Oxytocin versus carbetocin for prevention of postpartum hemorrhage in high risk cases: Randomized controlled trial

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obtained from all subjects included in the study.

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Abstract

Objective: To assess the effectiveness of oxytocin compared to carbetocin in patients with high risk factors for atonic postpartum hemorrhage who are undergoing elective caesarean section for prophylaxis against postpartum hemorrhage.

Subjects and methods: This randomized controlled study was conducted on 100 pregnant women undergoing elective caesarean section and had high risk factors for atonic PPH. Group (1): were given oxytocin 10 (IU) and Group (2): were given 1 ml of carbetocin. The study was approved by the Ethics Committee, and all patients gave their informed consent before inclusion in the study.

Results: We found that there was a statistically significant differences between the two groups as regard the need for additional uterotonic agents, need for uterine massage, estimated mean operative blood loss, hemoglobin 24 hours after operation and incidence of major obstetric hemorrhage (P-value < 0.05).

Conclusion: The current study has demonstrated that carbetocin can be alternative to traditional oxytocin in the prevention of postpartum hemorrhage in high-risk women undergoing elective caesarean section.

Key words: Oxytocin, carbetocin, high risk, postpartum hemorrhage, elective caesarean section, randomized controlled study.

INTRODUCTION

Postpartum haemorrhage (PPH) following CS is an important cause of maternal mortality and morbidity associated with the procedure. (1)

uterine atony is the main causative factor of postpartum haemorrhage which accounts for 80% of cases, especially in caesarean sections. (2)

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The aim of using uterotonics in the third stage of labour as an active management to reduce the amount of bleeding, the need for blood transfusion and maternal deaths. (3)

Oxytocin has a short biological half-life (<10 Min.), requiring an intravenous infusion when prolonged uterotonic effect is needed, mainly with women at high risk of PPH. (4)

Oxytocin has a high therapeutic index and in addition to treatment of PPH its use as a prophylactic uterotonic agent is justified as well. (5)

It is considered as the initial option for prevention of uterine atony in patients undergoing caesarean sections. NICE recommend intravenous administration of 5 International Units (IU) of oxytocin during caesarean section. (6)

Carbetocin is a synthetic oxytocin analogue that has a biological activity 10 times that of the parent drug. It has 4–10 times longer half-life in comparison to oxytocin. Therefore, it is given as a single dose of 100 mcg, through IV or IM route; thus eliminating the need for infusion. (7)

It was hypothesized to use single dose of carbetocin to act as 16 hours intravenous oxytocin infusion, regarding the increased uterine tone and reduced risk of postpartum haemorrhage in elective caesarean section. (8)

Several data of literature had suggested that prophylactic carbetocin administered intraoperative may be a good alternative to oxytocin to prevent postpartum haemorrhage, but which uterotonic agent is ideal for prophylactic use is being debated. So, primary prevention of postpartum haemorrhage starts with the evaluation of identifiable risk factors. (9)

Patients and methods

This study was conducted on 100 pregnant women undergoing elective caesarean section during the period from January 2022 to Juli 2022 in our Obstetrics and Gynaecology Department; the institutional ethical review board approved the study.

Inclusion and exclusion criteria:

Pregnant women aged 20–40 years with gestational age more than 37 completed weeks and at high-risk condition for atonic postpartum hemorrhage such as multiple pregnancy, polyhydramnios, Placenta previa, Fetal macrosomia, Previous uterine atony or Anemic patients were included in this study. Whereas, women with low risk factors for atonic PPH or with medical disorders, hypersensitivity to oxytocin and carbetocin and coagulopathy were excluded from the study.

Sample size:

Fifty participants were included in each group depending on the following equation

$$SS = \frac{Z^2 \times (P) \times (1-P)}{C^2}$$

Z = Z-value (e.g., 1.96 for a 95 percent confidence level).

P = Percentage of population affected.

C = Confidence interval (sampling error), expressed as decimal (e.g.,.04 = +/- 4 percentage points).

- Group (1): (n=50) were given oxytocin 10 (IU).
- Group (2): (n=50) were given 1 ml of carbetocin.

Ethical consideration:

Written informed consent was taken from the participants after they were informed about the purposes and objectives of the study. Confidentiality and privacy were maintained throughout the study. Collected data will not be used for any other purpose.

Full history was taken and abdominal US for each case, also preoperative lab and cross matched blood was prepared, then divided randomly into 2 groups: Group (1): were given oxytocin 10 (IU) and Group (2): were given 1 ml of carbetocin.

the drug was given by the anaesthetist immediately after cord clamping.

