

**SINGLE-CENTRE, RANDOMIZED, CLINICAL TRIAL OF OPIOID-FREE
ANALGESIA VERSUS ROUTINE OPIOID-BASED ANALGESIA REGIMEN FOR THE
MANAGEMENT OF ACUTE POST-OPERATIVE PAIN FOLLOWING CAESAREAN
SECTION**

ClinicalTrials.gov

NCT04539249

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INTRODUCTION

Background And Rationale

Traditionally, opioid analgesics have been the mainstay of analgesic management of acute post-operative pain due to their effectiveness.¹ However, liberal administration of opioid analgesics to achieve optimum pain control is associated with various side effects including respiratory depression, sedation (with associated impairment of mother and child bonding, delayed initiation of breastfeeding, reduced ambulation and increased risk of thromboembolism), post-operative nausea and vomiting (PONV), constipation, ileus, pruritus, urinary retention, opioid-induced hyperalgesia (OIH), opioid tolerance, dependence and addiction.¹⁻³ Kehlet and Dahl in the early 1990s recommended balanced analgesia or a multimodal approach to the management of acute post-operative pain and paved way for the “multimodal movement”.⁴ This was premised on a previous work by Kehlet that established that a single analgesic drug or technique cannot achieve optimal acute post-operative pain relief that allows normal function without significant side effects.⁵

Apart from combination of drugs, multimodal analgesia also employs different routes for the administration of analgesic agents, and has brought to the fore the roles of non-opioid analgesics, co-analgesics/adjuvant analgesics, peripheral nerve blocks and wound infiltration in the management of acute postoperative pain.⁶⁻⁸ Multimodal analgesia has successfully achieved control of post-operative pain and reduction in opioid related side effects, however, addiction, disability and deaths arising from opioid exposure and abuse have reached disturbing rates. Chronic opioid use and opioid use disorder is associated with intraoperative and post-operative opioid use, especially in previously opioid naive patients.^{3,9-11} Eighty percent of surgical patients receive opioids as a fundamental agent for pain relief.¹² A systematic review reported an incidence of opioid use disorder following opioid prescription for pain as high as 34%.¹³ Caesarean section is a commonly performed surgery and is a common source of initial exposure to opioids in women of reproductive age.⁹

The morbidity and mortality associated with opioid abuse has become of public health importance. Incidence of opioid abuse and related death is alarmingly high in the United States of America (USA),¹⁴⁻¹⁶ and on the rise in Canada,¹⁷ Australia,¹⁸ and in England and Wales.¹⁹ About 560 deaths were recorded in Colorado, USA in 2017 and 47,600 deaths same year in the whole of the USA from opioid overdose.¹⁶ Canada recorded 2,861 apparent opioid-related deaths in 2016,¹⁷ and 1,045 Australians died from opioid overdose in 2016.¹⁸ Nigeria is also experiencing an unprecedented degree of opioid abuse especially of codeine and tramadol.²⁰⁻²²

As a result, the trend in management of post-operative pain is moving towards avoidance of opioids. This is currently driving multimodal analgesia beyond being combinations of one opioid and one non-opioid, or one opioid and two non-opioids, towards a combination of non-opioid and adjuvant analgesics.²³ Opioid-free analgesia; a multimodal analgesia technique that combines non-opioid and adjuvant analgesics on a regular scheduled basis, with the use of opioids limited to rescue analgesia only if required, has a potential to tackle the fast rising and spreading opioid crises.^{24,25} Opioid-free analgesia also utilizes the principle of preventive analgesia; multimodal analgesia coverage starting pre-operatively and continued intraoperatively and post-operatively, to limit the intensity of post-operative pain through prevention of primary and secondary hyperalgesia, from nociceptive stimuli induced by surgical tissue injury.²⁶ Non-opioid analgesics,

adjuvant analgesics and techniques that have been studied for management of post-operative pain include paracetamol, NSAIDs (e.g. diclofenac, ketorolac, and ibuprofen), ketamine hydrochloride, magnesium sulphate, gabapentin, pregabalin, clonidine, dexmedetomidine, and bupivacaine, ropivacaine; for peripheral nerve block and wound infiltration.^{7,8}

Successful reductions in the peri-operative opioid consumption by up to 70% with implementation of opioid-free analgesia regimens have been documented.²⁷⁻²⁹ Paracetamol and a NSAID are considered basic components of a standard opioid-free analgesia regimen because apart from being safe, cheap and readily available, they offer superior analgesia and reduction of opioid consumption by their synergistic effect.³⁰ The effectiveness and opioid sparing effect of combined diclofenac suppository and intravenous paracetamol for post-operative pain after caesarean section is known and documented.³¹

