ORIGINAL RESEARCH

DOI: 10.5336/jcog.2023-99734

A Single-center, Randomized, Clinical Trial of Opioid-free Analgesia Versus Routine Opioid-Based Analgesia Regimen for the Management of Acute Postoperative Pain Following Cesarean Section

Olakunle Ifeoluwa MAKINDE[a], Egbaname Obozegie Samuel AIGERE[a], Nuvie OYEYEMI[a], Adedotun Daniel ADESINA[b]

[a]Department of Obstetrics and Gynecology, Federal Medical Center Yenagoa, Bayelsa State, Nigeria
[b]Nigerian Law School Medical Center, Yenagoa Campus, Yenagoa, Bayelsa State, Nigeria

ABSTRACT Objective: To determine if opioid-free analgesia is as effective and safe as opioid-based analgesia for post-cesarean section pain. **Material and Methods:** Non-inferiority, assessor-blinded randomized controlled trial. One hundred cesarean section patients were randomized into 2 arms. Opioid-free analgesia arm had 1 gram intravenous paracetamol infusion and bolus 4 grams intravenous 20% magnesium sulfate pre-operatively, then 1 gram/hour infusion of 20% magnesium sulfate intraoperatively until 2 hours post-operation. Postoperatively, they had 100 milligrams of rectal diclofenac 12-hourly and continued paracetamol 6-hourly for 24 hours. Opioid-based analgesia arm had 100 milligrams of rectal diclofenac 12-hourly, 30 milligrams of intramuscular pentazocine 6-hourly, and 1 gram of intravenous paracetamol 6-hourly, postoperatively for 24 hours. Both arms were allowed rescue analgesia with intramuscular pentazocine. Primary outcomes were pain intensity at 4, 8, and 24 hours post-operation and postoperative pentazocine use. Non-inferiority limit was a mean difference in pain score <1.3. **Results:** Postoperative pain scores at 4, 8, and 24 hours were lower in the opioid-free analgesia arm; mean difference -0.18; 95% confidence interval (CI): -0.70-0.34; p=0.499, -0.10; 95% CI: -0.78-0.59; p=0.782 and -0.31; 95% CI: -0.89-0.29; p=0.308 respectively. Mean pentazocine use was lower in the opioid-free analgesia arm (52.83±21.85 mg/164.40±28.59 mg; p=0.001). Serious adverse event occurred in one (2.0%) participant in the opioid-free analgesia arm and none in the opioid-based analgesia arm, p=0.315. There was no significant difference in the 5th-minute Apgar score (p=0.315). **Conclusion:** Opioid-free analgesia using perioperative intravenous magnesium sulfate, intravenous paracetamol, and postoperative rectal diclofenac is non-inferior to and as safe as the opioid-based analgesia and it reduced pentazocine consumption.

Keywords: Cesarean section; magnesium sulfate; opioid-free analgesia

Opioid abuse-associated morbidity and mortality remains a significant health concern with about 600,000 drug use-related deaths in 2019, 80% of them are opioid-related.[1] Chronic opioid use disorder is linked to perioperative opioid administration.[2] As cesarean section (CS) is a common procedure with rising rates globally, there is a valid concern and avoidance of opioids in the management of postoperative pain, that is, opioid-free multimodal analgesia has become a new goal. Recommendation of the Procedure Specific Postoperative Pain Management (PROSPECT) working group for post-CS pain management is a notable effort in this regard, but drawbacks include that the place of some prescribed techniques remains debatable, obstetricians do not yet commonly practice abdominal wall blocks, and techniques and administration routes prescribed is cumbersome and invasive.[3-5] Moreover, in the ma-

TO CITE THIS ARTICLE:
Makinde OI, Aigere EOS, Oyeyemi N, Adesina AD. A single-center, randomized, clinical trial of opioid-free analgesia versus routine opioid-based analgesia regimen for the management of acute postoperative pain following cesarean section. JCOG. 2024;34(1):25-35.