The effect was compared intra-operative by uterine tone, amount of blood loss (by number of soaked towels and vaginal packs weight), changes in pulse and blood pressure, need for message, need for blood transfusion and need for additional uterotonics, and post operative by uterine tone, vaginal blood loss, change in vital signs, and need for adding uterotonics. Hemoglobin and Haematocrit values were noted before CS and 24 hours postpartum.

Statistical analysis:

Collected data had been computerized and analyzed using Statistical Package for Social Science (SPSS) version 16. Descriptive statistics were used to describe variables; percent, proportion for qualitative variables. Mean, SD, range for quantitative variables. Comparison between groups was done using chi-Square test for qualitative variables, independent t- test for quantitative variables. P values with significance of less than 0.05 were considered statistically significant.

Results

The demographic characteristics showed no statistically significant difference (P value > 0.05) among the 2 groups as regard maternal age, gestational age and BMI (table 1).

No significant difference (P-value > 0.05) between the 2 groups regarding various risk factors of uterine atony (table 2).

However, there were statistically significant differences (P-value < 0.05) between the studied groups regarding need for additional uterotonic agents and uterine massage for the control of intraoperative bleeding and maintaining uterine tone. But there was no statistically significant difference (P-value > 0.05) as regard need for transfusion of blood or blood products postpartum (table 3).

There was a statistically significant difference (P-value < 0.05) among the studied groups regarding HB levels 24 hours post operative but there was no significant difference regarding HCT value 24 hours post operative (table 4).

There was a statistically significant difference (P-value < 0.05) among the 2 groups as regard mean operative blood loss as mean blood loss after carbetocin administration was about 176 ml less than after oxytocin administration (table 5).

There was a statistically significant difference (P-value < 0.05) among the 2 groups as regard SBP and DBP after CS as there is significant decrease in it 30 min. after operation in the carbetocin group than the oxytocin group (table 6).

Regarding the incidence of major obstetric hemorrhage among the two groups as blood loss more than 1000 cc was much less in the carbetocin group than oxytocin (table 7).

Also, there was a statistically significant difference (P-value <0.05) between the 2 groups regarding time elapsed for the second dose of uterotonic agents (table 8).

Discussion

Defective function of the uterine musculature or atony is considered the most common cause of PPH. This belief is based on the fact that in many cases of moderate haemorrhage there was no evidence of retained placental tissue or tears, and the bleeding has persisted until uterine contraction was achieved. (10)

This study included 100 pregnant women at high risk to develop postpartum haemorrhage; 50 patients received 100 Microgram of IV carbetocin as a uterotonic agent. Another 50 patients received 10 IU of IV bolus oxytocin.

In our study, demographic features were statistically insignificant among the two groups.

In this study, one of our primary outcomes

was to compare the occurrence of major obstetric haemorrhage (> 1000 ml), only 5 patients in the carbetocin group developed such haemorrhage compared to 15 patients in the oxytocin group.

Dansereau et al, (1999) found that the carbetocin group had a decreased incidence of PPH than the oxytocin group, and that matches with our study. (11)

According to the study of Dansereau et al, (1999) the incidence of the need for therapeutic oxytocics in the carbetocin group was decreased than oxytocin group (4.7% vs. 10.1%; $P < 0.05$), and that was similar to our study results.

Attilakos et al, (2010) found that 33.5% of women in the carbetocin group needed additional oxytocics vs 45.5% of women in the oxytocin group. Therefore, significantly more women required additional oxytocics in the oxytocin group, and that matches with our present study.

In the present study, number of patients in the carbetocin group who required at least one uterine massage were less (12 patients) than oxytocin group (23 patients).

In the present study, mean operative blood loss; estimated by the operative team was 176 ml less in the carbetocin group compared to the oxytocin group.

A randomized study by Borruto et al., (2009) declared that a single 100 microgram IV injection of carbetocin was as effective as a continuous 2hrs infusion of oxytocin in controlling intraoperative blood loss after placental delivery. (12)

In the present study, haemoglobin drop among patients received carbetocin was much less than those received carbetocin. Seow et al. (2017) found that estimated blood loss was more in the oxytocin group. There was a high drop in HB in this group. This matches with the present study. (13)

In the present study, Carbetocin produced more hypotension in the patients than oxytocin. For the carbetocin being more potent and having longer duration of action compared to oxytocin which already causes hypotension as a side effect, this may explain the more hypotension that occurs with the former.