A notable previous effort towards an opioid-free analgesia regimen for the management of acute post-operative pain was made by the Procedure Specific Postoperative Pain Management (PROSPECT) working group.²³ The PROSPECT working group is made up of surgeons and anaesthesiologists with procedure-specific management of post-operative pain as part of their aim. PROSPECT recommendations are based on consensus after undertaking systematic reviews of literature and reviews are updated as new data becomes available. Based on a systematic review performed until 2014, PROSPECT recommendation for caesarean section combines oral gabapentinoid preoperatively, neuraxial anaesthesia + intravenous paracetamol + intravenous NSAID + transversus abdominis plane block or iliohypogastric/ilioinguinal block or wound infiltration with local anaesthetic intraoperatively, then intravenous paracetamol + intravenous NSAID ± continuous wound infiltration with local anaesthetic, while systemic opioid is limited to rescue analgesic (if required) post-operatively.³²

Some drawbacks to this PROSPECT recommendation for caesarean section are that abdominal wall block techniques are not yet commonly practiced by obstetricians, the role of some of the techniques is still debatable^{33,34} and the combination of routes of administration and techniques recommended is in our opinion cumbersome and invasive. It is noteworthy that the PROSPECT recommendation only reflects how opioid-free analgesia can be achieved in principle and no multimodal peri-operative analgesia regimen can be considered sacrosanct at least at present.⁸ While efforts towards solving the ongoing opioid addiction crisis by addressing the contribution of peri-operative administration of opioids continue, in resource-limited settings especially, a readily available, less cumbersome, cheap and effective opioid-free analgesia regimen which can obviate or at least reduce peri-operative opioid consumption and can give a comparable degree of analgesia to opioid-based analgesia is necessary.

This study sets out to determine the effectiveness and safety of a combination of peri-operative intravenous magnesium sulphate, intravenous paracetamol, and post-operative rectal diclofenac as opioid-free, multimodal analgesia for management of acute post-operative pain after a caesarean section. Studies have shown that administration of magnesium sulphate in the peri-operative period prolongs the duration of spinal anaesthesia and decreases post-operative pain and opioid use without side effect.³⁵⁻⁴⁰ Our goal for presenting our protocol for this study is so that it may be replicated in other settings and possibly modified for future studies. In addition, if this study finds that peri-operative intravenous magnesium sulphate, intravenous paracetamol, and post-operative rectal diclofenac significantly reduces post-operative opioid consumption and is as effective and

safe as the opioid-based analgesia regimen compared, it will help reduce opioid prescription for women undergoing a caesarean section and join the efforts towards solving the ongoing opioid addiction crisis.

OBJECTIVES

General Objective

To determine the effectiveness; primarily, and the safety of a combination of peri-operative intravenous magnesium sulphate, intravenous paracetamol, and post-operative rectal diclofenac as opioid-free multimodal analgesia regimen for the management of acute post-operative pain, in women undergoing caesarean section.

Specific Objectives

- To determine current pain intensity in the first 24 hours after a caesarean section using the numerical rating scale for pain (NRS).
- To compare pain intensity in opioid-free analgesia treated women to that in opioid-based analgesia treated women.
- To determine and compare the need for rescue opioid analgesic among opioid-free analgesia treated women and opioid-based analgesia treated women.
- To determine adverse events associated with the opioid-free analgesia regimen.
- To determine the prevalence of opioid-related adverse events in opioid treated patients.

RESEARCH QUESTION AND HYPOTHESES

Research Question

This study sought to answer the question below.

Will peri-operative administration of intravenous magnesium sulphate, intravenous paracetamol, and post-operative rectal diclofenac (a) obviate or at least reduce peri-operative opioid consumption (b) be as effective and safe, as a routine opioid-based multimodal analgesia regimen in the management of acute post-operative pain in women undergoing caesarean section?

Study hypothesis

Null Hypothesis: Combination of intravenous magnesium sulphate, intravenous paracetamol, and rectal diclofenac as analgesia regimen for acute post-operative pain after a caesarean section is not as effective and safe as a routine opioid-based multimodal analgesia regimen used in the study setting.

Alternative Hypothesis: Combination of intravenous magnesium sulphate, intravenous paracetamol, and rectal diclofenac as analgesia regimen for acute post-operative pain after a caesarean section is as effective and safe as a routine opioid-based multimodal analgesia regimen used in the study setting.

METHODS: TRIAL DESIGN, PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Trial Design

Single-centre, non-inferiority, parallel, randomized, controlled, clinical trial with balanced randomization [1:1] into two arms.

Study Setting

This study will be conducted in the department of Obstetrics and Gynaecology of the Federal Medical Centre, Yenagoa, Bayelsa State, Nigeria. The hospital is a tertiary level health facility, with its main facility situated in Yenagoa, the capital of Bayelsa State, and an annex at Otuoke; a town in Ogbia local government area of Bayelsa State. The hospital receives patients directly, and serves as a referral hospital to all the primary and secondary level health facilities in the State, to private hospitals in Yenagoa and its environs, and also to the State-owned university teaching hospital. Bayelsa State has a population of about 1,700,000 people. The hospital records an average of 1800 deliveries annually. Unpublished data from the facility during the study period showed a hospital level caesarean section rate of 30.8%.

Study Population

The study population will be pregnant women who had caesarean section at the Federal Medical Centre, Yenagoa, Bayelsa State during the study period.

