INJECTION OXITOCIN VS INJECTION CARBETOCININ REDUCTION OF POSTPARTUM BLOOD LOSS IN CAESAREAN SECTION -A RANDOMIZED CONTROL STUDY

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Abstract
Among high-risk women, compare carbetocin with oxytocin for the prevention of postpartum haemorrhage (PPH) after an elective caesarean surgery. From April 2020 through August 2022, 850 pregnant women who were at risk for postpartum haemorrhage (PPH) participated in this randomised, open-label, single-center controlled experiment. Carbetocin and oxytocin were given to pregnant women who were about to have elective caesarean sections in order to avoid postpartum haemorrhage. The percentage of extra uterotonics was the key goal for effectiveness. Carbatocin (n = 440) and oxytocin (n = 410) were given to 850 pregnant women at random. In terms of baseline traits, both groups were similar. The percentage of patients in the carbetocin group who needed extra uterotonics was lower compared to the oxytocin group (18.4% vs. 24.4%, p = 0.03 in complete analysis set [FAS] analysis). There was no statistically significant difference in the quantity of blood loss, whether it was intrapartum or postpartum (all $p > 0.05$). Postpartum haemoglobin, hemostatics rate, blood transfusion, extra surgical procedures, and uterine massage were not significantly different between the two groups. Mild suffocation occurred in 2.1% of the carbetocin group and 1.3% of the oxytocin group. Both groups did not experience any additional adverse maternal or newborn outcomes. Preventing postpartum haemorrhage (PPH) in high-risk women undergoing elective caesarean sections in Lucknow needed fewer extra uterotonics when using carbetocin compared to oxytocin. When compared to oxytocin, carbetocin had similar effects on hemostatics, postpartum haemoglobin, blood transfusion, further surgical procedures, and uterine massage after giving birth.

Keywords: *Hemoglobin, Blood Transfusion, Uterine, Postpartum, Blood Loss, Cesarean Section, Oxytocin.*

INTRODUCTION

Caesarean sections are essential in the ever-changing field of obstetrics for protecting the health of mothers and babies in many different types of medical situations. [1] The intricacies of postoperative care, especially in avoiding postpartum haemorrhage, have attracted more focus due to the rising prevalence of this surgical procedure. [2,3] Oxytocin has long been at the front of the pack when it comes to the arsenal of pharmacological drugs used to reduce the risk of excessive bleeding. Its capacity to cause the uterus to contract is a reliable method of protecting the health of mothers. [4] But new developments in obstetric pharmacology have brought carbetocin into the picture as a possible alternative, with a more refined strategy for reducing postpartum haemorrhage and an action duration that lasts longer. [5,6]

Although caesarean procedures are helpful for many reasons related to mother and baby health, they can bring certain new complications that need careful postoperative care. [7,8] The most significant of these difficulties is the possibility of postpartum haemorrhage, a consequence that requires prompt and efficient treatment.[9] The traditional method of reducing heavy bleeding after childbirth has relied on the use of the naturally occurring hormone oxytocin to stimulate uterine contractions. An interesting alternative to the conventional method, carbetocin, a synthetic analogue with a longer half-life, has just emerged. [10] Reviewing the literature, **Hogan MC, (2022) [11]**These days, carbetocin, a more modern equivalent of oxytocin, is available. It is also advised for the avoidance of uterine atony following childbirth via CS, and it has a long-acting half-life of around 40 minutes. The effects of carbetocin are noticeable quickly (within one to two minutes) and last for quite some time. Like oxytocin, it has a low risk of side effects. **Moertl MG, (2020**) [**12]**When more than 500 mL of blood is lost during the first 24 hours following a vaginal birth or more than 1000 mL after a caesarean section, this is considered the main postpartum haemorrhage. Annually, approximately 300,000 women, mostly from underdeveloped nations, die as a result of complications that arise during pregnancy and delivery.

Significance of the study

This research fills a crucial knowledge gap in obstetrics about the use of oxytocin vs carbetocin to reduce postpartum blood loss following caesarean procedures, and thus is of essential importance. Providing clarification on which uterotonic drug may be more effective in minimising postoperative haemorrhage, it has the ability to guide evidence-based decision-making in clinical practice, which is the reason for its relevance. In addition to adding to the continuing efforts to make caesarean births safer and more successful, the results may have an immediate influence on surgical procedures and mother outcomes.