In the present study, only 3 patients in the carbetocin group received transfusion of blood or blood products, unlike the oxytocin group (6 patients). That was statistically insignificant.

At Attilakos et al. (2010) study, there were no statistically significant difference in the number of women requiring blood transfusion between the carbetocin and oxytocin groups. (9)

However, the high-risk nature of the patients for developing uterine atony and postpartum haemorrhage with its implications and morbidities, and the higher effectiveness of carbetocin being requiring less interventions; these factors promote the use of carbetocin for such patients to decrease the incidence of possible complications and morbidities that may finally lead to surgical interventions with more costs

Conclusion

We concluded that carbetocin can be an alternative to traditional oxytocin in the prevention of postpartum hemorrhage in high-risk women undergoing elective caesarean section. Single dose of IV carbetocin100 mcg is more effective as compared to IV oxytocin 10 IU.

References

1. Gülmezoglu AM, Lumbiganon P, Landoulsi S, Widmer M, Abdel-Aleem H, Festin M, et al. Active management of the third stage of labour with and without controlled cordtraction: a randomized controlled non-inferiority trial. Lancet 2012;380(9838): 218.
2. Miller HE, Ansari JR. Uterine atony. Curr Opin Obstet Gynecol.2022,1;34(2): 82-89.
3. Chong Y-S, Su L-L, Arulkumaran S. Current strategies for the prevention of postpartum haemorrhage in the third stage of labour. Curr Opin Obstet Gynecol, 2004,16 (2): 143-150.
4. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. Eur J Obstet Gynecol Reprod Biolology.2009, 147 (1): 15–20.
5. Yamaguchi E T, Cardoso M M, Torres M L. Oxytocin in cesarean sections: what is the best way to use it? Rev bRAS Anestesiol.2007, 57: 324-350.
6. Caesarean section: Evidence Update March 2013: A summary of selected new evidence relevant to NICE clinical guidance132.London: National institute for Health and Clinical Excellence.2013. PMID:31886991.
7. Sweeney G, Holbrook AM, Levine M, Yip M, Alfredsson K, Cappi S, et al. Pharmacokinetics of carbetocin, a long-acting oxytocin analogue, in non pregnant women. Current Therapeutic Res.1990, 47 (3): 528-40.
8. Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin PharmacolThe.1992, 52 :60–7.
9. Attilakos G, Psaroudakis D, Ash J, Buchanan R, Winter C, Donald F, et al. "Carbetocin versus oxytocin for the prevention of postpartum haemorrhage following caesarean section: the results of a double-blind randomized trial". BJOG.2010, 117 (8): 929–36.
10. Hazra S, Chilaka VN, Rajendran S, Konje JC. Massive postpartum haemorrhage as a cause of maternal morbidity in a large tertiary hospital. Journal of Obstetrics and Gynaecology. 2004,24 (5): 519-520.
11. Dansereau J, Joshi K, Helewa ME, Doran TA, Lange IR, Farine D, et al. Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section. Am J Obstet Gynecol. 1999,180(3): 670–6.
12. Borruto F, Treisser A, Comparetto C. Utilization of carbetocin for prevention of postpartum hemorrhage after cesarean section: a randomized clinical trial. Arch GynecolObstet.2009, 280(5): 707–12.
13. Seow KM, Chen KH, Wang PH, Lin YH, Hwang JL. Carbetocin versus oxytocin for prevention of postpartum hemorrhage in infertile women with twin pregnancy undergoing elective cesarean delivery. Taiwan J Obstet Gynecol. 2017, 56 (3): 273-275.

Legends to tables:

Table (1): Comparison between the studied groups regarding demographic data.

Table (2): Comparison between the studied groups regarding different high-risk factors.

Table (3): Comparison between the two groups regarding need for additional uterotonics, need for uterine massage and need for BL. Transfusion.

Table (4): Comparison between the studied groups regarding hemoglobin and hematocrit.

Table (5): Comparison between the studied groups regarding mean operative blood loss.

Table (6): Comparison between the studied groups regardingSBP and DBP.

Table (7): Comparison between the two groups regarding major obstetric haemorrhage.

Table (8): comparison between the two groups regarding time for second dose of uterotonics.

Legends to figures:

Figure (1): Need for additional uterotonic ttt among the studied groups.

Figure (2): Need for uterine massage among the studied groups.

Figure (3): HB level before and 24 hrs postpartum among the studied groups.