Correspondence: Olakunle Ifeoluwa MAKINDE
Department of Obstetrics and Gynecology, Federal Medical Center Yenagoa, Bayelsa State, Nigeria
E-mail: olakunleife@gmail.com

Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 30 Sep 2023 ***Received in revised form:*** 11 Feb 2024 ***Accepted:*** 26 Feb 2024 ***Available online:*** 11 Mar 2024

jority of the works relied on by PROSPECT for its recommendation, analgesic interventions were not evaluated against an opioid-based multimodal analgesic regimen, rather, single analgesic interventions were compared against opioid-only and placebo.[6] As efforts to address the contribution of perioperative administration of opioids to the persistent opioid crisis continue, especially in low-resource settings, there is a need for a less cumbersome, cheap, readily available, and effective opioid-free multimodal analgesia regimen that can outrightly avoid or reduce perioperative opioid administration and provide a degree of analgesia not inferior to opioid-based analgesia.

Among adjuvant analgesics that have been assessed for postoperative pain, magnesium sulfate ($MgSO_4$) is familiar to obstetricians and assessable in many settings that offer comprehensive emergency obstetric care, easily administered, and well tolerated clinically. Previous studies reported that $MgSO_4$ administered in the perioperative period prolongs spinal anesthesia duration and decreases postoperative pain intensity and opioid use with no side effects.[7-12] As far as we know, no study has particularly assessed $MgSO_4$ as a component of an opioid-free multimodal analgesia regimen for managing acute post-CS pain. With this study, we sought to evaluate $MgSO_4$ in this light, compared with the opioid-based multimodal analgesia regimen routinely used in the research facility. It was thought worthwhile to rely on the adjuvant analgesic effect of $MgSO_4$, on the preventive analgesia offered by paracetamol (PCM) and $MgSO_4$ administered intravenously before incision, then intraoperatively and postoperatively, and on the reduced opioid consumption offered by the synergistic analgesic effect of PCM and a non-steroidal anti-inflammatory drug. Given the established role and effectiveness of opioids in managing severe acute pain, the working assumption of this study is non-inferiority of the effectiveness of an opioid-free multimodal analgesia regimen that includes $MgSO_4$ to the opioid-based multimodal analgesia regimen that is routine. The study aimed to determine the effectiveness and safety of perioperative intravenous $MgSO_4$, intravenous PCM, and postoperative rectal diclofenac as opioid-free multimodal analgesia for managing acute post-CS pain.

MATERIAL AND METHODS

A single-center, non-inferiority, parallel, assessor-blinded, randomized controlled trial (RCT). Randomization was into two equal arms. Participants were CS patients at the Federal Medical Center Yenagoa, Bayelsa State, Nigeria. All procedures followed the 2013 Helsinki Declaration. The research ethics committee, Federal Medical Center Yenagoa approved the trial protocol (date: August 17, 2020, no: FMCY/REC/ECC/2020/AUGUST/257), and it was registered with ClinicalTrials.gov (Identifier: NCT04539249) and published in an open-access journal.[13] Each participant gave written informed consent to participate. Exclusion criteria included women 1) with active liver disease, liver failure, renal failure, and active peptic ulcer disease, 2) with a history of myocardial infarction/ischemic heart disease, heart failure, venous thrombosis, and stroke, 3) with hypersensitivity to $MgSO_4$, PCM, diclofenac or pentazocine, 4) with a history of abuse of opioids, 5) on $MgSO_4$ for another clinical indication, 6) having an emergency CS, 7) having CS under general or epidural anesthesia, 8) with problem communicating in English and colloquial English.

INTERVENTION

All participants had spinal anesthesia with 10 milligrams (2 milliliters) of 0.5% hyperbaric bupivacaine. Fixed-dose bupivacaine was for a uniform protocol and supported by RCT evidence that outcomes are similar with fixed-dose 10 mg bupivacaine compared to height and weight-adjusted dose.[14]

Figure 1 summarizes the analgesic interventions in both arms of the study. Participants in the opioid-free analgesia arm received 1 gram intravenous PCM infusion, then 4 g of 20% $MgSO_4$ as an intravenous bolus at 30 minutes and 10 minutes before spinal anesthesia, respectively. A 1 gram/hour continuous infusion of 20% $MgSO_4$ was administered intraoperatively until 2 hours post-operation. Postoperatively, 100 mg of rectal diclofenac was administered in the theater-continued every 12 hours for 24 hours, and one gram of intravenous PCM was continued every 6 hours for 24 hours. During the 24 hours post-operation, participants in the opioid-based analgesia arm received 100