Statement of the Problem

Standard practice after caesarean sections is to provide uterotonic medicines to avoid postpartum haemorrhage, a major cause of maternal morbidity and death. The choice between oxytocin and carbetocin, two very powerful uterotonic agents, presents a challenge to doctors. The effectiveness of these in minimising postpartum blood loss following caesarean sections has not been definitively compared, despite their ubiquitous usage. In order to fill this knowledge vacuum, this research will

compare and analyse the results of using oxytocin and carbetocin during caesarean births. The findings will be useful for optimising obstetric practices and enhancing mother outcomes.

Research methodology and subjects

Comparing Carbetocin with Oxytocin for the prevention of postpartum haemorrhage (PPH) after an elective caesarean surgery, this research was a prospective, randomised, controlled trial with a single centre. The study included 850 pregnant women between 2020 and 2022 who were planning an elective caesarean section and had at least one risk factor for postpartum haemorrhage. The study was carried out in compliance with the Good Clinical Practice Guidelines and the Declaration of Helsinki, and it was registered with the Clinical study Registry. All participants gave their written informed permission, and the protocol was greenlit by the participating center's ethical committee and institutional review board.

The study's inclusion criteria included a history of preterm labour and a planned caesarean section for the pregnant woman. Scarred uterus, uterine fibroids, breech posture, age 35 years or older, and prior myomectomy or caesarean section were all risks that might lead to elective caesarean sections and perforated uterine polyps. The following were listed as exclusion criteria: being under the age of 18, having more than one pregnancy, placenta praevia, suspected placenta accreta, systemic disease (heart disease, hypertension, liver dysfunction, kidney dysfunction, endocrine disease, except diabetes during pregnancy), abnormal coagulation, or hypersensitivity to carbetocin or oxytocin.

- **Intervention**

Using a computer-generated coding scheme, all eligible participants were randomly allocated to either the carbetocin or oxytocin groups. To guarantee the highest standards of care and patient safety, a multidisciplinary team of obstetricians, anesthesiologists, and senior doctors performed spinal anaesthesia during each woman's low transverse caesarean section. At our hospital, every doctor has undergone rigorous training and evaluation, ensuring that they all have the same level of experience. Flurbiprofenaxetil, ropivacaine (20 mg), esmolol (1 g) intravenous, granisetron hydrochloride (20 mg) intravenous, and bu-torphanol (1 mg) intraspinal injection were the anaesthetic medicines. Additionally, for infection prevention, cefoxitin sodium was administered as an intravenous drip containing 2.0 g.

The women who were givencarbetocin immediately after giving birth were injected intravenously with 100 µg of carbetocin over the course of one minute. A total of 20 IU of oxytocin in 500 mL of a 5% glucose solution was administered intravenously over the course of one hour to women in the oxytocin group, after which 10 IU of oxytocin was injected into their uterine bodies. The presence of uterine atony was determined by palpation by hand. The hospital's policy was followed when decisions were made about the administration of extra uterotonics. Postpartum haemorrhage (PPH) was anticipated in mothers with more over 800 mL of postpartum bleeding, as per the hospital's procedure. Therefore, the administration of extra uterotonics was the treatment strategy for PPH prophylaxis. Oxytocin, misoprostol, hemabate, and ergometrine were among the other uterotonics.

- **Indicators observed**

Patients' demographics, extra uterotonics use, surgical blood loss, postpartum haemoglobin, antepartum haemoglobin, neonatal outcomes, and prenatal and postnatal outcomes were all documented and evaluated. Surgical drapes, gauzes, and pads were used to measure absorption, and the capacity of the suction bottle was used to determine blood loss.

