Section: OBG

Original Research Article

COMPARISON OF EFFECTS OF CARBETOCIN AND OXYTOCIN IN CAESAREAN SECTION

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Abstract

Background: Oxytocin is commonly used as a uterotonic agent, carbetocin can be administered intravenously as a bolus instead of a continuous infusion of oxytocin. Aim of the study were to compare the haemodynamic effects of oxytocin and carbetocin and also to evaluate in terms of changes in hemoglobin level, effects on urine output and other side effects. **Materials and Methods:** 80 women undergoing elective caesarean section were consecutively enrolled, with normal antenatal. Firstly we recruited 40 women who received carbetocin (group A), then we enrolled 40 women who received oxytocin (group B). **Result:** The primary gestational age at caesarean section was found to be 36.61 ± 1.36 weeks in the carbetocin group, while in the control group it was 36.07 ± 1.30 weeks. The oxytocin group exhibited a statistically significant decrease in systolic blood pressure at the third and fifth minute after administration, during uterine closure, and at 12 and 24 hours postoperatively. Nevertheless, the oxytocin group exhibited lower diastolic blood pressures compared to the control group at specific time points, including the third and fifth minutes after administration, 1 hours after the operation. These reductions in diastolic blood pressure were found to be statistically significant. There was no statistically significant disparity observed in the estimated blood loss and the occurrence of primary post-partum haemorrhage between the two groups. Both study groups exhibited similar frequencies of nausea and vomiting. **Conclusion:** The administration of a solitary dose of carbetocin demonstrates a safer hemodynamic profile and reduced requirement for uterotonics.

INTRODUCTION

Postpartum hemorrhage (PPH) is a significant contributor to maternal morbidity and mortality,[1] affecting approximately 6% of all childbirths.[2] Uterine atony is identified as the primary etiological factor in the majority of cases of postpartum hemorrhage (PPH), accounting for approximately 80% of instances.[3] One notable risk factor for postpartum hemorrhage (PPH) is caesarean section (CS), and it is recommended to consistently administer uterotonic agents promptly following the delivery of the fetus.[4]

At present, oxytocin is commonly employed as the primary pharmacological intervention following a caesarean section. Continuous or frequent administration is necessary due to the short half-life of the substance, which typically ranges from 4 to 10 minutes. In recent times, carbetocin has emerged as a prolonged-acting agonist of oxytocin, which, upon administration, induces a sustained contraction of the uterus. According to a comprehensive analysis of randomized controlled trials, carbetocin has been found to be linked with a decreased requirement for supplementary uterotonic agents. However, no significant disparities have been observed in terms of postpartum hemorrhage (PPH), severe PPH, average estimated blood loss, or adverse effects.[5] Various adverse effects, such as nausea, vomiting, and arterial hypotension leading to symptoms of dizziness or syncope, have been investigated solely as secondary outcomes in randomized controlled trials.[6,7] Given that carbetocin is a derivative of oxytocin, it is reasonable to anticipate that potential adverse effects may exhibit similarities. The occurrence of hypotension, a significant hemodynamic adverse effect, has been documented with the administration of both oxytocin and carbetocin.[8] When conducting

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a comparison between carbetocin and low dose oxytocin, it is observed that the haemodynamic side effects exhibit a similar level of severity in both groups. There is no observed variation in hypotension across various doses ranging from 20 to 100 µg of carbetocin. Typically, hypotension is observed in approximately 40 to 55% of cases.[9] According to the practical guidelines provided by the Society of Obstetricians and Gynaecologists of Canada (SOGC), it is suggested that the active management of the third stage of labor is more effective in reducing the risk of postpartum hemorrhage (PPH) compared to expectant management. Therefore, it is recommended that all women be offered and advised to undergo active management of the third stage of labor. The administration of uterotonic drugs is widely recognized as an effective preventive measure against postpartum hemorrhage (PPH), as it significantly reduces the incidence of PPH. Consequently, it is considered a crucial component of active management strategies. The administration of Oxytocin at a dosage of 10 IU via the intra-muscular route is the recommended pharmacological intervention for the purpose of preventing postpartum hemorrhage (PPH) in both low-risk vaginal deliveries and caesarean deliveries. Healthcare providers should administer this medication following the delivery of the anterior shoulder. The administration of oxytocin through intravenous infusion, at a dosage range of 20 to 40 International Units (IU) diluted in 1000 milliliters (mL) of solution, and administered at a rate of 150 mL per hour, is considered a viable alternative for the active management. Ergonovine may be regarded as a secondary option to oxytocin, as its use is associated with a higher likelihood of maternal adverse effects. In the context of elective caesarean section, the administration of carbetocin at a dosage of 100 µg as an intravenous bolus over a duration of 1 minute, as an alternative to continuous infusion of oxytocin, may be considered for the purpose of preventing postpartum hemorrhage (PPH) and potentially reducing the requirement for therapeutic uterotonics.The given text consists of the numbers 10 and 11 enclosed in square brackets.