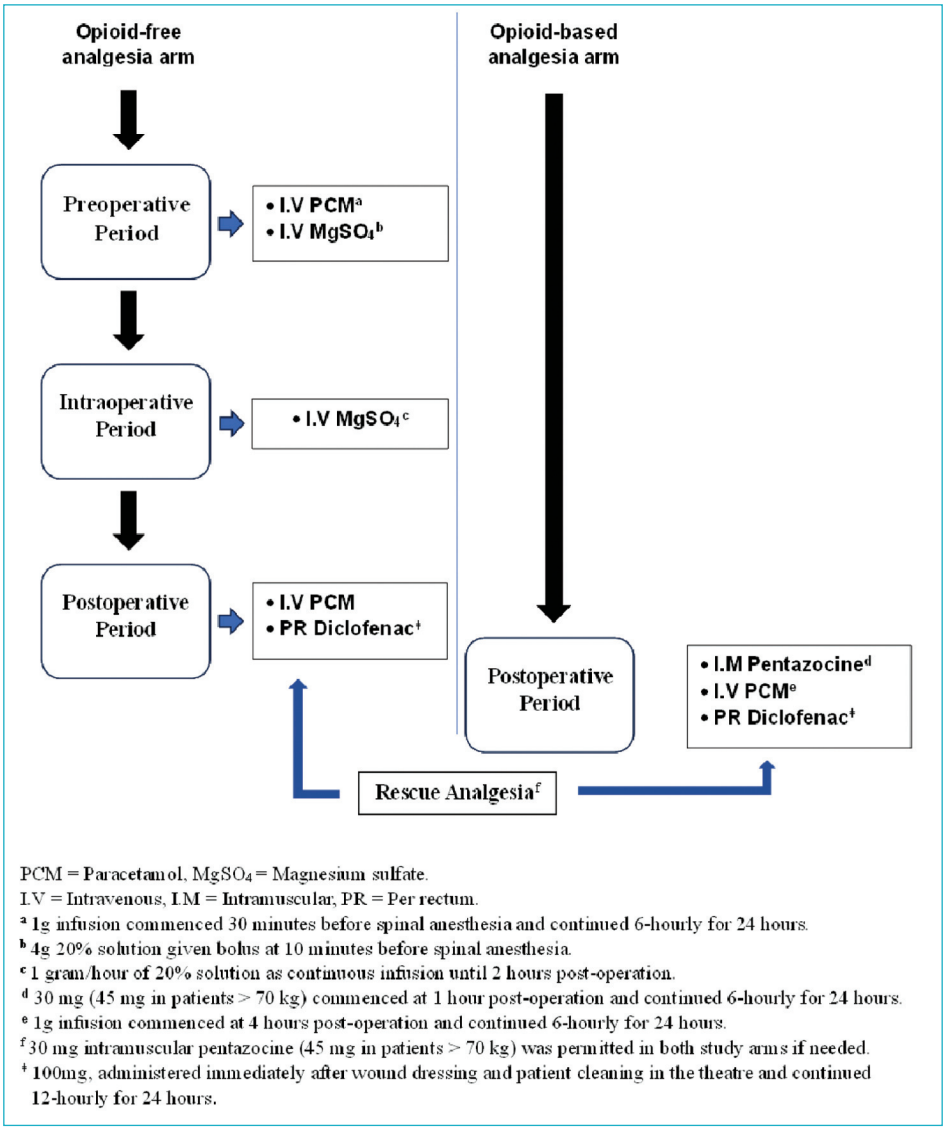

FIGURE 1: Analgesic intervention flowchart.

mg rectal diclofenac in the theater-continued every 12 hours, 30 mg intramuscular pentazocine (45 mg in patients >70 kilograms) commenced at 1 hour post-operation-continued every 6 hours, and 1 g intravenous PCM infusion commenced at 4 hours post-operation-continued every 6 hours. Rescue analgesia with 30 mg intramuscular pentazocine (45 mg in patients >70 kg) was permitted in both study arms if needed.

Cesarean Section Procedure: Pfannenstiel incision was used on the skin. The layers of the anterior abdominal wall and the peritoneum were bluntly separated to access the pelvic cavity. The loose uterovesical peritoneum overlying the lower uterine segment was divided and retracted downwards with the bladder. A 10 cm curvilinear incision was made on the lower uterine segment to deliver the fetus. After separating the umbilical cord and handing over the neonate to the neonatologist, the placenta and membranes were delivered, the uterus was exteriorized, and the uterine incision was repaired in two layers. The uterus was returned to the abdominal cavity after repair and the rectus fascia, subcutaneous tissue, and skin were closed.

