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Protocol

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: study protocol

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ABSTRACT

Background: Pain management post-caesarean section is a common source of exposure to opioids in women. To address the rising opioid addiction associated with peri-operative administration, trend in operative analgesia is moving towards opioid-free, multimodal analgesia. We present our protocol for this study so that it may be replicated in other settings and possibly modified for future studies.
Methods: In a Single-centre, non-inferiority, parallel, randomized, controlled, clinical trial with balanced allocation [1:1] into two arms, we compared a peri-operative opioid-free analgesia regimen with a routine post-operative opioid-based analgesia regimen in women undergoing caesarean section under spinal anaesthesia. Primary outcome measures were post-operative pain intensity at 4, 8 and 24 hours (using Numerical Rating Scale) and post-operative pentazocine use. Secondary outcome measures were the incidence of adverse events and Apgar score. Results will be published in a peer-reviewed, open access journal.
Conclusions: This protocol adopted the use of intravenous paracetamol and intravenous NSAID as baseline analgesics. Magnesium sulphate was introduced peri-operatively as part of our opioid-free multimodal analgesia regimen because of its established effect in decreasing post-operative pain and opioid use. 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. 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.
Trial registration: This protocol was registered with clinicaltrials.gov (Identifier: NCT04539249) on September 3, 2020, prospectively.

Keywords: Intravenous magnesium sulphate, Intravenous paracetamol, Suppository diclofenac, Caesarean section, Acute post-operative pain, Opioid addiction

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), and on the rise in Canada, Australia, and in England and Wales.[14-19] 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.[14-16] Canada recorded 2,861 apparent opioid-related deaths in 2016, and 1,045 Australians died from opioid overdose in 2016.[17,18] 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 and intravenous paracetamol and intravenous NSAID and transversus abdominis plane block or iliohypogastric/ilioinguinal block or wound infiltration with local anaesthetic intraoperatively, then intravenous paracetamol and 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 and the combination of routes of administration and techniques recommended is in our opinion cumbersome and invasive.[33,34] 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

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

Study setting

This study was 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 were pregnant women who had caesarean section at the Federal Medical Centre, Yenagoa, Bayelsa State during the study period.

Eligibility criteria

Eligibility was 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
• **Pregnant women booked for elective, scheduled and urgent caesarean section at the Federal Medical Centre, Yenagoa, Bayelsa State during the study period.** • **Pregnant women who give consent to participate in the study.**	• Pregnant women with active peptic ulcer disease, active liver disease, hepatic failure, and renal failure. • Pregnant women with previous history of ischaemic heart disease/myocardial infarction, heart failure, venous thrombosis and stroke. • Hypersensitivity to pentazocine, paracetamol, diclofenac or magnesium sulphate. • Pregnant women with history of non-medical use (abuse) of opioids. • Pregnant women on magnesium sulphate or have a clinical indication to receive magnesium sulphate. • Pregnant women booked for emergency caesarean section (because the urgency may not allow time for adequate patient counseling before recruitment). • Pregnant women booked for caesarean section under general anaesthesia or epidural anaesthesia. • Pregnant women who can neither communicate in English nor colloquial English.

Trial team recruitment and care team education

Research assistants were recruited and trained for the study. The research assistants who assessed 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 received spinal anaesthesia with 2 ml [10 mg] of hyperbaric 0.5% bupivacaine (Marcaine®- Aspen Pharma Trading Limited, Ireland) into the subarachnoid space, and patients were laid supine immediately. This fixed dose of bupivacaine was used 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 section.[41]

Participants in intervention arm A received 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: 1 g of intravenous paracetamol as an infusion slowly over 15 minutes, then 4 g 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 was 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 was administered. Intravenous paracetamol 1 g was continued 6 hourly and suppository diclofenac 100 mg continued 12 hourly, both over 24 hours post-operatively.

Participants in intervention arm B received 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 were commenced and administered 6-hourly. Suppository diclofenac 100 mg was continued 12-hourly, all for 24 hours post-operatively.

Rescue analgesia was 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) was used as rescue analgesia. It was 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 was no blinding at this stage of the study. Thus, the participants, the researcher, the research assistants who were involved in administration of the peri-operative analgesics and the research assistants and nurses who were involved in administration of the post-operative analgesics were aware of the allocated arm.

