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Comparative Study between Carbetocin Versus Oxytocin for the Prevention of Atonic Postpartum Hemorrhage after Repeated Elective Cesarean Sections

Dr. A. Himaja[1], Dr. Siva Jyothi[2], Dr. Sruthi[3]

Department of OBG, Santhiram Medical College and General Hospital, Nandyal, Andhra Pradesh, India

[2]Associate Professor, Department of OBG, Santhiram Medical College and General Hospital, Nandyal, 518502, Andhra Pradesh, India
Corresponding Author Email id: *jyothiidamakantireddy[at]gmail.com*
Phone N.o: 9908471200

Abstract: ***Background: Postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide. Prophylactic uterotonics are effective in reducing PPH. Objective: To compare the prophylactic effects of carbetocin with those of oxytocin in the prevention of atonic PPH in patients undergoing repeated elective cesarean section (CS) under spinal anesthesia. Patients and Methods: This comparative study was conducted on 100 pregnant women after 38 weeks underwent elective cesarean section under spinal anesthesia at santhiram medical college from October 2021 to m 2020, 50 patients received a single dose of 100 microgram intravenous carbetocin, the other 50 patients received 5 IU of oxytocin IV followed by 20-40 IU of oxytocin infusion on 1000 ml saline with a rate of 150 ml per hour. Results: Patients who received carbetocin developed less major obstetric hemorrhage, required less intervention in the form of uterine massage and less additional uterotonic agents than those received oxytocin. The estimated blood loss was significantly lower in the carbetocin group than the oxytocin group. Also, the carbetocin group showed less incidence of severe anemia and the need for blood transfusion than oxytocin but that was statistically insignificant. Conclusion: Carbetocin appeared to be more effective than oxytocin for prevention of atonic postpartum hemorrhage in patients undergoing elective cesarean section. Carbetocin reduced the use of additional oxytocics following cesarean section when compared with the licensed dose of oxytocin (5 IU). Also, carbetocin improved the hemodynamic states of the patients, decreased the need for blood transfusion and incidence of severe anemia.***

Keywords: Carbetocin, Oxytocin, atonic postpartum hemorrhage, repeated elective cesarean sections.

1. Introduction

Postpartum hemorrhage (PPH) is defined as a blood loss more than 500 ml following normal vaginal delivery or 1000ml following cesarian section within 24hrs of delivery. Mild PPH-Between 500 1000ml, Moderate -1000ml to 2000ml,severe >2000ml.

PPH is a serious condition remaining the single main cause of maternal morbidity and mortality. Postpartum hemorrhage (PPH) accounts for nearly one-quarter of all maternal deaths worldwide

The most frequent cause of PPH is uterine atony, contributing up to 80 % of the PPH cases. Although two-thirds of the PPH cases occur in women without predisposing factors, there are several risk factors for PPH such as previous PPH, preeclampsia, coagulopathy, multiple gestation and ante-partum hemorrhage. Also, cesarean section (CS) is a recognized risk factor for PPH and its prevalence is increasing

The administration of oxytocics after the delivery of the neonate reduces the like hood of PPH, and 5 IU oxytocin by slow intravenous injection is currently recommended in the UK for all cesarean sections. However, the use of additional oxytocic medication is common *(WHO, 2015)* to arrest bleeding, or prophylactically if there are risk factors for PPH

Oxytocin is currently the uterotonic of first choice. It has proven to decrease the incidence of PPH by 40 %, and has a rapid onset of action and a good safety profile. A disadvantage of oxytocin is its short half-life of 4–10 min, regularly requiring a continuous intravenous infusion or repeated intramuscular injections. Carbetocin (Pabal) is a long-acting oxytocin analogue indicated for the prevention of uterine atony after child birth by CS under epidural or spinal anesthesia. Carbetocin has a rapid onset of action (within 1–2 min) and a prolonged duration of action (approximately 1h) because of sustained uterine response with contractions of higher amplitude and frequency. Its safety profile is comparable to that of oxytocin. **The aim of the present study was to** compare the prophylactic effects of carbetocin with those of oxytocin in the prevention of atonic PPH in patients undergoing repeated elective CS under spinal anesthesia.

Patients and Methods

This was a computerized random cross sectional prospective comparative study that was conducted on 100 pregnant women at santhiram medical college from October 2021 to March 2022. Informed consents were obtained from all participants after simple and clear explanation about the research objectives.

Inclusion Criteria

- Singleton pregnancy,
- Gestational age > 38 weeks,

- Repeated C.S with cephalic, breech or any mal presentions.