Eligibility criteria

Eligibility will be determined through relevant information obtained from case folders and history obtained from the women. Table 1 shows the eligibility criteria for the study.

Table 1: Eligibility criteria

Inclusion Criteria:	Exclusion Criteria:
<ol style="list-style-type: none">1. Pregnant women booked for elective, scheduled and urgent caesarean section at the Federal Medical Centre, Yenagoa, Bayelsa State during the study period.2. Pregnant women who give consent to participate in the study.	<ol style="list-style-type: none">1. Pregnant women with active peptic ulcer disease, active liver disease, hepatic failure, and renal failure.2. Pregnant women with previous history of ischaemic heart disease/myocardial infarction, heart failure, venous thrombosis and stroke.3. Hypersensitivity to pentazocine, paracetamol, diclofenac or magnesium sulphate.4. Pregnant women with history of non-medical use (abuse) of opioids.5. Pregnant women on magnesium sulphate or have a clinical indication to receive magnesium sulphate.6. Pregnant women booked for emergency caesarean section (because the urgency may not allow time for adequate patient counseling before recruitment).

	<ol style="list-style-type: none"> 7. Pregnant women booked for caesarean section under general anaesthesia or epidural anaesthesia. 8. Pregnant women who can neither communicate in English nor colloquial English.
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Trial team recruitment and care team education

Research assistants were recruited and trained for the study. The research assistants who will assess pain intensity in the women were trained by a consultant anaesthetist. Part of their training was to resist the temptation to disbelieve the women's expression and self-report of pain. Cooperation by doctors, anaesthetists and surgical nurses during this study was ensured by prior presentation of the study to the Obstetrics and Gynaecology department and the relevant anaesthesia and surgical nursing units of the hospital. Interventions for groups A and B and instructions to anaesthetists were also printed out boldly and pasted on the wall of the theatre in a conspicuous manner.

Intervention

After preloading, all the women will receive spinal anaesthesia with 2 ml [10 mg] of hyperbaric 0.5% bupivacaine (Marcaine® - Aspen Pharma Trading Limited, Ireland) into the subarachnoid space, and patients will be laid supine immediately. This fixed dose of bupivacaine was chosen instead of height and weight-adjusted dose to make the protocol easy to follow for the anaesthetists. It is backed by evidence from a randomized controlled trial showing that a fixed dose of 10 mg of hyperbaric 0.5% bupivacaine had similar results to height and weight-adjusted dose in spinal anaesthesia for caesarean section⁴¹

Participants in intervention arm A will receive a combination of peri-operative intravenous magnesium sulphate (ANCALIMA® - LIFESCIENCES LTD, India), intravenous paracetamol (THERMODOL® - Unosource Pharma, India), and post-operative rectal diclofenac (LOFENAC® - BLISS GVS PHARMA LTD, India) as follows: 1g of intravenous paracetamol as an infusion slowly over 15 minutes, then 4g of a 20% solution of magnesium sulphate as an intravenous bolus slowly over 10 minutes preoperatively; during preloading for spinal anaesthesia. Thereafter, continuous infusion of 1g/hr of a 20% solution of magnesium sulphate will be delivered with a syringe pump intraoperatively (commenced at the time of skin incision) until the first 2 hours post-operatively. Post-operatively; immediately after wound dressing and patient cleaning, 100 mg of suppository diclofenac will be administered. Intravenous paracetamol 1g will be continued 6-hourly and suppository diclofenac 100 mg continued 12-hourly, both over 24 hours post-operatively.

Participants in intervention arm B will receive a combination of intramuscular pentazocine (ZOPENT® - GREENLIFE PHARMACEUTICALS LTD, Nigeria), intravenous paracetamol (THERMODOL® - Unosource Pharma, India) and rectal diclofenac (LOFENAC® - BLISS GVS PHARMA LTD, India) as follows: 100 mg suppository diclofenac post-operatively immediately after wound dressing and patient cleaning. Thereafter, intramuscular pentazocine 30 mg (45 mg if patient is > 70 kg) and intravenous paracetamol 1g will be commenced and administered 6-hourly. Suppository diclofenac 100 mg will be continued 12-hourly, all for 24 hours post-operatively.

Rescue analgesia will be allowed in this study outside the prescribed analgesia regimen for both arms of the study if needed. Intramuscular pentazocine 30 mg (45 mg if patient was > 70 kg) will be used as rescue analgesia. It will be administered only on patients' expression of moderate to severe pain or following an assessment of moderate to severe pain by ward nurses/research assistants, despite the planned analgesia regimen for both arms of the study.

There will be no blinding at this stage of the study. Thus, the participants, the researcher, the research assistants who will be involved in administration of the peri-operative analgesics and the research assistants and nurses who will be involved in administration of the post-operative analgesics will be aware of the allocated arm.

Primary Outcome Measures

The primary outcome measures to be evaluated are post-operative pain scores following caesarean section at 4, 8 and 24 hours post-operative and post-operative pentazocine use, pentazocine use as rescue analgesia, frequency of pentazocine use and cumulative dose of pentazocine used during the first 24 hours post-operative.