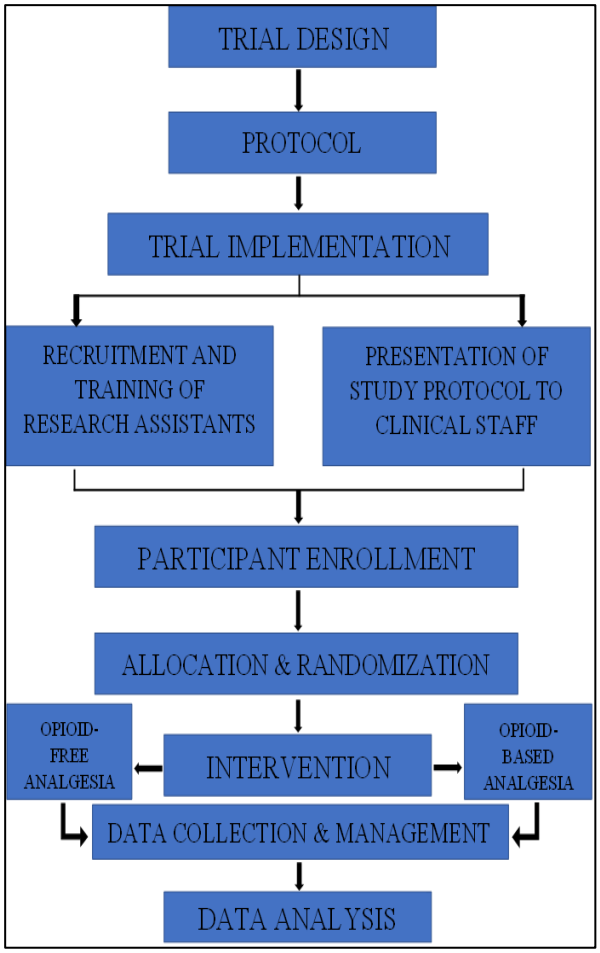

Figure 1: Study flow diagram.

Primary outcome measures

The primary outcome measures evaluated were 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 evaluated were 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 were 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 consisted of 21 weeks of intervention phase, between November, 2020 and March, 2021. All measurements were taken during the intervention phase. There was no follow-up phase.

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

Sample size calculation

Sample size was determined using the formula for sample size determination for non-inferiority clinical trials 42; $n=2\ (Z1-\alpha+Z1-\beta)\ 2 \times SD^2/d^2$; where n is the minimum sample size. Giving a level of significance (α) of 0.05 and power (1–β) of 80%, then Z1-α is the standard normal deviate at 95% confidence interval (1.96) and Z1-β 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, $n= 2\ (1.96+0.842)\ 2 \times 2.22 / 1.32 =44.97$; approximately 45. Using an attrition rate of 10%, this minimum sample size was increased by 5 (10% of 45). Fifty women were thus selected into each arm of this study, giving a total sample size of 100.

Recruitment

Participants were 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 were met by the researcher or trained assistant in the antenatal ward or labour ward. After the researcher or a trained research assistant had explained the aim and processes of the study and its benefits to eligible women in simple and clear terms, and an assurance of safety was given, participants who expressed an understanding of the study and showed willingness to participate were 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 was received into the theatre for a caesarean section, a research assistant picked an envelope according to the sequence. The letter inscribed on the card in the envelope was 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 was attached to the case folder, operation note and other documents for the study.

Blinding (masking)

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

Methods: data collection, management, and analysis

Data collection methods

The weight and height of the women were measured and recorded with other biodata of interest. The respiratory rate, pulse rate and blood pressure of the women were 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 were obtained from the anaesthesia chart. Any adverse event during this period was also recorded. The Apgar scores of the neonates at the first and fifth minutes after birth were recorded. Forms were provided on the ward to record any opioid-related adverse event and any other adverse event recorded during the first 24 hours post-operative. Hypotension for the purpose of the study was defined as a systolic blood pressure <90 mmHg and/or a diastolic blood pressure <60 mmHg. Bradycardia was 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 largely relied on the women's self-reporting of pain intensity and such reports were recorded exactly as stated by the women. Trained and blinded research assistants assessed 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 were house officers who were rotating through other postings other than obstetrics and gynaecology at the time of the study). It was ensured that all the trial documents were concealed in an opaque envelope during their visits to the ward.

At 48 hours post-operative, the researcher obtained 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 included the frequency of pentazocine administration and the cumulative dose of pentazocine administered during the first 24 hours post-operative. Forms and proformas used during the study are shown in appendix 1-5.