Exclusion Criteria

- Patients with placenta previa and placental abruption,
- Uterine fibroids
- Congenital uterine anomalies,
- Gestational age before 38 weeks
- Women having emergency cesarean section for fetal or maternal distress
- Patients with hepatic or pre-existing bleeding disorder were excluded from the study

2. Results

No statistically significant difference was found between groups according to demographic and pulse **(Table 1)**.

Table 1: Comparison between Carbetocin and Oxytocin group according to demographic data

Parameters \ Groups	Carbetocin Group *(n=50)*	Oxytocin Group *(n=50)*	P-value
Age (years)‡	29.41±2.38	28.56±3.31	0.144
Gestational age (wks) ‡	38.86±0.50	38.91±0.50	0.618
BMI [kg/m^2] ‡	27.60±2.70	27.80±2.50	0.661
Parity#	3 (IQR 2)	3 (IQR 1)	0.517

‡ Data were expressed mean and standard deviation; using Independent Sample t-test.
# Data were expressed Median and Interquartile range (IQR); using Mann-Whitney U-test.

There was a statistically significant difference between groups according to blood loss and Hb. Postoperative. The postoperative blood loss was significantly lower in carbetocin group when compared to the oxytocin group. The levels of Hb and HCT were evaluated pre and post-operative in both groups. The levels of preoperative Hb and HT showed non- significant difference between the two groups while the levels of postoperative Hb and HCT were significantly higher in carbetocin group than oxytocin group concluding that carbetocin showed the better results in controlling the blood loss and maintaining the levels of Hb and HCT volume. Statistically significant difference was found between groups according to Hb change and HCT change.

Table 2: Comparison of hemoglobin and hematocrit (HCT) and estimated blood loss of women enrolled to the study

Parameters \ Groups	Carbetocin group *(n=50)*	Oxytocin group *(n=50)*	P-value
Blood loss#	732 (IQR 232)	910 (IQR 318)	0.004*
Hb preoperative‡	11.19±0.45	11.05±0.37	0.092
Hb postoperative‡	10.02±0.52	9.23±0.56	<0.001**
Hb Change #	-1.17 (IQR 0.34)	-1.82 (IQR 0.53)	<0.001**
HCT preoperative‡	33.77±1.45	33.17±1.75	0.065
HCT postoperative‡	29.41±2.83	28.44±2.14	0.056
HCT Change#	-4.36 (IQR 0.76)	-4.73 (IQR 0.84)	0.019*

‡ Data were expressed mean and standard deviation; using Independent Sample t-test. # Data were expressed Median and Interquartile range; using Mann-Whitney U-test.

As for the administration of uterotonic agents, the carbetocin group showed less need for administration of uterotonic agents (20%) in comparison with (32%) in oxytocin group but with no statistically significant difference

Table 3: Comparison between Carbetocin and Oxytocin group according to required uterotonic agents administration

Uterotonic agents	Non-administered	Administered	OR	(95%CI)	P-value
Carbetocin	40 (80%)	10 (20%)	0.531	0.213-1.324	0.171
Oxytocin	34 (68%)	16 (32%)			

Carbetocin group showed (10%) when compared with the oxytocin group (20%)according to severe anemia, there is no statistically significant difference (p- value= 0.161

Table 4: Comparison between Carbetocin and Oxytocin group according to suffered from severe anemia

Occurrence of severe anemia (Hb<7gm)	No severe anemia	Severe anemia	OR	(95%CI)	P-value
Carbetocin	45 (90%)	5 (10%)	0.444	0.140-1.411	0.161
Oxytocin	40 (80%)	10 (20%)			

Carbetocin group showed (6%) when compared with the oxytocin group (10%) according to need for blood transfusion,

Table 5: Comparison between Carbetocin and Oxytocin group according to need for blood transfusion

Need for Blood transfusion	No-need	Need	OR	(95%CI)	P-value
Carbetocin	47 (94%)	3 (6%)	0.574	0.130-2.545	0.461
Oxytocin	45 (90%)	5 (10%)			

The carbetocin group showed (16%) when compared with the oxytocin group (28%) according to post-partum there is no statistically significant difference (p-value= 0.461).