Secondary Outcome Measures

The secondary outcome measures to be evaluated are incidences of magnesium-related adverse effects including hypersensitivity reaction, respiratory depression, bradycardia, hypotension, nausea and vomiting, lightheadedness, presyncope, and any other adverse event recorded from the time of first administration of peri-operative analgesia to 2 hours postoperative. Others are the Apgar scores of the neonates at the first and fifth minutes after birth and incidences of opioid-related adverse effects including constipation, ileus, pruritus, urinary retention and any other adverse event recorded during the first 24 hours post-operative.

Participant Timeline

This trial is planned to commence in November, 2020. All measurements will be taken during the intervention phase. There will be no follow-up phase.

Figure 1 is a flow diagram of the steps to be taken to conduct this study.

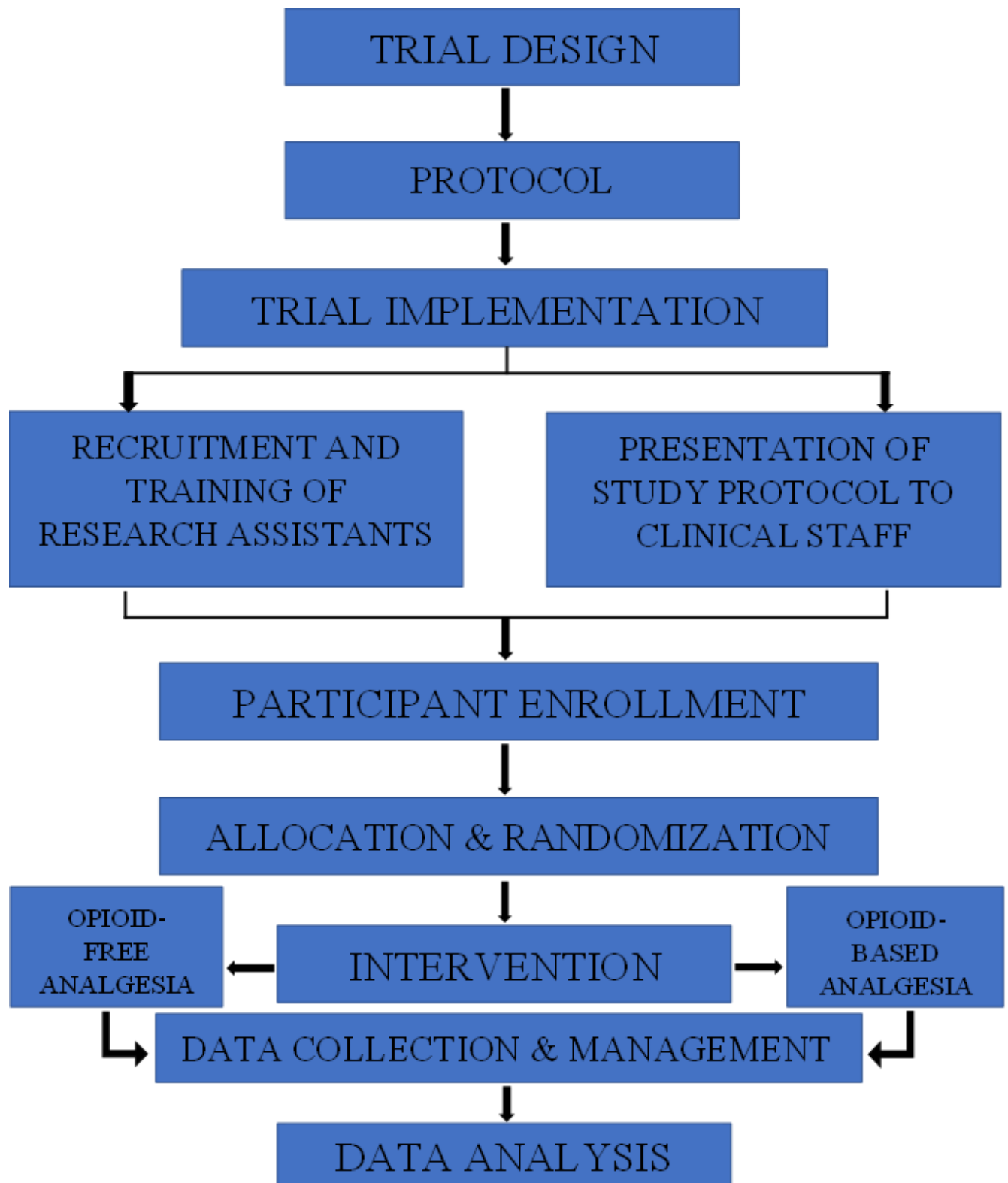


Figure 1: Study flow diagram

Sample Size Calculation

Sample size was determined using the formula for sample size determination for non-inferiority clinical trials⁴²; $n = 2 (Z_{1-\alpha} + Z_{1-\beta})^2 \times SD^2 / d^2$; where n is the minimum sample size. Giving a level of significance (α) of 0.05 and power ($1 - \beta$) of 80%, then $Z_{1-\alpha}$ is the standard normal deviate at 95% confidence interval (1.96) and $Z_{1-\beta}$ is the standard normal deviate for power of 80% in this study (0.84). SD is the standard deviation of the pain intensity after caesarean section (primary outcome measure) in a study done in Brazil and reported as 2.2,⁴³ and d (non-inferiority limit) = 1.3, as derived from a previous study.⁴⁴

Therefore, $n = 2 (1.96 + 0.842)^2 \times 2.22^2 / 1.32^2 = 44.97$; approximately 45. Using an attrition rate of 10%, this minimum sample size was increased by 5 (10% of 45). Fifty women will be selected into each arm of this study, giving a total sample size of 100.