Figure (4): Total blood loss (ml) intra operative among the studied groups.

Figure (5): SBP before and 30 min. after Operation among the studied groups.

Figure (6): DBP before and 30 min. after Operation among the studied groups.

Figure (7): Incidence of major obstetric Hge among the studied groups.

Figure (8): Time (min) for second dose of uterotonic agents among the studied groups

List of abbreviation:

BMI: Body mass index.

CS: Caesarean section.

HB: Haemoglobin.

HCT: Haematocrit.

PPH: Postpartum haemorrhage.

SBP: Systolic blood pressure.

DBP: Diastolic blood pressure.

SD: Standard deviation.

SPSS: Statistical Package of Social Science.

US: Ultrasound.

Table (1)

	Drug used								P value
	Group (2)				Group (1)				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Age (years)	29.56	5.45	22.00	37.00	28.70	4.32	19.00	36.00	0.368
Age (years)	26.00	1.38	24.00	28.00	26.10	1.34	24.00	28.00	0.826
GA (weeks)	38.16	.37	38.00	39.00	38.24	.59	38.00	41.00	1

Table (2)

		Drug used				P value
		Group (2)		Group (1)		
		Count	%	Count	%	
Risk	1. History of pp Hge	13	26.0%	9	18.0%	0.786
	2. Macrosomic baby	22	44.0%	26	52.0%	
	3. Polyhydramnios	7	14.0%	8	16.0%	
	4. Twin pregnancy	6	12.0%	4	8.0%	
	5. uterine wall fibroid	2	4.0%	3	6.0%	

Table (3)

		Drug used				P value
		Group (2)		Group (1)		
		Count	%	Count	%	
1. Need for additional uterotonic ttt	**Yes**	9	18.0%	18	36.0%	0.043*
	No	41	82.0%	32	64.0%	
2. Need for uterine massage	**Yes**	12	24.0%	23	46.0%	0.021*
	No	38	76.0%	27	54.0%	
3. Need for BL transfusion	**Yes**	3	6.0%	6	12.0%	0.295
	No	47	94.0%	44	88.0%	

Table (4)

	Drug used								P value
	Group (2)				Group (1)				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
HB before (mg/dl)	10.87	0.69	10.00	12.00	11.16	0.81	10.00	12.80	0.06
HB after (mg/dl)	10.12	0.92	7.90	11.50	9.47	1.01	7.90	11.50	0.001*
HCT % before	32.57	3.38	27.00	37.00	33.38	5.71	25.60	43.00	0.386
HCT % after	29.24	2.76	24.00	33.00	28.64	3.32	24.00	33.00	0.329

Table (5)

	Drug used								P value
	Group (2)				Group (1)				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Total blood loss (ml)	706.64	177.11	387.00	1030.00	882.74	168.72	443.00	1100.00	< 0.001*

Table (6)

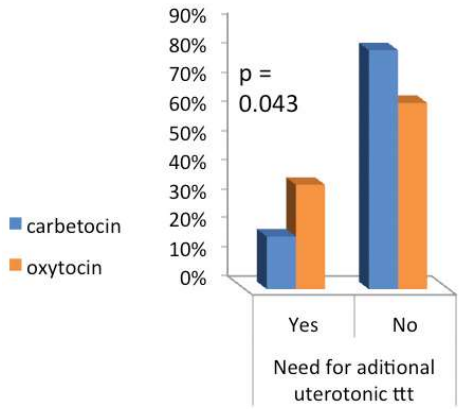
	Drug used								P value
	Group (2)				Group (1)				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
SBP before op.	112.76	10.35	100.00	130.00	113.56	9.63	90.00	130.00	0.690
SBP 30min. after op.	91.44	7.19	80.00	115.00	97.48	8.99	80.00	115.00	<0.001
DBP before op.	67.70	9.99	50.00	80.00	69.38	6.12	60.00	80.00	0.313
DBP 30min. after op.	56.84	7.70	50.00	70.00	62.68	6.75	50.00	70.00	< 0.001

Table (7)

		Drug used				P value
		Group (2)		Group (1)		
		Count	%	Count	%	
Major obstetric Hge	**Yes**	5	10.0%	15	30.0%	0.012*
	No	45	90.0%	35	70.0%	

Table (8)

	Drug used								P value
	Group (2)				Group (1)				
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Time elapsed for second dose (min)	55.16	2.95	50.00	59.00	94.68	3.09	90.00	100.00	<0.001