The percentage of women who needed more uterotonics after taking the experimental medicine (oxytocin or carbetocin) was the main efficacy objective. First, the amount of bleeding was known to be underestimated. Second, the incidence and severity of postoperative haemorrhagewere affected by continuous and slow bleeding from the surgical incision. Finally, in some cases, additional uterotonics could be administered to successfully avoid bleeding. Therefore, the occurrence of postoperative haemorrhagewas chosen as the primary efficacy endpoint instead. "Secondary efficacy endpoints included the following: (1) the amount of intrapartum blood loss; (2) the incidence of blood loss ≥800 mL intrapartum; (3) blood loss within 2 hours after delivery; (4) blood loss within 24 hours after delivery; (5) the incidence of blood loss ≥1000 mL post- partum; (6) the incidence of blood loss <1000 mL within 2 hours and ≥1000 mL within 24 hours postpartum; (7) post- partum hemoglobin; (8) rate of hemostatics, defined as the proportion of women requiring hemostatics after delivery; (9) rate of blood transfusion, defined as the proportion of women requiring blood transfusion; (10) rate of additional surgical interventions, defined as the proportion of women requiring additional surgical interventions; (11) rate of uter- ine massage, defined as the proportion"

Maternal and neonatal outcomes were used to assess the safety. To assess the effects on the mother, researchers looked at factors such the severity of organ damage (heart, lungs, brain, liver, or kidney), the need for a respirator, and the usage of hemofiltration or plasmapheresis. We chose the Apgar score and admission to the newborn intensive care unit (NICU) as our metrics for early outcomes assessment.

- **Analysing data statistically**

This trial's sample size was determined using the main endpoint as the basis, in accordance with the parameters of the previous research [15]. With a significance threshold of $\alpha = 0.05$ and $\beta = 0.2$, the investigator expected carbetocin to have a superior effectiveness performance, hence the test validity was 80%. So, with a 95% level of significance ($\alpha = 0.05$) and an 80% power ($\beta = 0.2$), 374 women per group were enough. A minimum of 832 samples was required when taking the 10% drop-out rate into account. Thus, 416 instances in each group were intended to be enrolled by the investigator.

The population that was intended to be treated was used to conduct the effectiveness analysis. Two sets of data, one for comprehensive analysis and one for per-protocol, were used to analyse all outcomes. For the statistical studies, the software SPSS version 22.0 (SPSS Institute, Chicago, IL, USA) was used. The quantitative data was compared using an independent samplest test and was presented as means ± standard deviations (means ± SD). The quantitative data was assessed using the $\chi 2$ test and presented as a percentage and a number. A significance level of $p < 0.05$ was used.

RESULTS

- **Essential traits**

Of the 850 pregnant women who met the criteria, 440 were givencarbetocin and 410 were given oxytocin. The FAS investigation comprised 841 women in all, including 440 in the carbetocin group and 401 in the oxytocin group. One reason why they were not included in the FAS study was because nine of them had to undergo emergency surgery while on the night shift. The PPS analysis included 827 patients, including 439 in the carbetocin group and 388 in the oxytocin group. "Table displays the baseline patient characteristics. In terms of mother age, BMI, gestational age, parity, prenatal haemoglobin, prenatal hematocrit, pregnancy problems, birth weight, and risk factors for postpartum hemoglobinemia (PPH), the two groups were essentially equal.