Data management

The envelopes containing the trial documents were 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 were sent to this research assistant for data entry into the excel spreadsheet on weekly basis. During weekly data entry, participants were 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 was disclosed to the research assistant for inclusion in the data by matching with the serial number / identification number previously entered. The completed data was thereafter sent to the data analyst.

Data monitoring

As part of the protocol of the research ethics committee of the institution for internal audit of clinical trials, a research auditor was appointed to inspect the study materials and occasionally observe (on a weekly basis) the study procedure. Adverse events or serious adverse events were reported to the office of the research ethics committee of the Federal Medical Centre, Yenagoa at 48 hours post-operative or as they occur for each participant. Filled study forms and proforma collated on weekly basis were first sent to the office of the research auditor, where they were 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 $p<0.05$ 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.

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

Availability of data and materials

Study materials 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.

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 reserved the right to voluntarily participate in the study and to give a written informed consent. She also reserved the right to withdraw from the study at any stage if she so wished. Data obtained from this study was anonymized to ensure the confidentiality of participants.** **Contents of such counseling included: the procedure to be followed in the study, the benefits to the individual, the discomforts and risks that are reasonably expected, the options of therapy, the willingness of the investigator to answer questions, the right to refuse or to withdraw from the study without prejudice.** **The language of communication was English language, but where the patient did not understand English language, she was communicated to in colloquial English.** **Every woman was treated with fairness, equity and a sense of human dignity, irrespective of the age, socioeconomic circumstance, ethnic or religious lineage.**
Beneficence **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.** **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 were not subjected to harm in any way. Drugs used in this study were drugs with already known side effects and established safety profiles. Drugs with the same batch number were sourced from reliable drug companies with reputation. There was no patient with contraindication to administration of any of the drugs during the study. Calcium gluconate/calcium chloride and naloxone; antidotes for magnesium toxicity and opioid-induced respiratory depression respectively, were 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) were made available.
Safety of researchers Appropriate Infection Prevention and Control (IPC) measures were 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.

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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REFERENCES

1. Yim N, Parsa FD. From the Origins of the opioid use (and misuse) to the challenge of opioid-free pain management in surgery. In: Cascella M, ed. From conventional to innovative approaches for pain treatment. London, UK: IntechOpen; 2018. Available at: http://dx.doi.org/10.5772/intechopen.82675. Accessed on 7 November, 2020.
2. Schaefer CP, Tome ME, Davis TP. The opioid epidemic: a central role for the blood brain barrier in opioid analgesia and abuse. Fluids Barriers CNS. 2017;14:32.
3. Koekpe EJ, Manning EL, Miller TE, Ganesh A, Williams DGA, Manning MW. The rising tide of opioid use and abuse: the role of anaesthesiologist. Perioper Med. 2018;7:16. Available at: https://dx.doi.org/10.1186/s13741-018-0097-4. Accessed on January 24, 2020.

4. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77(5):1048-56.
5. Kehlet H. Surgical stress: the role of pain and analgesia. Br J Anaesth. 1989;63(2):189-95.
6. Malek J, Sevcik P, Bejsovec D, Gabrhelik T, Hnilicova M, Krikava I, et al. Postoperative pain management. 3rd ed. Prague, Czech Republic: Mlada fronta a.s.; 2017. Available at: https://www.wfsahq.org/components/com_virtual_library/media/125136f77e1b7daf7565bd6653026c35-Postoperative-Pain-Management-170518.pdf. Accessed on 24 January, 2020.
7. Zukowski M, Kotfis K. The use of opioid adjuvants in perioperative multimodal analgesia. Anestezjol Intens Ter. 2012;44(1):42-6.
8. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg. 2017;152(7):691-7.
9. Bateman BT, Franklin JM, Bykov K, Avorn J, Shrank WH, Brennan TA, et al. Persistent opioid use following Cesarean delivery: patterns and predictors among opioid naive women. Am J Obstet Gynecol. 2016;215(3):353-18.
10. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152(6):e170504.
11. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med. 2016;176(9):1286-93.
12. Zhao S, Chen F, Feng A, Han W, Zhang Y. Risk factors and prevention strategies for postoperative opioid abuse. Pain Res Manag. 2019;2019:7490801.
13. Klimas J, Gorfinkel L, Fairbairn N, Amato L, Ahamad K, Nolan S, et al. Strategies to identify patient risks of prescription opioid addiction when initiating opioids for pain: a systematic review. JAMA Netw. Open. 2019;2(5):e193365.
14. Centers for Disease Control and Prevention. Drug overdose deaths. Washington, D.C, U.S. Department of Health & Human Services; 2019. Available at: https://www.cdc.gov/drugoverdose/data/statedeaths.html. Accessed on 1 November, 2019.
15. Moghe S. Opioid history: from 'wonder drug' to abuse epidemic. Atlanta, Georgia: Cable News Network; 2016. Available at: www.cnn.com/2016/05/12/health/opioid-addiction-history/. Accessed on 1 November, 2019.
16. Adeosun AA. Opioid crisis: a public health concern in Colorado, United States. J Glob Health Rep. 2019;3:e2019056.
17. Belzak L, Halverson J. Evidence synthesis – The opioid crisis in Canada: a national perspective. Health Promot Chronic Dis Prev Can. 2018;38(6):224-33.
18. National Drug & Alcohol Research Centre (AU). Majority of opioid overdose deaths in Australia are related to pharmaceutical opioids. Sydney, AU: University of New South Wales; 2019. Available at: http://connections.edu.au/news/majority-opioid-overdose-deaths-australia-are-related-pharmaceutical-opioids. Accessed on 24 January, 2020.
19. Royal Pharmaceutical Society. Opioid overdose deaths 'rising sharply' in England and Wales OECD says. London, UK: Royal Pharmaceutical Society; 2019. Available at: https://doi.org/10.1211/PJ.2019.20206561. Accessed on 24 January, 2020.
20. Federal Ministry of Health, Government of Nigeria; National Bureau of Statistics, Government of Nigeria; Centre for Research and Information on Substance Abuse (CRISA); United Nations office on Drugs and Crime (UNODC). Drug use in Nigeria. Vienna, Austria: United Nations office on Drugs and Crime. 2018:57.
21. Loewenstein A, Zalk N. West Africa's opioid crisis. Doha, Qatar: Al Jazeera Media Network; 2019. Available at: https://www.aljazeera.com/programmes/peopleandpower/2019/08/west-africa-opioid-crisis-190827135612104.html. Accessed on 4 November, 2020.
22. Kazeem Y. A national survey has confirmed the massive scale of Nigeria's drug problem. New York: Quartz Media, Inc.; 2019. Available at: https://qz.com/africa/1538843/nigeria-drug-abuse-14-million-adults-use-drugs/amp/. Accessed November 4, 2020.
23. Lee B, Schug SA, Joshi GP, Kehlet H. Prospect Working Group. Procedure-specific pain management (PROSPECT) – an update. Best Pract Res Clin Anaesthesiol. 2018;32(2):101-11.
24. Kamdar NV, Hoftman N, Rahman S, Cannesson M. Opioid-free analgesia in the era of enhanced recovery after surgery and the surgical home: implications for postoperative outcomes and population health. Anesth. Analg. 2017;125(4):1089-91.
25. Fiore Jr. JF, Olleik G, Charbel EAK, Alldrit A, Figueiredo AG, Marquez-Gdev SA, et al. Preventing opioid prescription after major surgery: a scoping review of opioid-free analgesia. Br. J. Anaesth. 2019;123(5):627-36.
26. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. Local Reg Anesth. 2014;7:17-22.
27. Kim M. An opioid success story: efforts to minimize painkillers after surgery appear to be working. Johannesburg, South Africa: The Conversation Africa, Inc.; 2019. Available at: https://www.google.com/amp/s/theconversation.com/amp/an-opioid-success-story-efforts-to-minimize-painkillers-after-surgery-appear-to-be-working-119148. Accessed on 5 November, 2019.