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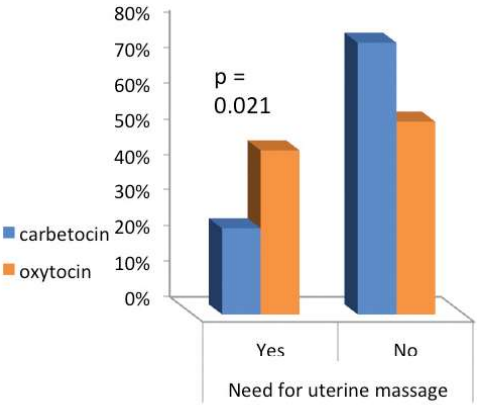

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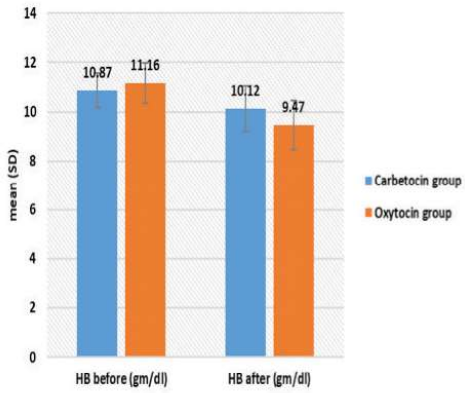

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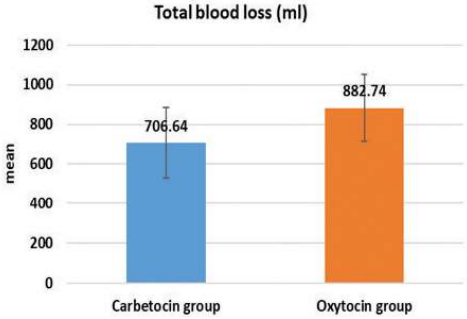

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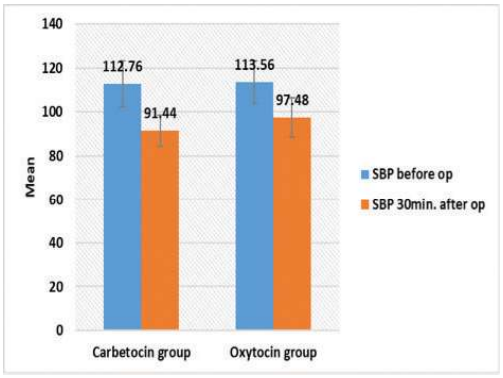

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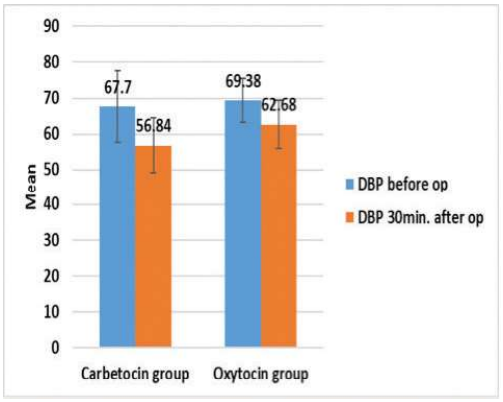

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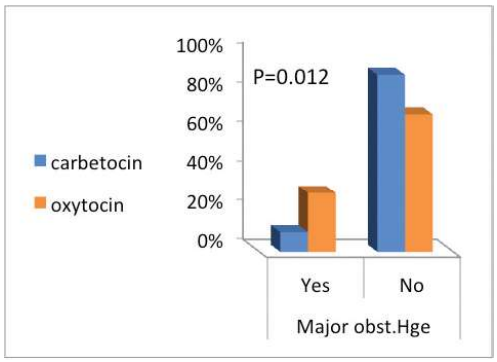

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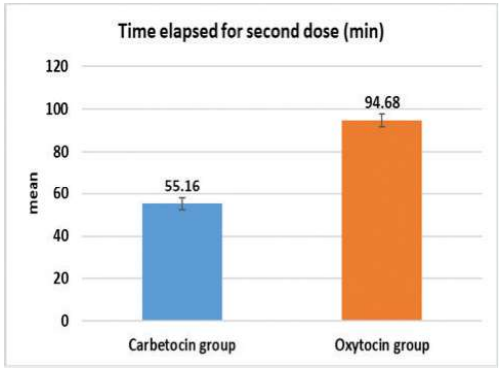

Fig. (8)