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Research Protocol

Anaesthesia Section

Comparison of Oxytocin versus Carbetocin in Reducing Intraoperative Bleeding during Caesarean Section: A Research Protocol for Randomised Controlled Trial Planned in a Tertiary Care Hospital in Central India

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ABSTRACT

Introduction: Caesarean Section (CS) is a common obstetric procedure associated with the risk of intraoperative bleeding, necessitating the use of uterotonic agents such as oxytocin and carbetocin to reduce blood loss.

Need of the study: Given the clinical significance of intraoperative bleeding during CS and the potential implications for maternal outcomes, there is a need for well-designed comparative studies. Therefore, the present study was planned to address this gap in the literature by comparing the efficacy of oxytocin and carbetocin in reducing intraoperative bleeding during CS.

Aim: To evaluate and compare the effectiveness of oxytocin versus carbetocin in reducing intraoperative bleeding during caesarean sections.

Materials and Methods: A prospective, randomised, double-blind controlled trial will be conducted at the Department of Anaesthesiology, Jawaharlal Nehru Medical College (JNMC), Datta Meghe Institute of Higher Education and Research, Sawangi (M), Wardha, Maharashtra, India from October 2024 to March 2026. One hundred female patients aged 18-35 years with American Society of Anaesthesiologists (ASA) grade I and II, scheduled for CS under spinal anaesthesia, will be included in the study and divided into the oxytocin and carbetocin groups during CS. The amount of blood loss exceeding 1000 mL during CS, haemodynamic changes, the requirement for vasopressors and antifibrinolytics and the duration of surgery will be assessed between the two groups. Statistical analysis will be conducted using experimental and inferential statistics, including the Chi-square test, Student's paired and unpaired t-tests and Tukey test, with a significance level set at $p<0.05$.

Keywords: Antifibrinolytics, Blood loss, Haemodynamic changes, Postpartum haemorrhage, Uterotonic agents, Vasopressors

INTRODUCTION

The CS is one of the most commonly performed surgical procedures worldwide, with rates increasing steadily over the past few decades [1]. While CS is often a life-saving intervention for both maternal and foetal indications, it is associated with various risks, including intraoperative bleeding [2]. Excessive blood loss during CS can lead to maternal morbidity, including Postpartum Haemorrhage (PPH), transfusion requirements and prolonged hospital stays [3]. Uterotonic agents play a crucial role in managing intraoperative bleeding during CS by promoting uterine contraction and reducing blood loss [4]. Oxytocin, a synthetic analogue of the endogenous hormone, is the most commonly used uterotonic agent for this purpose [5]. Carbetocin, a longer-acting synthetic analogue of oxytocin, has also been proposed as an alternative uterotonic agent with potential advantages, including a prolonged duration of action and a reduced need for repeated dosing [6].

Several studies have investigated the efficacy and safety of oxytocin and carbetocin in reducing blood loss during CS [7-10]. However, studies comparing the effectiveness of these agents in reducing intraoperative bleeding are limited. Furthermore, existing evidence regarding the superiority of one agent over the other is inconclusive, with conflicting results reported in the literature [9,10]. Given the clinical significance of intraoperative bleeding during CS and the potential implications for maternal outcomes, there is a need for well-designed comparative studies to evaluate the effectiveness of oxytocin versus carbetocin in this context. Therefore, the present study aims to address this gap in the literature by comparing the efficacy of oxytocin and carbetocin in reducing intraoperative bleeding during CS.

Primary Objectives

1. To compare the amount of blood loss (>1000 mL) between the oxytocin and carbetocin groups during CS.
2. To assess the requirement for uterotonics in both groups for surgical maneuvers during CS in preventing uterine atony and intraoperative haemorrhage, as well as the need for additional uterotonics.