MATERIALS AND METHODS

80 women undergoing elective caesarean section were consecutively enrolled, normal antenatal. A written informed consent was asked from eligible women on admission.

Inclusion Criteria

- Pregnant with singleton fetus >37th week
- Patients giving birth with regional anesthesia

Exclusion Criteria

- Oxytocin and carbetocin contraindicatied
- < 18 years of age
- < 37 weeks of gestation
- Multiple pregnancies
- Cesarean section with GA
- 2 or more previous caesarean sections
- Placenta insertion anomaly
- HELLP syndrome

Firstly we recruited 40 women who received carbetocin (group A), then we enrolled 40 women who received oxytocin (group B).

Carbetocin Group: In the carbetocin group,1 mL containing 100 µg of carbetocin was diluted to 10ml, and then administered within 1 minute of delivery of the baby intravenously within 60 seconds by slow infusion.

Oxytocin Group: Women giving birth by cesarean section between were divided into two groups according to the uterotonic administration; carbetocin or oxytocin. In the oxytocin group, within 1 minute of delivery of the baby, 10 IU oxytocin was administered as an intravenous infusion in 500 ml of saline. Since oxytocin is a short-acting uterotonic agent, subsequent maintenance therapy was initiated after the loading dose. Maintenance dose was titrated according to the tonicity of uterus.

The main objective of this study was to assess the immediate hemodynamic effects of carbetocin and oxytocin by examining their impact on blood pressure (BP) immediately following administration. All subjects received identical spinal anesthesia. Following the administration of anesthesia, the subjects were placed in a supine position. To facilitate continuous blood pressure monitoring, a limb cuff was affixed. In order to assess the haemodynamic impacts of carbetocin and oxytocin, we examined the decrease in blood pressure following the administration of these drugs during a spinal anesthesia procedure. Specifically, we measured blood pressure levels at 1 minute, 3 minutes, and 5 minutes after drug administration, both during uterine repair and at the conclusion of the caesarean procedure. These measurements were taken while the patient was in a supine position only. The researchers documented the presence of symptoms such as nausea, vomiting, flushing, headache, dyspnea, and tachycardia. The second significant result of this study pertained to the necessity of supplementary uterotonic agents and the assessment of the decrease in hemoglobin levels by comparing the hemoglobin concentration upon admission with measurements taken at 24 hours postpartum. Additionally, the assessment of blood loss is promptly conducted following a caesarean section, with haemorrhage being defined as a blood loss exceeding 1000 ml or greater. The surgeon estimated the amount of blood loss using conventional methods. The midwife monitored blood pressure (measured in millimeters of mercury), uterine tone, and uterine position at three time points: 2 hours, 12 hours, and 24 hours postpartum. The Foley catheter and urobag were retained in all patients for a duration of 24 hours following caesarean section. The midwife was

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responsible for monitoring the volume of urine at 24 hours post-delivery.

Statistical analysis: The statistical tests employed in this study are the Student's t-test and the Mann-Whitney U test. The U test was employed to compare two groups of variables that exhibited a normal distribution. The Pearson chi-square test, Fisher's exact test, and Fisher-Freeman-Halton test were employed to conduct a comparative analysis of the qualitative data. The statistical significance was assessed at a significance level of $p<0.05$.