PRIMARY OUTCOME MEASURES

Primary outcomes were postoperative pain scores following CS at 4, 8, and 24 hours post-operation using

the Numerical Rating Scale (NRS) for pain and postoperative pentazocine use in the 24 hours post-operation (obtained from the medication chart), i.e., pentazocine use, pentazocine use as rescue analgesia, frequency and nature of pentazocine use and mean dose of pentazocine used.

SECONDARY OUTCOME MEASURES

Secondary outcomes were incidences of perioperative (magnesium-related) adverse events including hypersensitivity reaction, hypotension, lightheadedness, presyncope, nausea and vomiting, bradycardia, respiratory depression, and any other adverse event that occurred from the time of first perioperative analgesia administration to 2 hours post-operation. Others were 1st and 5th-minute Apgar scores of delivered neonates and incidences of postoperative (opioid-related) adverse events including pruritus, urinary retention, ileus, constipation, and any other adverse event that occurs in the 24 hours post-operation.

Participants' weight, height and other baseline data were documented. First pulse rate, respiratory rate, and blood pressure (BP) at the theater and the lowest values from the time of first administration of perioperative analgesia to 2 hours post-operation were extracted from the anesthesia chart. Any adverse event within the period was documented. The neonates' Apgar scores at the 1st and 5th minute of life were documented. Adverse events in the 24 hours post-operation were documented on the ward. For this study, hypotension was a systolic BP<90 millimeters of mercury (mmHg) and/or a diastolic BP<60 mmHg. Bradycardia was a pulse rate <60 beats/minute and respiratory depression was a respiratory rate <12 cycles/minute.

SAMPLE SIZE CALCULATION

Based on the formula for non-inferiority clinical trials; $n=2\ (Z1\text{-}\alpha+Z1\text{-}\beta)^2xSD^2/d^2$; where n is minimum sample size, at 95% level of confidence and 80% power; $Z1\text{-}\alpha=1.96$ and $Z1\text{-}\beta=0.84$, SD (standard deviation of pain intensity after CS in a previous study)=2.2, and d (non-inferiority margin)=1.3, from a previous study.[15-17]

Therefore, $n=2\ (1.96+0.842)^2x2.2^2/1.3^2=45$. At 10% attrition, the sample size was 50 women for each arm of the study: a total of 100.

RANDOMIZATION AND ALLOCATION CONCEALMENT MECHANISM

Using the Windows Programs for Epidemiologist (WINPEPI) software, balanced randomization of numbers 1 to 100 to letters A and B (A=Opioid-free analgesia arm and B=Opioid-based analgesia arm) was done. Opaque and identical envelopes were outwardly labelled, serially from 1 to 100, sealed and arranged sequentially. Concealed within the envelopes were cards bearing the letter A or B as they matched the randomly assigned numbers 1 to 100.

Implementation

As each enrolled woman got to the theater for a CS, an envelope was picked in sequence by a research assistant. The inscribed letter on the card was allocated to the woman.

Blinding (masking)

Assessors of postoperative pain intensity and the data manager were blinded.

DATA ANALYSIS

Statistical analysis was done using IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA). Categorical data were summarized with frequencies and percentages and continuous data with mean and standard deviation. Comparisons between the study arms were done using the Chi-square test for categorical variables and the Student's t-test for continuous variables. Non-inferiority limit was a difference in the mean pain score of NRS<1.3. Statistical significance was p-value <0.05.

RESULTS

Figure 2 shows the trial participant flow.

The recruitment, intervention, and data collection lasted 21 weeks from November 4, 2020, to March 31, 2021. The study had no follow-up phase.