Secondary Objectives

1. To evaluate haemodynamic changes, including heart rate, systolic blood pressure and diastolic blood pressure, following the administration of oxytocin and carbetocin.
2. To compare the requirement for vasopressors after placenta delivery between the two groups.
3. To determine the need for antifibrinolytics after placenta delivery in both groups.
4. To compare the duration of surgery between the oxytocin and carbetocin groups.
5. To compare postoperative complications and length of hospital stay between the oxytocin and carbetocin groups.

Null hypothesis: Carbetocin and oxytocin have equivalent efficacy and safety profiles in preventing PPH during caesarean section.

Alternative hypothesis: Carbetocin is more effective and/or safer than oxytocin in preventing PPH during CS.

REVIEW OF LITERATURE

The use of uterotonics, such as carbetocin and oxytocin, is crucial in preventing PPH during caesarean sections. Several studies have compared the efficacy and safety of these two agents in reducing intraoperative bleeding. A study conducted by Larciprete G et al., compared carbetocin with oxytocin in high-risk patients undergoing caesarean sections. The results showed that a single injection of carbetocin was more effective than a continuous infusion of oxytocin in maintaining adequate uterine tone, with a similar safety profile and a minor antidiuretic effect [11]. Another study by Gürsoy A et al., found that carbetocin was more effective in reducing haemoglobin levels, platelet counts and estimated Blood Loss (eBL) compared to oxytocin. Additionally, carbetocin had fewer negative effects on urine output than oxytocin. However, the study noted that carbetocin is only recommended for preventing PPH and not for other conditions such as birth induction or PPH treatment [12].

In contrast, a retrospective study by Delorme P et al., found that carbetocin was not superior to oxytocin in preventing PPH, despite the advantage of requiring only a single injection [13]. Another study by Kang S et al., compared carbetocin and oxytocin among 852 pregnant women with one or more PPH risk factors. The carbetocin group had a lower proportion of patients requiring additional uterotonics (18.4% vs. 24.4%). There was no significant difference in blood loss, postpartum haemoglobin, haemostatics, blood transfusions, or additional surgical interventions between the groups. The rates of mild asphyxia were similar (2.1% vs. 1.3%). No other adverse maternal or neonatal outcomes were observed. Carbetocin requires a lower rate of additional uterotonics than oxytocin for PPH prevention, with comparable efficacy and safety profiles [14]. A similar study by Arunshankar R et al., reported that the oxytocin group experienced a significant decrease in systolic blood pressure at various time points, as well as lower diastolic blood pressure compared to the carbetocin group. However, there was no significant difference in eBL or primary PPH between the two groups. Notably, the carbetocin group demonstrated a safer haemodynamic profile and reduced the requirement for additional uterotonics. These findings suggest that carbetocin may be a preferable option for preventing PPH due to its more stable haemodynamic effects [15].

Overall, the findings from past literature suggest that carbetocin may be a viable alternative to oxytocin in preventing PPH during caesarean sections, with potential benefits in terms of efficacy and safety. However, further studies are needed to confirm these findings and establish the optimal use of carbetocin in clinical practice.

MATERIALS AND METHODS

A prospective, randomised, double-blind controlled trial will be conducted in the Department of Anaesthesiology at JNMC, Datta Meghe Institute of Higher Education and Research, Sawangi (M), Wardha, Maharashtra, India from October 2024 to March 2026. Ethical approval for the study protocol has been obtained from the Institutional Ethics Committee (IEC) prior to the commencement of the study, with registration number {DMIHER(DU)/IEC/2024/196} on 01-03-2024. The trial has been registered on the CTRI website with the reference number (CTRI/2024/08/071777). All eligible participants will be provided with detailed information about the study's objectives, procedures, risks and benefits. Informed consent will be obtained from each participant or their legally authorised representative before enrollment in the study. Participants will have the opportunity to ask questions and withdraw from the study at any time without repercussion. Recruitment will be carried out throughout the study period, with efforts to ensure a steady flow of participants. Patients who provide consent will be randomly assigned to either the oxytocin or carbetocin group according to the predetermined allocation sequence. Randomisation will be performed using computer-generated software to ensure allocation concealment and minimise selection bias.