RESULTS

All pertinent maternal subject characteristics in both study groups were comparable during pregnancy in the carbetocin group (20% vs 2.5%, $p<0.05$), as outlined in [Table 1]. The primary gestational age at caesarean section was found to be 36.61 ± 1.36 weeks in the carbetocin group, while in the control group it was 36.07 ± 1.30 weeks. In relation to the haemodynamic impacts of carbetocin and oxytocin, it is observed that both medications elicit a hypotensive response. The oxytocin group exhibited a statistically significant decrease in systolic blood pressure at the third and fifth minute after administration, during uterine closure, and at 1 hours postoperatively (P = 0.01, 0.03, 0.01, and 0.01, respectively) [Table 2]. Nevertheless, the oxytocin group exhibited lower diastolic blood pressures compared to the control group at specific time points, including the third and fifth minutes after administration, as well as 1 hours after the operation. These reductions in diastolic blood pressure were found to be statistically significant (P = 0.03, 0.01, and 0.002, respectively) according to the data presented in [Table 3].

Table 1: Characteristics of the study population

	Carbetocin (A) (n=40)	Oxytocin (B) (n=40)	P value
Maternal age	25.74 ± 3.69	26.77 ±3.61	0.34
Gestational age	36.61 ± 1.36	36.07 ± 1.30	0.27
Parity	1.79 ± 0.29	1.61 ± 0.77	0.07
BMI	25.88 ± 4.49	26.26 ± 4.55	0.37
Use of anticoagulant in pregnancy	8 (20%)	1 (2.5%)	0.01

Table 2: Systolic blood pressure (mm Hg) during and after cesarean section

Items	Carbetocin (n=40)	Oxytocin (n=40)	Test result	P
Preoperative baseline systolic BP	104.77±5.85	103.98±5.37	1.52*	0.21
Systolic BP at skin incision	108.11±6.37	107.54±6.47	0.67*	0.64
Systolic BP after uterotonic administration by 1 min	109.44±4.58	103.33±5.69	1.49*	0.41
Systolic BP after uterotonic administration by 3 min	103.44±6.37	97.99±6.17	2.71*	0.01**
Systolic BP after uterotonic administration by 5 min	101.11±5.61	75.94±6.14	3.01*	0.03**
Systolic BP at uterine repair	99.78±4.85	93.89±6.46	2.73*	0.01**
Systolic BP at suturing of the skin	99.71±5.34	94.11±5.51	2.25*	0.07
Systolic BP 1 h after CS	100.32±5.45	98.78±5.66	0.95*	0.31

BP, blood pressure; CS, cesarean section. * Student's t test. **Statistically significant.

Table 3: Diastolic blood pressure (mm Hg) during and after cesarean section

Items	Carbetocin (n=40)	Oxytocin (n=40)	Test result	P
Preoperative baseline diastolic BP	77.01±4.15	72.15±4.36	3.12*	0.63
Diastolic BP at skin incision	75.11±4.44	74.01±4.16	1.015*	0.44
Diastolic BP after uterotonic administration by 1 min	70.21±4.12	68.55±4.36	1.31*	0.34
Diastolic BP after uterotonic administration by 3 min	61.89±3.89	67.17±3.47	1.47*	0.03**
Diastolic BP after uterotonic administration by 5 min	59.88±3.64	63.55±3.39	1.31*	0.01**
Diastolic BP at uterine repair	64.01±4.19	62.22±3.69	1.45*	0.17
Diastolic BP at suturing of the skin	64.01±4.19	62.03±3.34	1.54*	0.19
Diastolic BP 1 h after CS	64.74±3.63	62.41±3.46	1.71*	0.21

BP, blood pressure; CS, cesarean section. *Student's t test. **Statistically significant.

Table 4: Comparison between carbetocin group and oxytocin & ergometrine groups as regards estimated blood loss, hematocrit pre and postoperative.

Group	Carbetocin	Oxytocin	P value
Hematocrit pre-op	36.45 ± 4.69	35.78 ± 4.44	0.22
Hematocrit 24hrs postoperative	32.77 ± 3.66	30.44 ± 3.12	0.013
Hematocrit drop	4.02 ± 0.03	5.74 ± 0.04	0.36
Estimated blood loss	354.78 ± 25.52	474.52 ± 35.58	0.25

Table 5: Hemoglobin levels before and after cesarean section.