BASELINE DATA OF PARTICIPANTS

One hundred participants were enrolled in this study, 50 in each arm. As shown in Table 1, most women in the intervention arm A were in the age range of 30-34 years; n=25 (50.0%) and most of the women in the

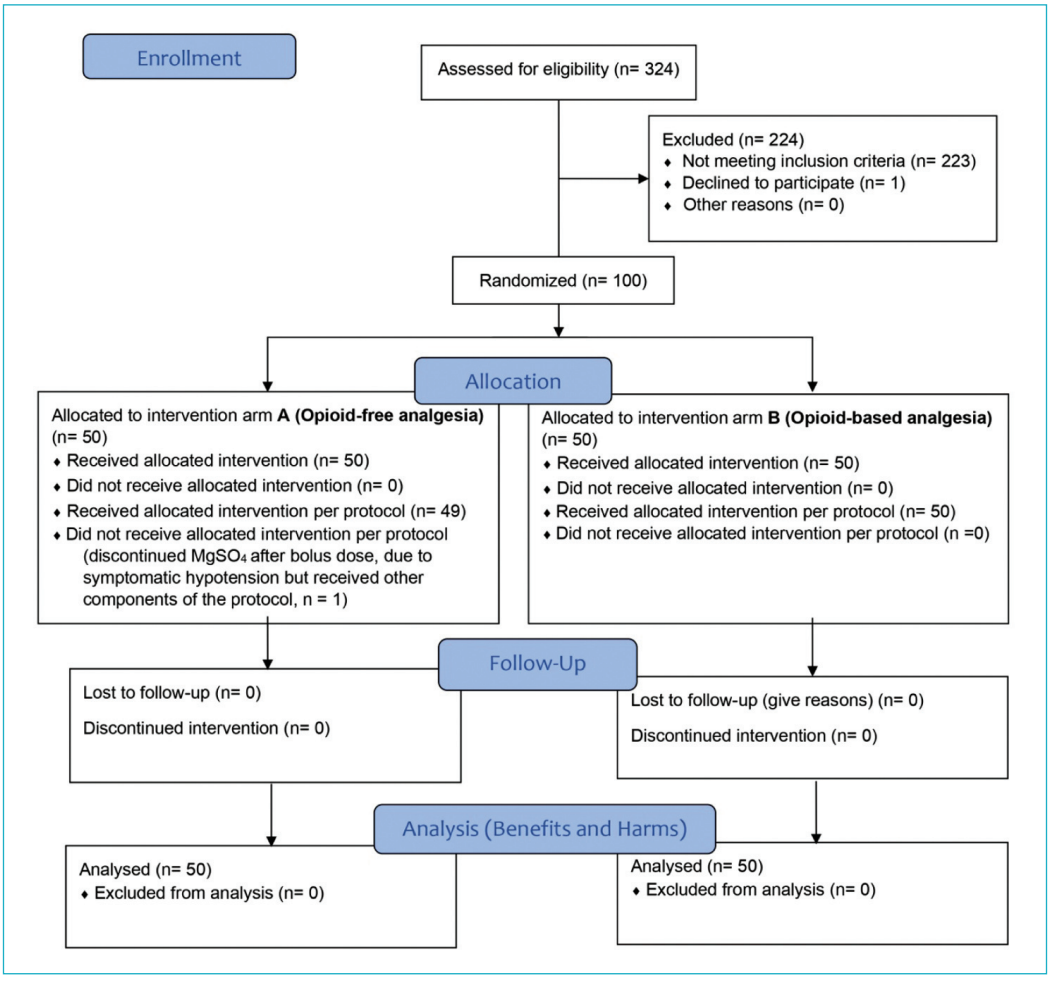

FIGURE 2: Participant flow diagram.

TABLE 1: Baseline data of participants.

Variable	Total	Intervention arms		Significance test	p value
		Arm A n=50 (%)	Arm B n=50 (%)		
Age range (years)					
• 20-24	1 (1.0)	0 (0.0)	1 (2.0)	4.59[a]	0.204
• 25-29	31 (31.0)	12 (24.0)	19 (38.0)		
• 30-34	41 (41.0)	25 (50.0)	16 (32.0)		
• 35-39	27 (27.0)	13 (26.0)	14 (28.0)		
Mean age±SD	31.29±3.87	31.74±3.43	30.84±4.30	1.16[b]	0.250
Mean weight±SD	81.2±11.5	84.45±12.83	77.91±8.94	2.95[b]	0.004
Ethnicity					
• Igbo	39 (39.0)	21 (42.0)	18 (36.0)	2.44[a]	0.295
• Ijaw	43 (43.0)	23 (46.0)	20 (40.0)		
• Others	18 (18.0)	6 (12.0)	12 (24.0)		
Parity					
• Nulliparous	17 (17.0)	6 (12.0)	11 (22.0)	2.94[a]	0.230
• Primiparous	17 (17.0)	11 (22.0)	6 (12.0)		
• Multiparous	66 (66.0)	33 (66.0)	33 (66.0)		