Recruitment

Participants will be enrolled into the study in order of appearance, based on their eligibility and willingness to participate in the study (consecutive recruitment). All women being prepared for urgent, scheduled or elective caesarean section will be met by the researcher or trained assistant in the antenatal ward or labour ward. After the researcher or a trained research assistant has explained the aim and processes of the study and its benefits to eligible women in simple and clear terms, and an assurance of safety is given, participants who express an understanding of the study and show willingness to participate will be given the consent form for the study to sign.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation Sequence Generation

Participants were allocated to receive either an opioid-free multimodal analgesia regimen in the intervention arm A (experimental) or a routine opioid-based multimodal analgesia regimen in the intervention arm B (control). Using the WINPEPI software for randomization, a random and balanced allocation [1:1] of numbers 1 to 100 to letters A and B was conducted by the Researcher.

Allocation Concealment Mechanism

Identical and opaque envelopes were labelled outwardly using serial numbers from 1 to 100. The envelopes had cards inscribed with letter A or B concealed within them according to the randomly assigned letter to each number from 1 to 100. They were then sealed and sequentially arranged.

Implementation

As each eligible woman are received into the theatre for a caesarean section, a research assistant will pick an envelope according to the sequence. The letter inscribed on the card in the envelope will be announced and shown to the researcher, anaesthetist and peri-operative nurse (A = experimental arm and B = control arm). The serial number / identification number on the envelope selected will be attached to the case folder, operation note and other documents for the study.

Blinding (masking)

The research assistants who will assess the post-operative pain intensities (primary outcome measure) and that who will be responsible for data entry will be blinded in this study.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data Collection Methods

The weight and height of the women will be measured and recorded with other biodata of interest. The respiratory rate, pulse rate and blood pressure of the women will be measured using patient monitor on admission to the theatre and noted. The lowest values of these parameters from the time of first administration of peri-operative analgesia to 2 hours post-operative will be obtained from the anaesthesia chart. Any adverse event during this period will also be recorded. The Apgar scores of the neonates at the first and fifth minutes after birth will be recorded. Forms will be provided on the ward to record any opioid-related adverse event and any other adverse event occurring during the first 24 hours post-operative. Hypotension for the purpose of the study is defined as a systolic blood pressure < 90 mmHg and/or a diastolic blood pressure < 60 mmHg. Bradycardia is defined as a pulse rate < 60 beats per minute and respiratory depression as a respiratory rate < 12 cycles per minute.

Pain assessment for this study will rely on the women's self-reporting of pain intensity and such reports will be recorded exactly as stated by the women. Trained and blinded research assistants will assess the post-operative pain intensities of the women at 4, 8 and 24 hours after the surgery using the Numerical Rating Scale (NRS) for pain (they are house officers who will be rotating through other postings other than obstetrics and gynaecology at the time of the study). It will be ensured that all the trial documents are concealed in an opaque envelope during their visits to the ward.

At 48 hours post-operative, the researcher will obtain records of pentazocine use during the first 24 hours after caesarean section from the drug chart of the women using a purpose designed proforma. This will include the frequency of pentazocine administration and the cumulative dose of pentazocine administered during the first 24 hours post-operative. Forms and proformas to be used during the study are shown in appendix 1 – 5.

Data Management

The envelopes containing the trial documents will be retrieved by the researcher at 48 hours post-operative for each participant. A Microsoft excel spreadsheet template designed to capture all the participant information and assessment obtained in the study was saved electronically by a blinded research assistant responsible for data entry. The retrieved envelopes will be sent to this research assistant for data entry into the excel spreadsheet on weekly basis. During weekly data entry, participants will be identified by the serial number / identification number on the envelope and trial documents. At the completion of the study, the allocation information (A or B) for each participant will be disclosed to the research assistant for inclusion in the data by matching with the serial number / identification number previously entered. The completed data will thereafter be sent to the data analyst.

Data Monitoring

As part of the protocol of the research ethics committee of our institution for internal audit of clinical trials, a research auditor will be appointed to inspect the study materials and occasionally observe the study procedure. Adverse events or serious adverse events will be reported to the office of the research ethics committee of the Federal Medical Centre, Yenagoa at intervals. Filled study forms and proforma that will be collated will first be sent to the office of the research auditor, where they will be assessed for substantial compliance with the protocol for the study.