Table 6: Comparison between Carbetocin and Oxytocin group according to occurrence of post-partum hemorrhage

Occurrence of post-partum hemorrhage	No(PPH)	(PPH)	OR	(95%CI)	P-value
Carbetocin	42 (84%)	8 (16%)	0.490	0.185-0.1.300	0.148
Oxytocin	36 (72%)	14 (28%)			

3. Discussion

During the study, the postoperative blood loss was significantly lower in carbetocin group when compared to the oxytocin group. Also, there was a statistically significant difference between the two groups regarding the occurrence of postpartum hemorrhage. The carbetocin group showed less occurrence of hemorrhage (12%) in comparison with 32% in oxytocin group.

In accordance with the present study, *Holleboom et al. (2013)* demonstrated a lower rate of additional oxytocic usage after carbetocin compared with oxytocin, carbetocin may be more effective in preventing uterus atony and thereby PPH. Also, another study found that the estimated blood loss was significantly lower in the carbetocin group *(Debbie-Lyn uy et al., 2013)*. In addition, *Mohamed et al.*

(2015) showed that blood loss was significantly higher in the oxytocin group compared to carbetocin group but not to the degree of PPH, and this could be attributed to that carbetocin causes a tetanic uterine contraction produced 2min after an intravenous injection of 8-30mg or intramuscular injection of 10-70mg, which persists for approximately 1 min. Rhythmic uterine contractions persistfor60 and 120min after intravenous and intramuscular injection respectively which decrease the uterine atony.

Moreover, another study found that a single injection of carbetocin appears to be more effective than a continuous infusion of oxytocin to prevent the PPH, with a similar hemodynamic profile and minor antidiuretic effect *(Larciprete et al., 2013)*.

Holleboom et al. (2013) performed a randomized controlled trial (RCT) at Canada comparing the incidence of PPH in women undergoing elective Caesarean section who received either carbetocin a 100 microgram IV bolus or oxytocin as a continuous infusion for 8 hours. The carbetocin group had a decreased incidence of PPH.

In our present study, the levels of Hb and HT were evaluated pre and post- operative in both groups. The levels of preoperative Hb and HT showed non- significant difference between the two groups while the levels of postoperative Hb and HCT were significantly higher in carbetocin group than oxytocin group concluding that carbetocin showed the best results in controlling the blood loss and maintaining the levels of Hb and HCT values. Also, the change in pre and postoperative HCT and Hb levels were significantly lower in carbetocin group in comparison with oxytocin.

In agreement with these results, post- operatively, hemoglobin and hematocrit levels in the carbetocin group were statistically higher *(Debbie-Lyn uy et al., 2013)*.

During the present study, the need for administration of uterotonic agents was significantly lower in carbetocin group in comparison with oxytocin.

In consistence with our results, carbetocin seemed to be most beneficial compared with the oxytocin group(5 IU bolus) with less need for additional uterotonic medication and significantly less need for blood transfusions *(Holleboom et al., 2013)*.

In agreement with these results, another study confirmed that a single intravenous injection of carbetocin administered during CS significantly reduced the need for additional uterotonic interventions in comparison with classic I.V. oxytocin treatment, has the same safety profile of oxytocin, since vital signs, hematologic values (hemoglobin levels drop) and incidence of adverse effects were not statistically different in the two groups *(De Bonis et al., 2012)*.

Other studies, evaluated the effect of an I.V. injection of carbetocin after cesarean delivery under regional anesthesia, showed that a single intravenous injection of carbetocin significantly reduced the need for additional uterotonic interventions to maintain adequate uterine tone and prevent/treat excessive bleeding following caesarean delivery versus intravenous oxytocin *(Attilakos et al., 2010* and *Holleboom et al., 2013)*.

Also, in another study, there was statistically lower proportion of women in the carbetocin group who required additional uterotonic agents post- operatively. Uterine massage was less required in the same group *(Debbie-Lyn uy et al., 2013)*.During this study, the number of women who suffered from severe anemia and in need for blood transfusion was not significantly different between the two groups, but less patients in the carbetocin group showed severe anemia (8%), or need for blood transfusion (4%) in comparison with the oxytocin group.

In contrast with our results, *Debbie- Lyn UY et al. (2013)* showed that the two studied groups did not significantly differ in neither terms of blood transfusion requirements nor the occurrence of severe anemia.

Attilakos et al. (2010) study, showed no significant differences in the number of women requiring blood transfusions between oxytocin and carbetocin groups.

In agreement with this, carbetocin seemed to be most beneficial compared with the subgroup oxytocin 5 IU bolus with significantly less need for blood transfusions *(Holleboom et al., 2013)*.

4. Conclusion

Carbetocin was superior to oxytocin for preventing perioperative and postoperative blood loss in atonic PPH in patients underwent elective CS.Both oxytocin and carbetocin had similar safety profile.

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