[a]Chi-square test; [b]Student's t-test; SD: Standard deviation.

intervention arm B were in the age range of 25-29 years, n=19 (38.0%). The mean age in intervention arm A was 31.74±3.43 years while in intervention arm B, it was 30.84±4.30 years (p=0.250). The mean weight in the intervention arm A was 84.45±12.83 kg while that in the intervention arm B was 77.91±8.94 kg (p=0.004). The majority were either Ijaw or Igbo in both intervention arms A; n=45 (90.0%) and B; n=31 (62.0%), p=0.295, and most of the women in both arms were multiparous; n=33 (66.0%) each, p=0.230.

PRIMARY OUTCOME MEASURES

Postoperative Pain Scores Following Caesarean Section

As shown in Table 2, there was no statistically significant difference in pain intensity between both intervention arms. The mean NRS for pain was lower in the intervention arm A at 4, 8, and 24 hours postoperative with a mean difference of -0.18 [95% confidence interval (CI) -0.70-0.34; p=0.496], -0.10 (95% CI -0.78-0.59; p=0.782) and -0.31 (95% CI -0.89-0.29; p=0.308), respectively. As shown in Figure 3, given a non-inferiority limit of mean difference in NRS for pain <1.3 and a lower pain score indicating a better outcome, the upper bound of the 95% confidence intervals of the mean differences in NRS scores at 4, 8, and 24 hours post-operation are <1.3. Non-inferiority of the opioid-free analgesia regimen is thus established.

Postoperative Pentazocine Use

Most of the women; n=46 (92.0%) in the intervention arm A required pentazocine as rescue analgesia and the rest (n=4; 8.0%) did not use pentazocine at all, while none of those in the intervention arm B required rescue doses of pentazocine, (p=0.001). There was also a lower requirement of pentazocine in the intervention arm A; 35 (70.0%) of the women used pentazocine only once, 11 (22.0%) used pentazocine only twice, and 4 (8.0%) did not use it, compared to the use of pentazocine four times per protocol in the intervention arm B, p<0.001. Mean opioid consumption was lower (52.83±21.85 mg vs 164.40±28.59 mg; p=0.001) in the intervention arm A (Table 3).

SECONDARY OUTCOME MEASURES

Perioperative Adverse Events

As shown in Table 4, two participants in the intervention arm B had perioperative bradycardia and none in the intervention arm A (p=0.153). There was a higher occurrence of perioperative systolic hypotension (n=14; 28.0% vs n=5; 10.0%, p=0.022) in intervention arm A than in the intervention arm B. Perioperative diastolic hypotension also occurred more (n=24; 48.0% vs n=18; 36.0%, p=0.224) in the intervention arm A than intervention arm B but the difference was not statistically significant. Severe (symptomatic) hypotension occurred in one of the participants with hypotension in the intervention arm A, accounting for one incidence of vomiting, lightheadedness, and presyncope with no statistical significance (p=0.315).

First and Fifth Minute Apgar Score

Table 5 shows that most neonates had Apgar score ≥7 at the 1st minute in both intervention arms. More neonates (n=6; 12.0% vs n=2; 4.0%, p=0.140) in the intervention arm B than in the intervention arm A had Apgar scores of 4-6 at the 1st minute and required resuscitation at birth, but this was not statistically significant. All the neonates in the intervention arm A

TABLE 2: Postoperative pain scores in opioid-free and opioid-based analgesia arms.

	Intervention Arms			
Variable	Arm A $\bar{X}$±SD	Arm B $\bar{X}$±SD	Mean difference (95% CI)	Student's t-test (p-value)
4 hours postop	2.98±1.18	3.16±1.45	-0.18 (-0.70-0.34)	0.68 (0.499)
8 hours postop	2.58±1.81	2.68±1.63	-0.10 (-0.78-0.59)	0.28 (0.782)
24 hours postop	2.06±1.42	2.37±1.54	-0.31 (-0.89-0.29)	1.02 (0.308)

SD: Standard deviation; CI: Confidence interval.