Statistical Methods

An intention-to-treat (ITT) analysis will be performed as the primary analysis for the study. Statistical analysis of the data obtained from the study will be done using Statistical Package for Social Sciences (SPSS) version 22. Frequencies and percentages of categorical data will be determined. Mean and standard deviation of numerical data will also be determined. Continuous data like pain score, age, weight and dose of pentazocine used will be assessed for normality using the Shapiro-Wilk statistical analysis test. Normally distributed data will be compared between experimental and control groups using Student 't' test. Non-normally distributed data will be compared using a Mann-Whitney U test. Chi-square test of proportions will be used to compare categorical data like age-range, ethnicity, parity, pentazocine use, frequency of pentazocine use between experimental and control groups. A p-value < 0.05 will be considered significant statistically. If there are statistically significant differences in covariates like age, age-range, ethnicity, parity and weight between the experimental and control groups, a multivariate analysis will be carried out to determine associations with the outcome measures. A clinically relevant difference in mean pain score of NRS < 1.3 will be the basis for non-inferiority of experimental group to control group.

Ethical Considerations

The study protocol was approved by the institutional review board in the study centre on August 17, 2020 and updated on October 12, 2020.

Other ethical considerations for the study include voluntary participation, informed consent, respectful care, confidentiality, beneficence, non-maleficence and safety of researchers. Steps to be taken to address these ethical issues are elaborated in Table 2.

Table 2: Ethical considerations

Voluntary Participation, Informed Consent, Respectful Care and Confidentiality

After an explanation of the aims and processes of this study to an eligible pregnant woman in simple and clear terms, she reserves the right to voluntarily participate in the study and to give a written informed consent. She also reserves the right to withdraw from the study at any stage if she so wishes. Data obtained from this study will be anonymized to ensure the confidentiality of participants.

Contents of such counseling included:

1. The procedure to be followed in the study,
2. The benefits to the individual,
3. The discomforts and risks that are reasonably expected,
4. The options of therapy,
5. The willingness of the investigator to answer questions,
6. The right to refuse or to withdraw from the study without prejudice.

The language of communication will be English language, but where the patient does not understand English language, she will be communicated to in colloquial English.

Every woman will be treated with fairness, equity and a sense of human dignity, irrespective of the age, socioeconomic circumstance, ethnic or religious lineage.

Beneficence

1. If this study suggests that a combination of intravenous magnesium sulphate, intravenous paracetamol and rectal diclofenac as preventive, opioid-free, multimodal analgesia for acute post-operative pain after caesarean section is as effective and safe as the routine opioid-based multimodal analgesia regimen used at Federal Medical Centre, Yenagoa,
then,
 - I. Pregnant women who participated would have contributed to efforts needed to address opioid abuse and addiction attributable to peri-operative administration of opioids.
 - II. Pregnant women who participated in the experimental arm would also have had the opportunity to avoid repeated administration of opioids peri-operatively thus prevent abuse and associated sequelae.
2. The cost of all analgesics administered for control of acute post-operative pain after caesarean section was taken off the participants in the study and born by the investigator.

Non-Maleficence

The participants in this study will not be subjected to harm in any way. Drugs to be used in this study are drugs with already known side effects and established safety profiles. Drugs with the same batch number were sourced from reliable drug companies with reputation. Any patient with contraindication to administration of any of the drugs will be excluded the study. Calcium gluconate/calcium chloride and naloxone; antidotes for magnesium toxicity and opioid-induced respiratory depression respectively, will be made available during the study, although these complications are rarely encountered from clinical experience with the use of these drugs within the stipulated dose range. Emergency drugs to manage hypersensitivity reactions (should they occur despite precautionary measures taken) will be made available.

Safety of Researchers

Appropriate Infection Prevention and Control (IPC) measures will be ensured during the course of the research. Research assistants engaged in the study were given a refresher course on the use of personal protective equipment and safe administration of parenteral medications.

Availability of Data and Materials

Study materials to be used are attached as appendices to this protocol. Once the data analysis for the study described in this protocol is complete, the datasets analysed will be available from the corresponding author on reasonable request from 3 months after publication of results.

Dissemination of Results

At the results stage of the study, the protocol and results will be submitted to clinicaltrials.gov as required. Study results will be published in a peer-reviewed, open access journal. The authors will also seek to present the study in professional scientific conferences.

DISCUSSION

To the best of our knowledge, no study has specifically assessed the effectiveness and safety of a combination of peri-operative intravenous magnesium sulphate, intravenous paracetamol, and post-operative rectal diclofenac as opioid-free analgesia for management of acute post-operative pain after a caesarean section. Similar to the PROSPECT recommendation, our study protocol adopted the use of intravenous paracetamol and intravenous NSAID as baseline analgesics. We chose to introduce magnesium sulphate as part of our opioid-free multimodal analgesia regimen because of its adjuvant analgesic effect established from studies that found that administration of magnesium sulphate in the peri-operative period decreases post-operative pain and opioid use without side effect.³⁵⁻⁴⁰ We also relied on the preventive analgesic effect of administration of intravenous paracetamol and intravenous magnesium sulphate before surgical incision, continued intraoperatively and post-operatively. Our regimen is less cumbersome and less invasive compared to use of abdominal wall block techniques. In addition, magnesium sulphate is a familiar drug to the obstetrician, readily available and affordable in most settings where comprehensive emergency obstetric care is offered, easy to administer and it has been well tolerated clinically.