Patients and the investigators involved in data collection and outcome assessment will be blinded to the assigned intervention. The study drugs (oxytocin and carbetocin) will be prepared by an anaesthesiologist who will not be involved in patient care or data collection. The drugs will be labeled with the patient's study identification number to maintain blinding. Additionally, the infusion bags containing the study drugs will be identical to ensure blinding for both the patients and the healthcare providers administering the interventions. Only the pharmacist or anaesthesiologist responsible for drug preparation will have access to the allocation sequence and they will not participate in outcome assessment or data analysis. Blinding will help minimise bias and ensure the validity and reliability of the study results.

Inclusion criteria: Female patients aged between 18 to 35 years with ASA grade I or II, scheduled for CS under spinal anaesthesia with singleton pregnancy and term gestation, decision made for CS during labour, patients who have provided signed informed consent will be included in the study.

Exclusion criteria: Patients with ASA grade III or IV, known coagulopathy, hypersensitivity to study drugs, oligohydramnios or polyhydramnios, cardiac disease, including dysrhythmias, hypertension liver, renal, or endocrine disease (except for gestational diabetes), uterine fibroids or suspicion of placental pathology (accreta, previa, or abruption) will be excluded from the study.

Sample size calculation: The sample size for this study is determined based on detecting a clinically significant mean difference in calculated Estimated Blood Loss (cEBL) between the oxytocin and carbetocin groups.

The sample size formula used is as follows:

$$n_2=\frac{(\sigma_1^2+\sigma_2^2/\kappa)(z_{1-\alpha/2}+z_{1-\beta})^2}{d^2}$$

The cEBL is a parameter used in PPH and is calculated using the following formula [16]:

1. Calculated pregnancy blood volume="0.75×{maternal height (inches)×50}+{maternal weight in (pounds)×25}"
2. Percent of blood volume lost=(Predelivery Hct-Postdelivery Hct)/Predelivery Hct.
3. cEBL=Calculated pregnancy blood volume×Percent of blood volume lost.

Mean cEBL in carbetocin group=504.57, Mean cEBL in oxytocin group=639.27

σ1=SD of cEBL in carbetocin group=284.39, σ2=SD of cEBL in oxytocin group=370.59 [12].

For detecting mean difference of 134.7 i.e., Δ=639.27-504.57=134.7 K=1

N=(284.39*284.39+370.59*370.59) (1.96+0.84)2 134.7*134.7=94.28

The total sample size calculated was 94; however, 100 samples will be included in the study. The power of the test is 80.

Interventions:

1. Group O (Oxytocin): Group O comprises 50 patients:
   - An intravenous (i.v.) bolus of 5 IU of oxytocin over one minute [7].
   - Followed by an i.v. infusion of 15 IU of oxytocin in a 500 mL normal saline drip [7,12].
2. Group C (Carbetocin): Group C comprises 50 patients:
   - An i.v. bolus of 100 µg of carbetocin over one minute [7].
   - Followed by an i.v. infusion of 1.5 mL of carbetocin in a 500 mL normal saline drip [7].

Data collection process: The data collection process for this study will involve the systematic and meticulous recording of various parameters and outcomes relevant to the research objectives. This process will be conducted by trained research personnel familiar with the study protocols and procedures. Here is an outline of the data collection process:

1. **Preoperative data collection:**
   - Demographic information: Age, gestational age, parity, obstetric history, etc.
   - Preoperative vital signs: Blood pressure, heart rate, respiratory rate, oxygen saturation.
   - Baseline laboratory investigations: Haemoglobin level, coagulation profile, etc.
   - Preoperative assessment of co-morbidities and risk factors.
2. **Intraoperative data collection:**
   - Administration of study drugs: Type, dose and timing of oxytocin or carbetocin administration.
   - Intraoperative vital signs: Heart rate, blood pressure, oxygen saturation, respiratory rate.
   - Surgical details: Duration of surgery, type of caesarean section (elective or emergency), eBL, use of uterotonics, use of antifibrinolytics, requirement for vasopressors, any intraoperative complications.
3. **Postoperative data collection:**
   - Postoperative vital signs: Heart rate, blood pressure, respiratory rate, oxygen saturation.
   - Postoperative complications: Including but not limited to, PPH, thromboembolic events, allergic reactions and adverse effects of study drugs.
   - Length of hospital stay: Time from surgery to discharge from the hospital.
4. **Follow-up data collection (if applicable):**
   - Follow-up visits: Scheduled follow-up visits to assess for any delayed complications or adverse events.
   - Long-term outcomes: If applicable, long-term outcomes include maternal morbidity, neonatal outcomes and maternal satisfaction with anaesthesia care.
5. **Data management:**
   - Data will be recorded on standardised Case Report Forms (CRFs) or electronic data capture systems.
   - Data will be double-checked for accuracy and completeness.
   - All data will be securely stored and managed in accordance with regulatory requirements and institutional policies.

Outcomes

Primary outcome:

1. **Amount of Blood Loss (>1000 mL):** The primary outcome measure will involve comparing blood loss exceeding 1000 mL between the oxytocin and carbetocin groups during CS. Blood loss will be estimated using standardised techniques such as visual estimation, gravimetric measurement, or cEBL.
   - **Visual assessment:** The obstetrician and anaesthetist will closely monitor the operating room during surgery and estimate blood loss, reporting the amount after the procedure.
   - **Gravimetric measurement:**
     1. The weight of dry and blood-soaked surgical pads (sponges and swabs) will be measured before and after surgery, with the difference indicating the amount of blood absorbed.
     2. The volume of blood in suction canisters will be recorded before amniotomy and subtracted from the volume at the end of the delivery.
2. **Calculated Estimated Blood Loss (cEBL):** A formula will be applied using preoperative and postoperative haemoglobin values to calculate intraoperative blood loss [16,17].

Secondary outcomes

1. **Haemodynamic changes:** Evaluation of changes in heart rate, systolic blood pressure and diastolic blood pressure following the administration of oxytocin and carbetocin. All readings will be recorded at specific time points: one minute, three minutes and five minutes following drug administration, during two distinct periods: while the uterus is being repaired and at the end of the CS procedure. All measurements will be taken with the patient in a supine position.
2. **Requirement of vasopressors:** The need for vasopressor support after the delivery of the placenta will be assessed between the two study groups.
3. **Requirement of antifibrinolytics:** An assessment of the requirement for antifibrinolytic agents after the delivery of the placenta to prevent excessive bleeding.
4. **Duration of surgery:** Comparison of the duration of surgery between the oxytocin and carbetocin groups, reflecting the efficiency and complexity of the surgical procedure.
5. **Postoperative complications:** An assessment of postoperative complications and the length of hospital stay between the oxytocin and carbetocin groups will be conducted to enhance patient care and outcomes, as well as to identify areas for improvement in surgical techniques or patient management.

Quality control and monitoring:

- Regularly monitor and audit data collection procedures to ensure adherence to study protocols.
- Training and retraining research personnel as needed to maintain data quality and integrity.

Criteria for discontinuing or modifying allocated interventions: The allocated interventions may be discontinued or modified based on the following criteria:

1. Development of severe adverse or hypersensitivity reactions to the study drugs.
2. Emergence of complications that necessitate deviation from the planned intervention, as deemed necessary by the attending anaesthesiologist.
3. A patient's request for the discontinuation or modification of the allocated intervention.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 27.0 and GraphPad Prism version 7.0 will be utilised for statistical computations. Descriptive statistics will be employed to summarise the baseline characteristics of the study population, encompassing the mean, median, standard deviation and range for continuous variables, as well as frequencies or percentages for categorical variables. Comparative analysis between the oxytocin and carbetocin groups will be conducted utilising appropriate statistical tests based on data distribution and type, such as the Student's t-test and Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Sensitivity analyses will evaluate the robustness of the findings. Statistical significance will be set at a p-value of <0.05.

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