28. Johnson SR. Hospitals look to cut opioids from surgery and beyond. Detroit, Michigan: Crain communications, Inc.; 2019. Available at: https://www.modernhealthcare.com/care-delivery/hospitals-look-cut-opioids-surgery-and-beyond. Accessed on 24 January, 2020.
29. Dennis J, Soto E, Chauhan SP, Sibai B. Non-opioid versus opioid analgesia after hospital discharge from a caesarean delivery: a randomized clinical trial. Am J Obstet Gynecol. 2019;220(1):S34.
30. Egede JO, Ajah LO, Umeora OU, Ozumba BC, Onoh RC, Obuna JA, et al. Pentazocine alone versus pentazocine plus diclofenac for pain relief in the first 24 hours after Caesarean section: a randomized controlled study. J Clin Diagn Res. 2017;11(4):1-5.
31. Bakhsha F, Niaki AS, Jafari SY, Yousefi Z, Aryaie M. The effects of diclofenac suppository and intravenous paracetamol and their combination on the severity of postoperative pain in patients undergoing spinal anaesthesia during caesarean section. J Clin Diagn Res. 2016;10(7):UC09-12.
32. European Society of Regional Anaesthesia & Pain Therapy. Overall recommendations: pain management for elective caesarean section surgery. Geneva, Switzerland: European Society of Regional Anaesthesia & Pain Therapy; 2020. Available at: https://esraeurope.org/prospect/procedures/c-section/prospect-recommendations/. Accessed on 5 November, 2019.
33. Sravani P, Indrani C, Rajanna SP. Efficacy of Surgical Transversus Abdominis Plane Block in Patients Undergoing Cesarean Delivery. J South Asian Feder Obst Gynae. 2020;12(5):302-6.
34. Wehbe SA, Ghulmiyyah LM, Dominique EH, Hosford SL, Ehleben CM, Saltzman SL, et al. Prospective randomized trial of iliohypogastric-ilioinguinal nerve block on post-operativbe morphine use after inpatient surgery of the female reproductive tract. J Negat Results Biomed. 2008;7:11.
35. Kahraman F, Eroglu A. The effect of intravenous magnesium sulphate infusion on sensory spinal block and postoperative pain score in abdominal hysterectomy. Biomed Res Int. 2014;2014:236024.
36. McKeown A, Seppi V, Hodgson R. Intravenous magnesium sulphate for analgesia after caesarean section: a systematic review. Anesthesiol Res Pract. 2017;2017:9186374.
37. Shin HJ, Kim EY, Na HS, Kim TK, Kim MH, Do SH. Magnesium sulphate attenuates acute postoperative pain and increased pain intensity after surgical injury in staged bilateral total knee arthroplasty: a randomized, double-blinded, placebo-controlled trial. Br J Anaesth. 2016;117(4):497-503.
38. Kalani N, Sanie MS, Zabetian H, Radmehr M, Sahraei R, Jahromi HK, et al. Comparison of the analgesic effect of paracetamol and magnesium sulphate during surgeries. World J Plast Surg. 2016;5(3):280-6.
39. Murphy JD, Paskaradevan J, Eisler LL, Ouanes JP, Tomas VA, Freck EA, et al. Analgesic efficacy of continuous intravenous magnesium infusion as an adjunct to morphine for postoperative analgesia: a systematic review and meta-analysis. Middle East J Anesthesiol. 2013;22(11);11-20.
40. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013;68(1):79-90.
41. Alam W, Yaqub KM, Saeed MA. Fixed dose vs height and weight adjusted dose of bupivacaine for caesarean section: A randomised controlled trial. J Pak Med Assoc. 2018;68(9):1345-9.
42. Flight L, Julious SA. Practical guide to sample size calculations: non-inferiority and equivalence trials. Pharm Stat. 2016;15(1):80-9.
43. Borges NC, Silva BC, Pedroso CF, Silva TC, Tatagiba BSF, Pereira LV. Postoperative pain in women undergoing caesarean section. Enferm. Glob. 2017;16(4):374-83.
44. Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? Pain. 2003;105(1-2):151-7.
45. European Society of Regional Anaesthesia & Pain Therapy. Evidence review process: procedure specific pain management for elective caesarean section surgery 2020. Geneva, Switzerland: European Society of Regional Anaesthesia & Pain Therapy; 2020. Available at: https://esraeurope.org/prospect/procedures/caesarean-section-2020/evidence-review-process-16/. Accessed on 5 April, 2021.
46. European Society of Regional Anaesthesia & Pain Therapy. Summary recommendations: procedure specific pain management for elective caesarean section surgery 2020. Geneva, Switzerland: European Society of Regional Anaesthesia & Pain Therapy; 2020. Available at: https://esraeurope.org/prospect/procedures/caesarean-section-2020/summary-recommendations-20/. Accessed on 5 April, 2021.
47. European Society of Regional Anaesthesia & Pain Therapy. Prospect Methodology: procedure specific pain management for elective caesarean section surgery. Geneva, Switzerland: European Society of Regional Anaesthesia & Pain Therapy; 2020. Available at: https://esraeurope.org/prospect-methodology/. Accessed on 5 April, 2021.

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