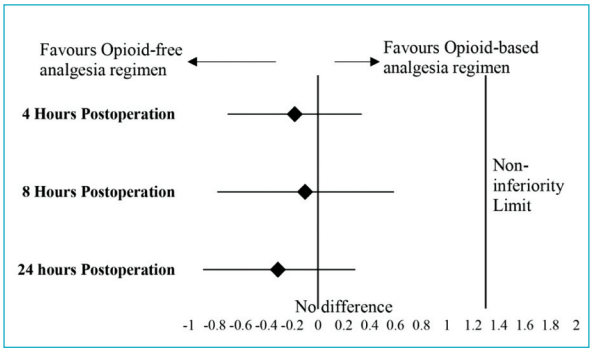

FIGURE 3: Treatment difference (Opioid-free analgesia-Opioid-based analgesia).

had Apgar scores ≥7 at the 5th minute, while one in the intervention arm B had a 5th minute Apgar score <4 with no statistical significance (p=0.315).

Postoperative Adverse Event

No adverse event was recorded in the postoperative period.

Potential Harms with the Analgesic Regimens Used in the Study

As shown in Table 6, there was no case of mortality. One participant (n=2; 2.0%) in the intervention arm A had a serious adverse event, severe (symptomatic) hypotension, while none occurred in intervention arm B. Other adverse events [bradycardia, mild (asymptomatic) hypotension] occurred in 46.0% and 40.0% of participants in the intervention arms A, and B respectively.

DISCUSSION

This trial found that there was no significant difference in pain intensity between the opioid-free analgesia and opioid-based analgesia arms. While women in the opioid-based analgesia arm had the routine four doses of opioid (per protocol), most women in the opioid-free analgesia arm required only one to two doses of opioid as rescue analgesia. Therefore, opioid administration and mean opioid consumption were lower in the opioid-free analgesia arm. Severe (symptomatic) hypotension occurred in one participant in the opioid-free analgesia arm. Most neonates had 1st minute Apgar score ≥7 in both intervention arms. No adverse event was recorded in the postoperative period.

Mean pain scores at 4, 8, and 24 hours post-operation were lower for opioid-free analgesia. This finding agrees with the work of Kahraman and Eroglu, where although only a continuous infusion dose of 3.8 g/hr of $MgSO_4$ was used intraoperatively, pain score was lower or at least equal post-surgery compared to the control at 4, 8, and 12 hours postop-

TABLE 3: Postoperative pentazocine use in opioid-free and opioid-based analgesia arms.

Variable	Intervention arms: Arm A n=50 (%)	Arm B n=50 (%)	Significance test	p-value
Pentazocine use				
• Pentazocine used	46 (92.0)	50 (100.0)	4.17[a]	0.041*
• Pentazocine NOT used	4 (8.0)	0 (0.0)		
Pentazocine use as rescue analgesia				
• Used	46 (92.0)	0 (0.0)	85.19[a]	0.001*
• Not used	4 (8.0)	50 (100.0)		
Frequency and nature of pentazocine use				
• More than 4 times (PP and as RA)	0 (0.0)	0 (0.0)	100.00[a]	0.000*
• Four times (PP)	0 (0.0)	50 (100.0)		
• Four times (as RA)	0 (0.0)	0 (0.0)		
• Three times (as RA)	0 (0.0)	0 (0.0)		
• Two times (as RA)	11 (22.0)	0 (0.0)		
• Once (as RA)	35 (70.0)	0 (0.0)		
• Not used at all	4 (8.0)	0 (0.0)		
Mean dosage used:	52.83±21.85 mg	164.40±28.59 mg	22.35[b]	0.001*

[a]Chi-square test; [b]Student's t-test; *Statistically significant; PP: Per protocol; RA: Rescue analgesia.

TABLE 4: Adverse events in opioid-free and opioid-based analgesia arms.