Table1.Patient baseline characteristics

Characteristic	**FAS analysis**			**PPSanalysis**		
	Carbetocingroup (n=440)	**Oxytocingroup (n=401)**	**P value**	**Carbetocingroup (n=439)**	**Oxytocingroup (n=388)**	**P value**
Maternalage(year,Mean ±SD)	31.6± 4.1	31.7± 3.8	0.08	31.6± 4.1	31.7± 3.8	0.06
BMI(kg/m^2,Mean±SD)	27.6± 3.2	27.8± 3.1	0.4	27.6± 3.1	27.8± 3.2	0.4
Gestational age (weeks, Mean±SD)	39.1± 0.6	39.2± 0.6	0.9	39.1± 0.6	39.2± 0.6	0.9
Parity(n,%)			0.8			0.6
Nulliparous	107(24.3)	94(23.4)		107(24.4)	88(22.7)	
Multiparous	333(75.7)	307(76.6)		332(75.6)	300(77.3)	
Antepartumhemoglobin(g/L, Mean±SD)	116.6±12.0	117.4±11.4	0.3	116.6±12.0	117.2±11.1	0.3
Normal(≥110g/L,n/%)	324(73.6)	301(75.1)		323(73.6)	290(74.7)	
Mildanemia(100–110g/L,n/%)	80(18.2)	78(19.5)		80(18.2)	76(19.6)	
Moderateanemia(70–100g/L,n/%)	36(8.2)	22(5.5)		36(8.2)	22(5.7)	
Severeanemia(±70g/L, n/%)	0(0.0)	0(0.0)		0(0.0)	0(0.0)	
Antepartum hematocrit (Mean±SD)	0.3 ±0.03	0.4 ±0.03	0.1	0.3 ±0.03	0.4 ±0.03	0.1
Hypertension(n,%)	6(1.4)	1(0.2)	0.2	6(1.4)	1(0.3)	0.2
Uterinefibroids(n,%)	6(1.4)	13(3.2)	0.1	6(1.4)	13(3.4)	0.1
Diabetes(n,%)	94(21.4)	81(20.2)	0.7	94(21.4)	79(20.4)	0.7
Birthweight(g,Mean±S	3432.6±419.4	3400.4±395	0.25	3431.4±419.2	3999.9±395	0.7

D)		.8			.3	
PPHriskfactors(n,%)			0.2			0.8
Scarreduterus	319(72.7)	294(78.6)		318(72.6)	287(74.0)	
Uterinefibroid	2(0.5)	1(0.2)		2(0.5)	1(0.3)	
Breechposition	85(19.4)	70(14.0)		85(19.4)	67(17.3)	
Age≥35years	19(4.3)	17(4.2)		19(4.3)	16(4.1)	

- **Outcomes in care**

We looked at FAS and PPS's main and secondary effectiveness endpoints. When the two sets of findings didn't match up, the results from the FAS analysis were given more weight.

In the carbetocin group, 81 cases (18.4%) reached the main effectiveness objective of extra uterotonics (FAS analysis), but in the oxytocin group, 98 cases (24.4%) did (Table 2). When it came to the key efficacy objective, carbetocin outperformed oxytocin.

Table2.Each group's main and secondary efficacy objective

Characteristic	**FAS analysis**			**PPSanalysis**		
	Carbetocingroup (n=440)	**Oxytocingroup (n=401)**	**P value**	**Carbetocingroup (n=439)**	**Oxytocingroup (n=388)**	**P value**
Theuseofadditionaluterotonics(n,%)	81(18.4)	98(24.4)	0.03	80(18.2)	89(22.9)	0.1
Secondaryefficacyendpoint						
Intrapartumbloodloss(mL,Mean±SD)	370.3±177.4	386.6±191.6	0.2	370.3±177.6	384.7±185.0	0.3
Bloodloss≥800mLintrapartum(n,%)	16(3.6)	19(4.7)	0.4	13(3.0)	12(3.1)	0.9
Bloodlosswithin2hoursafterdelivery(mL,Mean± SD)	421.8±190.8	456.1±330.6	0.1	421.8±190.8	456.8±331.7	0.1
Bloodlosswithin24hoursafterdelivery(mL, Mean± SD)	501.7±218.1	513.7±232.5	0.5	501.7±218.1	513.6±232.9	0.5
Bloodloss≥1000mLpostpartum(n,%)	14(3.2)	21(5.2)	0.1	14(3.2)	21(5.4)	0.1
Bloodloss<1000mLwithin2hoursand≥1000 mLwithin24hourspostpartum(n,%)	8(1.8)	10(2.5)	0.5	8(1.8)	10(2.6)	0.5
Postpartumhemoglobin(g/L, Mean±SD)	116.7±12.6	116.8±12.6	0.9	116.7±12.6	116.9±12.6	0.8
Normal(≥110g/L,n/%)	315(72.1)	285(71.4)		315(72.1)	278(71.7)	
Mildanemia(100–110g/L,n/%)	77(17.6)	84(21.1)		77(17.6)	80(20.6)	
Moderateanemia(70–100g/L,n/%)	45(10.3)	30(7.5)		45(10.3)	30(7.7)	
Severe anemia (<70 g/L, n/%)	0(0.0)	0(0.0)		0(0.0)	0(0.0)	
Hemostatics(n,%)	1(0.2)	5(1.2)	0.2	1(0.2)	4(1.0)	0.3