Group	Carbetocin	Oxytocin	P value
Pre-operative Hb (g/dl)	10.45 ± 1.16	10.22 ± 1.17	0.41
Postoperative Hb 24hrs (g/dl)	9.69 ± 1.11	9.23 ± 1.01	0.01
Hb drop (g/dl)	0.76 ± 0.06	0.99 ± 0.16	0.001

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Table 6: Drug side effect

	Carbetocin	Oxytocin	P -value
Nausea	5	5	0.41
Vomiting	6	6	0.25
Headache	10	3	0.04

[Table 4] demonstrates that there was no statistically significant disparity observed in the estimated blood loss and the occurrence of primary post-partum haemorrhage between the two groups. In a comparative analysis, it was observed that the levels of haemoglobin before and 24 hours following delivery were comparable in both study groups. This finding supports the conclusion that there is no substantial disparity in the amount of blood loss [Table 5]. However, it is worth noting that there was a slight tendency towards a lower decrease in Hb levels at 24 hours after delivery in the carbetocin group (-0.8 g/dl compared to -1.2 g/dl, p 0.08). Simultaneously, notable variations were observed in both uterine tone and fundal height. The group administered with carbetocin exhibited superior uterine contractility compared to the control group at 2, 12, and 24 hours following caesarean section. Notably, the disparity in contractility was found to be statistically significant at the 24-hour mark ($p<0.05$). Patients in group A exhibited a fundus position that was notably lower than 2 cm from the umbilical point (-2UP) at both the 2-hour and 12-hour marks during their hospital stay ($p<0.05$), when compared to patients who received oxytocin administration. The study found that patients who received carbetocin exhibited a greater level of diuresis compared to patients in the oxytocin group, particularly at the 24-hour mark following a caesarean section. This disparity was determined to be statistically significant. No significant adverse effects were documented in either study group. However, both study groups exhibited similar frequencies of nausea and vomiting.

DISCUSSION

This study represents a limited number of investigations that have compared the efficacy of carbetocin and oxytocin in elective caesarean sections involving individuals with risk factors for primary postpartum haemorrhage. The study aims to examine the haemodynamic impact of these drugs as well as their potential for preventing postpartum haemorrhage. However, there is an ongoing debate regarding the most appropriate uterotonic agent for prophylactic use, and the existing literature does not provide clear endpoints on this matter.

The main objective of this study is to assess the immediate hemodynamic effects of carbetocin administration. The haemodynamic effects of an oxytocin bolus are characterized by systemic vasodilation, which leads to significant hypotension, tachycardia, and an increase in cardiac output. These effects are observed in a dose-dependent manner, as documented in previous studies.[12-14] The occurrence of haemodynamic side effects, particularly in patients with hypovolaemia or cardiac diseases, has the potential to result in myocardial ischemia.[15] According to a recent study conducted by Moertl et al., it was found that patients who received oxytocin treatment exhibited a more significant decrease in blood pressure and experienced a more pronounced rebound in their cardiovascular system compared to patients who received carbetocin treatment. The effects on the cardiovascular system were found to be similar between the two treatment groups.[16]

We concur with the findings, as we observed a favorable hemodynamic profile in the carbetocingroup, characterized by relatively stable systolic and diastolic blood pressure levels throughout the surgical procedure. Additionally, we noted lower blood pressure levels in the control group at various time points following drug administration. However, it is important to note that these differences were not consistently statistically significant, indicating a tendency rather than a definitive outcome. The findings of this study indicate that carbetocin exhibits a satisfactory hemodynamic safety profile. At present, the use of carbetocin is contraindicated in cases of pre-eclampsia, eclampsia, and general anesthesia. However, the findings of this study propose a potential revision of these contraindications, thereby expanding the therapeutic indications for carbetocin administration.