After the commencement of our study by this protocol, the PROSPECT recommendation for caesarean section was updated by December, 2020, following an updated systematic review of literatures on post caesarean section analgesia between May, 2014 and October, 2020.⁴⁵ The new recommendation saw the addition of intraoperative intravenous dexamethasone, specific mention of use of Joel-Cohen incision and abdominal binders under surgical technique and use of transcutaneous electrical nerve stimulation as an adjuvant postoperatively (Grade A recommendations).⁴⁶ Preoperative oral gabapentinoid was replaced with oral paracetamol.⁴⁶ Part of the limitations of studies used by PROSPECT in making its recommendation are that the majority of the analgesic intervention was not evaluated against a multimodal analgesic regimen; most of the RCTs assessed a single-analgesic intervention against opioid monotherapy and placebo, and that the studies were only in women undergoing planned caesarean section.^{45,47} These issues have been addressed already in the protocol for our own study, in that, magnesium sulphate was evaluated as part of an opioid-free analgesia regimen against a routine opioid-based multimodal analgesia regimen used in the study setting, and our study included women undergoing urgent caesarean section.

The RCT design of our study gives it strength while the subjectivity of the perception, expression and assessment of pain was a limitation. The intensity of pain cannot be perfectly compared between one person and the other, neither can it be objectively measured. In addition, this being a single-centred study limits the generalizability of the findings to other populations.

Conclusion

We have described our protocol for a randomized, controlled, single-centred clinical trial to determine the effectiveness and safety of a combination of peri-operative intravenous magnesium sulphate and intravenous paracetamol, plus post-operative rectal diclofenac as opioid-free, multimodal analgesia for management of acute post-operative pain after a caesarean section. Our

goal for presenting our protocol for this study is so that it may be replicated in other settings, possibly modified for future studies and ultimately join the efforts towards solving the ongoing opioid addiction crisis.

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Appendix 1: Proforma for biodata and study consent form

<p style="text-align: center;">OPIOID-FREE ANALGESIA FOR THE MANAGEMENT OF ACUTE POST- OPERATIVE PAIN FOLLOWING CAESAREAN SECTION.</p> <p style="text-align: center;">(OFAAPPCS TRIAL)</p> <p style="text-align: center;">BIODATA AND CONSENT FORM</p>	
<p>PATIENT'S IDENTIFICATION NUMBER: FMCY/O&G/OFAAPPCS/2020/ _____</p>	
<p>Mrs/Miss _____ (Initials Only)</p>	
<p>Age _____, Ethnicity _____, Weight _____ kg, Height _____ cm,</p>	
<p>Parity _____.</p>	
<p>I acknowledge that:</p>	
<ol style="list-style-type: none">1. I have been duly informed that this research study seeks to determine if use of Magnesium Sulphate can avoid or reduce the use of Pentazocine as part of pain medications for caesarean section,2. I have been duly informed that I will be randomly allocated to be in either the group that will be given magnesium sulphate or that will be given pentazocine, with other usual drugs,3. I have been duly informed that I will not be left in uncontrolled pain at any time during this research study,4. The benefits of this research study to me have been explained,5. I have been assured that I will not be subjected to harm in any way,6. All questions I have concerning this research have been answered,7. I have been informed that I reserve the right to withdraw from the study at any stage without prejudice.	
<p>I hereby consent to participate in this research study.</p>	
<p>_____</p> <p>Patient's Signature/Thumb print</p>	<p>_____</p> <p>Researcher's Signature</p>

Appendix 2: Proforma for theatre/recovery room vital signs and adverse event

OPIOID-FREE ANALGESIA FOR THE MANAGEMENT OF ACUTE POST- OPERATIVE PAIN FOLLOWING CAESAREAN SECTION. (OFAAPPCS TRIAL) THEATRE/RECOVERY ROOM CHART/ADVERSE EVENT FORM			
PATIENT'S IDENTIFICATION NUMBER: FMCY/O&G/OFAAPPCS/2020/_____			
SECTION ONE (VITAL SIGNS ON THEATRE ADMISSION)		SECTION TWO (INTRAOPERATIVE VITAL SIGNS)	
Blood pressure _____ mmHg		Lowest intraoperative Blood pressure _____ mmHg	
Pulse rate _____ bpm		Lowest intraoperative Pulse rate _____ bpm	
Respiratory rate _____ cpm		Lowest intraoperative Respiratory rate _____ cpm	
SECTION THREE: ANY INCIDENCE OF THE FOLLOWING EVENT? (Tick as appropriate)		SECTION FOUR: ANY OTHER CLINICALLY SIGNIFICANT ADVERSE EVENT? (Tick and write as appropriate)	
Drug given	I.V MgSO₄ <input type="checkbox"/>	I.M Pentazocine <input type="checkbox"/>	• NO <input type="checkbox"/>
	I.V Paracetamol <input type="checkbox"/>	Supp. Diclofenac <input type="checkbox"/>	• YES <input type="checkbox"/>
• Hypersensitivity reaction (not from blood transfusion) <input type="checkbox"/>		If Yes, Please give details.	
• Respiratory depression <input type="checkbox"/>			
• Bradycardia <input type="checkbox"/>			
• Hypotension <input type="checkbox"/>			
• Vomiting <input type="checkbox"/>			
• Light-headedness/Presyncope <input type="checkbox"/>			
SECTION FIVE (OTHERS)			
• Apgar Score _____ • Any previous caesarean section? Yes <input type="checkbox"/> , No <input type="checkbox"/>			
If Yes, how many? <input type="checkbox"/>			