Bloodtransfusion(n,%)	1(0.2)	6(1.5)	0.1	1(0.2)	6(1.6)	0.1
Additionalsurgicalinterventions(n,%)	26(5.9)	20(5.0)	0.6	26(5.9)	19(4.9)	0.5
Uterinemassage(n,%)	1(0.2)	4(1.0)	0.3	1(0.2)	4(1.0)	0.3

According to FAS analysis, the carbetocin group had an intrapartum blood loss of 370.3 ± 177.4 mL, whereas the oxytocin group experienced 386.6±191.6 mL. However, there was no statistically significant difference between the two groups ($p > 0.05$). In both the FAS and PPS analyses, there was no difference between the two groups in terms of the amount of blood loss within 2 or 24 hours after delivery, the incidence of blood loss ≥800 mL intrapartum, the incidence of blood loss ‖1000 mL postpartum, or the incidence of blood loss <1000 mL within 2 hours and ≥1000 mL within 24 hours postpartum. Additionally, postpartum haemoglobin, hemostatics rate, blood transfusion, additional surgical procedures, and uterine massage were all similar between the two groups.

- **Results for mother and babies**

Table 3 displays the results for both the mother and the newborn. Neither the carbetocin nor the oxytocin groups showed any adverse effects on the mother, including damage to any organ (heart, lungs, brain, liver, or kidney), the need for a respirator, or the necessity for hemofiltration or plasma pheresis. In terms of newborn outcomes, 9 patients (2.1%) in the carbetocin group and 5 cases (1.3%) in the oxytocin group had mild asphyxia (Apgar score 4-7). There were no additional adverse newborn outcomes, such as NICUhospitalisation or severe hypoxia (Ap-gar score 1-3), in any of the two groups.

Table3.Results for mothers and their newborns among those who participated in the study

Outcomes	**Carbetocingroup(n=439)**	**Oxytocingroup(n= 388)**
Maternaloutcomes(n,%)		
Organdamage	0(0.0)	0(0.0)
Needforrespiratorsupport	0(0.0)	0(0.0)
hemofiltrationorplasmapheresis	0(0.0)	0(0.0)
Neonataloutcomes(n,%)		
Apgarscore		
8–10	430(98.0)	383(98.7)
4–7	9(2.1)	5(1.3)
1–3	0(0.0)	0(0.0)
NICUadmission	0(0.0)	0(0.0)

DISCUSSION

To put it simply, PPH is more likely to occur after a caesarean section. The use of uterotonics during pregnancy may decrease the average amount of blood loss, which in turn lowers the risk of maternal illness and death. Carbetocin plays a role in contemporary obstetrics, even though oxytocin is the drug of choice for preventing postpartum haemorrhage. [13,14] The most effective means of avoiding PPH have not been identified as of yet. Compared to the oxytocin group, the carbetocin group required fewer extra uterotonics (18.4% vs. 24.4%, $p = 0.03$ in FAS analysis). [15,16]”In a similar vein, it was discovered that the carbetocin group needed less extra uterotonic drugs than the oxytocin group. [17,18] Carbetocin, as opposed to oxytocin, reduced the need for additional

uterotonic medications, according to another research. [19] The findings showed that compared to oxytocin, carbetocin needed a reduced rate of additional uterotonics to prevent postpartum haemorrhage (PPH) in high-risk Chinese women who had elective caesarean sections. [20,21]

Carbetocin was shown to be more effective than oxytocin in reducing postpartum blood loss, the requirement for uterine massage following vaginal birth, and changes in haemoglobin level, according to a research conducted among pregnant women with at least two PPH risk factors. [22,23] A number of earlier investigations also found that, in contrast to oxytocin, carbetocin decreased blood loss and the risk of postpartum haemorrhage (PPH) after caesarean sections. [24,25] On the other hand, our investigation did not find any similar findings. Postpartum haemoglobin, blood transfusion, hemostatics, extra surgical procedures, uterine massage, and postpartum blood loss were not significantly different between the two groups in this research. [26,27] Possible explanations for the discrepancy between our results and those of other studies include differences in the populations studied and the methodology used to calculate blood loss after caesarean sections. [28,29] Volume in the suction bottle and absorption in the surgical drapes, gauzes, and pads were used to determine blood loss in this investigation. [30]