In their studies published in the Cochrane database in 2007 and 2012, Su et al. examined the efficacy of oxytocin agonists, specifically carbetocin, in preventing antenatal. Their findings suggest that carbetocin may be more effective than oxytocin in preventing antenatal in women who undergo caesarean section. However, it is important to note that the available data and evidence were deemed insufficient to draw definitive conclusions.[17]

In the literature pertaining to carbetocin, Danzereau et al,[18] initially reported a reduced requirement for supplementary uterotonic treatment in women who received carbetocin shortly following childbirth, specifically in relation to the management of uterine atony.

In their study, Borruto et al,[19] reported a reduced incidence of requiring additional oxytocic agents in women who received carbetocin during cesarean section (CS). Our findings align with those of other researchers who have reached similar conclusions.[20,21] However, comparing our study with the aforementioned ones is challenging due to the stringent selection criteria applied to our study population based on risk factors. Attilakos et al,[21] excluded placenta previa, multiple pregnancies, and

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pregnant women under 37 weeks' gestation from their study.

A clear absence of supplementary requirement for uterotonic agents following cesarean section (CS) is observed in women at high risk for normal antenatal who receive carbetocin. Additionally, our findings indicate the efficacy of carbetocin in comparison to oxytocin with respect to uterine contraction and tonicity. Our findings demonstrate that the group administered with carbetocin exhibited improved uterine contractility at 2, 12, and 24 hours following caesarean section. Additionally, patients in group A displayed a significantly lower fundus position, measuring below 2 cm from the umbilical point (-2UP), after 2 and 12 hours.

The study findings indicate that there was no significant variation observed in the quantity of blood loss following caesarean section, as well as in the decline of haemoglobin levels within the timeframes of 24 hours. However, it was observed that the oxytocin group exhibited a notable requirement for supplementary uterotonic agents. Prior research has indicated that the administration of carbetocin has been associated with the occurrence of maternal tachycardia and facial flushing.[22,23] However, in our specific subgroup analysis focusing on carbetocin, none of the participants experienced these adverse events. The investigation into the impact of carbetocin on diuresis dates back to the early 1960s, when clinical observations revealed that the administration of high doses of oxytocin to obstetric patients resulted in antidiuresis, suggesting similarities to the effects of vasopressin.[24,25]

Indeed, the synthesis of these two hormones occurs within the hypothalamus of human beings. Subsequently, they are transported via the neurohypophysial tract to the posterior pituitary gland, where they are either stored or secreted. Additionally, these hormones exhibit significant similarities in terms of their chemical structure.[26]

In recent years, there has been a growing body of research focused on investigating the molecular mechanisms underlying the antidiuretic effect. Specifically, these studies have explored the impact of this effect on the renal acquaporin water channels found within the cells of the collecting duct. It has been observed that these effects can manifest both in the short-term and long-term, and are mediated by V2 receptors. The prolonged impact results in heightened expression of AQP, while the immediate effects entail the transportation of AQP to the apical membrane of the principal cells.[27,28] Hence, it can be inferred that oxytocin functions as an antidiuretic hormone, imitating the immediate effects of vasopressin on water permeability, albeit with slightly reduced effectiveness.[29] Furthermore, prolonged administration of oxytocin may induce antidiuresis, leading to water intoxication.[24,25]

Within the realm of literature, there exists a solitary investigation that examines the impacts of carbetocin and oxytocin on diuresis. This study reveals that carbetocin possesses a moderate antidiuretic effect, yet fails to demonstrate any statistically significant disparity in urine output between women subjected to carbetocin or oxytocin treatment.[30]

In contrast to the aforementioned findings, our study reveals a notable reduction in diuresis at 24-hour marks following caesarean section in the oxytocin group (group B). Conversely, we observe a significantly greater diuresis in the carbetocin group (group A) compared to the oxytocin group, particularly at the 24-hour mark post-caesarean section. Hence, although carbetocin is classified as a synthetic analogue of oxytocin, the slight variance in its molecular structure plays a crucial role in not only enhancing its uterotonic properties but also differentiating its biological function, specifically by eliminating the antidiuretic effect. This finding holds significant implications in the ongoing efforts to establish a more comprehensive understanding of the profile of carbetocin.

CONCLUSION

The administration of a solitary dose of carbetocin demonstrates a safer hemodynamic profile and reduced requirement for uterotonics.

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