Appendix 3: Proforma for adverse event that may occur on the ward

**OPIOID-FREE ANALGESIA FOR THE MANAGEMENT OF ACUTE POST-
OPERATIVE PAIN FOLLOWING CAESAREAN SECTION.**

(OFAAPPCS TRIAL)

WARD ADVERSE EVENT FORM

PATIENT'S IDENTIFICATION NUMBER: FMCY/O&G/OFAAPPCS/2020/_____

SECTION ONE: ANY INCIDENCE OF THE FOLLOWING EVENT?

(Tick as appropriate)

Drug given	I.V MgSO₄	I.M Pentazocine	I.V Paracetamol	Supp. Diclofenac
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Hypersensitivity reaction (not related to blood transfusion)				<input type="checkbox"/>
• Respiratory depression				<input type="checkbox"/>
• Bradycardia				<input type="checkbox"/>
• Hypotension				<input type="checkbox"/>
• Vomiting				<input type="checkbox"/>
• Light-headedness/Presyncope				<input type="checkbox"/>
• Constipation				<input type="checkbox"/>
• Ileus				<input type="checkbox"/>
• Pruritus				<input type="checkbox"/>
• Urinary retention				<input type="checkbox"/>

SECTION TWO: ANY OTHER CLINICALLY SIGNIFICANT ADVERSE EVENT?

(Tick and write as appropriate)

• NO	<input type="checkbox"/>
• YES	<input type="checkbox"/>
• If Yes, Please give details.	

Appendix 4: Proforma for pain score

OPIOID-FREE ANALGESIA FOR THE MANAGEMENT OF ACUTE POST- OPERATIVE PAIN FOLLOWING CAESAREAN SECTION.

(OFAAPPCS TRIAL)

PROFORMA FOR PAIN SCORE

PATIENT'S IDENTIFICATION NUMBER: FMCY/O&G/OFAAPPCS/2020/_____

NUMERICAL RATING SCALE (NRS) PAIN SCORE AT 4, 8 AND 24 HOURS

	NUMERICAL RATING SCALE (NRS) SCORE										
Time (hours postoperative)	0	1	2	3	4	5	6	7	8	9	10
4											
8											
24											

Instruction to patient (graphical administration): “if 0 means no pain and 10 mean the worst pain imaginable, on the scale of 0 to 10, point to a number that represents how much pain you feel now”

Instruction to patient (Verbal Administration): “if 0 means no pain and 10 mean the worst pain imaginable, on the scale of 0 to 10, say a number that represents how much pain you feel now”

Appendix 5: Proforma for pentazocine use

OPIOID-FREE ANALGESIA FOR THE MANAGEMENT OF ACUTE POST- OPERATIVE PAIN FOLLOWING CAESAREAN SECTION. (OFAAPPCS TRIAL)		
PROFORMA FOR PENTAZOCINE USE		
PATIENT'S IDENTIFICATION NUMBER: FMCY/O&G/OFAAPPCS/2020/_____		
SECTION ONE: USE OF INTRAMUSCULAR PENTAZOCINE (Tick as appropriate)		
<ul style="list-style-type: none">Intramuscular pentazocine was used	As prescribed <input type="checkbox"/>	As rescue analgesia <input type="checkbox"/>
<ul style="list-style-type: none">Intramuscular pentazocine was not used		
SECTION TWO: FREQUENCY OF PENTAZOCINE USE (Tick as appropriate)		
<ul style="list-style-type: none">More than four times		
<ul style="list-style-type: none">Four times		
<ul style="list-style-type: none">Three times		
<ul style="list-style-type: none">Two times		
<ul style="list-style-type: none">Once		
SECTION THREE: TOTAL DOSE OF PENTAZOCINE USED (Tick as appropriate)		
<ul style="list-style-type: none">30 mg pentazocine used		
<ul style="list-style-type: none">45 mg pentazocine used		
<ul style="list-style-type: none">60 mg pentazocine used		
<ul style="list-style-type: none">90 mg pentazocine used		
<ul style="list-style-type: none">120 mg pentazocine used		
<ul style="list-style-type: none">135 mg pentazocine used		
<ul style="list-style-type: none">180 mg pentazocine used		
<ul style="list-style-type: none">> 180 mg pentazocine used		