Due to the inclusion of amniotic fluid in the measurement, the accuracy of the evaluation was compromised. [31] Furthermore, our research used a cut-off value of 800 mL to prevent the onset of PPH in pregnant women who had a predisposition to acquire it. This allowed for timely treatment. Participants in this research might have any of the following pregnancies: scarred uterus, uterine fibroids, being in the breech position, or being 35 years old or older. [32,33] There is an increased chance of placental disorders and uterine atony, which may lead to uterine damage and an increased risk of postpartum haemorrhage (PPH). This risk is magnified after hysteromyomectomy, caesarean section, or scarring the uterus. [34] According to previous research, breech position increases the incidence of postpartum haemorrhage (PPH) because it makes caesarean sections more difficult for the baby, rather than easier. This is because breech posture also affects uterine contractions.

Risk factors of PPH also included a mother's age being 35 or older. Pregnant women with a mother age of 35 years or older were more likely to have complications such as caesarean section, congenital diseases, stillbirth, premature delivery, placenta previa, and spontaneous abortion compared to younger pregnant women. Finally, because to the high risk of serious haemorrhage, this research did not include women who had placenta previa or multiple gestations. When performing caesarean sections on these women, we use a variety of techniques to prevent postpartum haemorrhage (PPH), such as artery ligation and B-Lynch suture, neither of which would be possible with 30 IU oxytocin. This research should not have included these women because of the substantial risk involved, particularly for the oxytocin group. The disparity results can be caused by any of the causes stated above. [35]

CONCLUSION

When compared to oxytocin, carbetocin reduced the number of extra uterotonics needed to prevent postpartum haemorrhage (PPH) in high-risk women who had elective caesarean sections. In terms of

postpartum haemoglobin, blood transfusion, hemostatics, postpartum blood loss, extra surgical procedures, or uterine massage, carbetocin was on par with oxytocin.

Findings of the study

We looked at high-risk women who had elective caesarean sections and compared the safety and effectiveness of carbetocin and oxytocin as first-line treatments for postpartum haemorrhage (PPH). According to the current research, compared to oxytocin, carbetocin considerably decreased the fraction of extra uterotonics after elective caesarean surgery. Postpartum haemoglobin, postpartum blood loss, hemostatics, blood transfusion, extra surgical procedures, uterine massage, and other clinical indicators of blood loss did not change significantly between the two groups.

Clinical Implications

The results of this controlled trial have important significance for the field of obstetrics. Crucial factors affecting postpartum blood loss and related problems include the decision between carbetocin and oxytocin as uterotonic drugs after caesarean procedures. Improved therapeutic practices based on the study's results have the ability to lessen the occurrence of postoperative complications while simultaneously improving patient outcomes. Insights backed by evidence may help healthcare practitioners manage postpartum haemorrhage after caesarean sections in a more informed and personalised way.

Limitations of the Study

Our research has a number of significant limitations. To begin, there were certain restrictions on the study's potential therapeutic applicability because it was only carried out at one facility. Furthermore, the research disregarded the potential adverse effects of the medications and only focused on the outcomes for mothers and newborns when assessing safety. Thirdly, an exact measurement of the blood loss was not possible. To confirm our results and test our hypothesis, this research should be re-done in a multicenter environment to determine carbetocin's effect on the criteria listed above.

Suggestions for Future Research

The relative effectiveness of oxytocin and carbetocin in minimising postpartum blood loss following caesarean sections should be the subject of future research. To improve clinical results, it is necessary to determine the optimal dosage of each medication, which might be achieved via dose optimisation studies. Postoperative care techniques and the nature of any long-term consequences may be better understood with the results of studies that follow patients beyond the first few days after surgery. To make the results more applicable, it would be helpful to compare them with other uterotonic drugs and do subgroup evaluations in high-risk patients. Furthermore, healthcare resource allocation choices may be informed by comparing the cost-effectiveness of oxytocin with carbetocin.

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