population

Table 12- Distribution of mean blood loss among the study population

	MEAN BLOOD LOSS
CARBETOCIN	120ML
OXYTOCIN	171ML

Difference between mean blood loss between 2 groups was 51ml, statistically significant. (p=0.020)

Table 13- Comparision of blood loss by visual estimation and objective measurement among the study population

Sterile under buttock drape	Visual estimation (ml)						Accuracy(%)	Underestimation (%)
measurement (ml)								
	0-100	101-200	201-300	301-400	401-499	>500		
0-100	7	2	0	0	0	0	77.8	0
101-200	23	12	1	0	0	0	33.7	64.4
201-300	7	15	3	0	0	0	11.8	86.8
301-400	3	20	14	5	0	1	11.6	86
401-499	0	2	1	1	0	0	0	100
>500	0	2	4	1	1	4	34.6	65.4

This table compares the accuracy of visual estimation versus objective measurement with the sterile under buttock drape at 100ml discrete categories of postpartum blood loss. The incidence of immediate PPH, as assessed by visual estimation and objective measurement with the sterile under buttock drape was 3.5% and 9.1% respectively with uterine atony being the most common cause of PPH. Comparatively visual estimation

had poor agreement and low correspondence rates. In each category after 100ml of blood loss visual estimation also showed an under estimation of blood loss in majority of cases. Overall only 34.6% of patients were diagnosed with immediate PPH.

DISCUSSION

For a long time, visual assessment of postpartum blood loss has been a normal practice. Despite some researchers' claims to the contrary, this method is straightforward and easily portable, and it understates the real volume of blood loss(66). The quality of measurement has not improved despite simulation training to enhance visual estimation. Error, impreciseness, and unpredictability persist, particularly in instances of significant bleeding. According to earlier research, there is a 25%–89% measuring inaccuracy in the ocular estimation of postpartum blood loss, regardless of the training or expertise of medical professionals(67).

Similar findings were reported in a study by **Prasertcharoensuk et al**., which evaluated the measurement error between visual estimating and direct measurement; however, the specifics of the direct measurement methodology were not described. In addition, the incidence of immediate PPH was relatively high (up to 27.63%) and seemed to be an overexpectation. The objective measurement methodology using the sterile under-buttock drape was thoroughly reported in the current study. The 9.1% incidence of immediate PPH in the present study was three times lower than that of Prasertcharoensuk et al's study(68).

Visual estimation is an unreliable tool for the measurement of postpartum blood loss. In earlier research, individuals with a high postpartum blood loss volume had a far higher visual estimating error, whereas patients with a low postpartum blood loss volume had a lot smaller error(66). The results of the current investigation, however, were different. When visual estimation was used in place of objective measurement using the under-buttock drape, all 100 mL discrete categories of blood loss were underestimated.

The incidence of underestimation using visual estimation was over 50%, with very low accuracy, a low correspondence rate (27.6%) and poor agreement (Cohen's kappa coefficient 0.07; $p < 0.05$).

In addition, it caused a patient with a minimal blood loss to be misdiagnosed with PPH, resulting in needless intervention and resource waste.(69)

Two-thirds of immediate PPH (65.4%) was missed using this subjective method. As a result, we discovered that visual assessment is a poor quality, imprecise technique that commonly results in underestimating across all distinct blood loss categories. While the current investigation did not reveal any unfavorable outcomes for any of the patients, it is reasonable to presume that visual estimating may cause a delay in diagnosis and is therefore not a suitable method for the early detection of acute PPH(70).

An appropriate way for assessing postpartum blood loss for an early diagnosis of acute PPH is objective measurement, particularly with the use of a postpartum calibrated drape or bag. The use of a gravimetric approach, which involves weighing blood collected in all delivery materials on a sensitive scale, to diagnose PPH right away was reported by **Al Kadri et al**. in 2011(71).

The authors reported that this method was superior to visual estimation, which had a blood loss measurement error of about 30%. While the results of our study are comparable to those of Al Kadri et al.'s study, our goals and outcomes are different. Al Kadri et al.'s study, on the other hand, sought to evaluate the precision of the gravimetric approach against experts' ocular assessments of postpartum blood loss. Our study compared the error of visual estimation against a better measurement tool (i.e. the sterile under-buttock drape).

The gravimetric method is more accurate than visual estimation, but it is also more difficult and time-consuming to employ, particularly in busy clinical settings. The authors acknowledged this limitation(72).

The sterile under-buttock drape, on the other hand, is a better method for measuring postpartum blood loss due to its relative simplicity and ease of use. Blood vessels at the placental
implantation site hemorrhage as a result of inadequate contraction of the uterine myometrium following placental delivery and the episiotomy wound, which typically produces significant postpartum bleeding(73).

To avoid contamination with amniotic fluid, we recommend that the drape be used immediately after delivery of the baby and before delivery of the placenta(74). The accuracy of visual estimating at 100 mL distinct categories of postpartum blood loss was also investigated in this study, and considerable mistakes in this method were confirmed(71).

Al Kadri et al's study reported that the actual incidence of PPH in Saudi Arabia was very low, at only 1.47%;(6) Even though this study was carried out in a developing nation with a small sample
size, the incidence might have been underestimated. The incidence of PPH was determined by ocular estimation of blood loss volume in the current study, which had a higher sample size than the previous study. It was 3.5%, while that of objective measurement using the sterile under- buttock drape was 9.1%. Our results are consistent with those of **Tourné et al.** (75), who observed a 10% incidence of PPH when measuring blood loss volume using a collecting bag. This further demonstrates the value of the under-buttock drape as a quick and affordable method of determining blood loss in PPH.

According to a 2010 Zhang et al.(76) study, using a collecting bag did not lower the incidence of severe PPH. However, more research is needed to completely understand this result. The study, which included numerous developed nations, did not provide a common PPH treatment strategy for these nations. The study also included caesarean deliveries, for which the volume of postpartum blood loss is challenging to quantify (77). As a result, not all clinical circumstances can be treated using the same methodology as **Zhang et al**.'s study, particularly in poor or low-resource nations.

Using a combination of under-buttock drapes and collecting pouches, Tixier et al. prospectively compared the postpartum blood loss volume of 122 patients in 2011, measuring changes in hemoglobin and hematocrit levels.

They found a 14.75% incidence of immediate PPH and concluded that the collection pouch was highly sensitive in the early diagnosis of immediate PPH, especially if postpartum blood loss volume had reached 300 mL. **Patel et al**.(5), who employed the BRASS-V blood collection drape as the gold standard for determining PPH volume, corroborate the findings of **Tixier et al** (78).

Due to its high correlation with standard photospectrometry (r = 0.93). The blood collection bag was shown to be beneficial, practical, and substantially more accurate than visual measurement of blood loss in their investigation(79) .

The prospective trial design of the current investigation, which included more people than previous studies and yielded extremely trustworthy results, is its strongest point. Birth attendants with varying levels of experience visually estimated postpartum blood loss; also, a different care provider's measurement of the sterile under-buttock drape was extremely accurate based on standardised objective measurements. As a result, there was no bias in the data gathering for this study. Additionally, the study concentrated primarily on the usefulness of visual estimation and presented convincing proof that this approach is ineffective and inaccurate in assessing the extent of postpartum hemorrhage and identifying PPH.

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