	Intervention arms			
Perioperative adverse event	**Arm A n=50 (%)**	**Arm B n=50 (%)**	**X^2**	**p-value**
Bradycardia				
Present	0 (0.0)	2 (4.0)	2.041	0.153
Absent	50 (100.0)	48 (96.0)		
Systolic hypotension				
Present	14 (28.0)	5 (10.0)	5.263	0.022*
Absent	36 (72.0)	45 (90.0)		
Diastolic hypotension				
Present	24 (48.0)	18 (36.0)	1.478	0.224
Absent	26 (52.0)	32 (64.0)		
Severe (Symptomatic) hypotension				
Present	1 (2.0)	0 (0.0)	1.010	0.315
Absent	49 (98.0)	50 (100.0)		
Severe (Symptomatic) systolic hypotension	**n=14 (%)**	**n=5 (%)**		
Present[a,b]	1 (7.1)	0	(0.0)	
Absent	13 (92.9)	5 (100.0)		
Severe (Symptomatic) diastolic hypotension	**n=24 (%)**	**n=18 (%)**		
Present[a,c]	1 (4.2)	0 (0.0)		
Absent	23 (95.8)	18 (100.0)		
Vomiting[d]				
Present	1 (2.0)	0 (0.0)	1.010	0.315
Absent	49 (98.0)	50 (100.0)		
Lightheadedness[d]				
Present	1 (2.0)	0 (0.0)	1.010	0.315
Absent	49 (98.0)	50 (100.0)		
Presyncope[d]				
Present	1 (2.0)	0 (0.0)	1.010	0.315
Absent	49 (98.0)	50 (100.0)		
Postoperative				
Adverse event				
Present	0 (0.0)	0 (0.0)		
Absent	50 (100.0)	50 (100.0)		

[a]Number analyzed under severe (symptomatic) systolic hypotension (n=14; intervention arm A, n=5; intervention arm B) and under severe (symptomatic) diastolic hypotension (n=24; intervention arm A, n=18; intervention arm B) are subsets of the outcome measure systolic hypotension and diastolic hypotension respectively; [b]Same participant had severe (symptomatic) diastolic hypotension; [c]Same participant had severe (symptomatic) systolic hypotension; [d]Occurred in the participant with severe (symptomatic) hypotension; *Statistically significant.

TABLE 5: Apgar score in opioid-free and opioid-based analgesia arms.

	Intervention arms			
Variable	**Arm A n=50 (%)**	**Arm B n=50 (%)**	**X^2**	**p-value**
1st minute Apgar score				
Less than 4	0 (0.0)	0 (0.0)	2.17	0.140
4-6	2 (4.0)	6	(12.0)	
7-10	48 (96.0)	44 (88.0)		
5th minute Apgar score				
Less than 4	0 (0.0)	1 (2.0)	1.010	0.315
4-6	0 (0.0)	0 (0.0)		
7-10	50 (100.0)	49 (98.0)		

TABLE 6: Harms.

	Intervention arms		Total	
	Arm A	Arm B	Intervention arms	
Variable	Affected/At risk (%)	Affected/At risk (%)	Arm A affected/ At risk (%)	Arm B affected/ At risk (%)
Mortality	0/50 (0.0)	0/50 (0.0)	0/50 (0.0)	0/50 (0.0)
Serious adverse event[a]				
Severe (Symptomatic) hypotension[b]	1/50 (2.0)	0/50 (0.0)	1/50 (2.0)	0/50 (0.0)
Other adverse events[a]				
Bradycardia[b]	0/50 (0.0)	2/50 (4.0)	23/50 (46.0)	20/50 (40.0)
Mild (Asymptomatic) diastolic hypotension[b]	23/50 (46.0)	18/50 (36.0)		
Mild (Asymptomatic) systolic hypotension[b]	13/50 (26.0)	5/50 (10.0)		

[a]Time frame was preoperative, intraoperative and 24 hours postoperative; [b]Systematic assessment.

erative.[7] Hwang et al., used a regimen of bolus 50 mg/kg and a continuous infusion dose (15 mg/kg/hr), very similar to what this research used, and they reported significantly lower pain scores in the magnesium group in the 48 hours post-surgery.[18] Akinyele also used bolus 30 mg/kg and continuous infusion (10 mg/kg/hr) and concluded that intravenous $MgSO_4$ as adjuvant analgesic under subarachnoid block improved postoperative analgesia and reduced postoperative opioid consumption with no side effects.[19] Apan et al. administered bolus 5 mg/kg and 500 mg/hr infusion for 24 hours and pain scores were assessed 4-hourly in the 24 hours post-operation.[20] Pain scores were found to be similar in the magnesium and control groups except at 12 hours post-operation, showing unsustained pain control. Although, in their study, $MgSO_4$ was administered for 24 hours, the authors attributed the unsustained effect to the low cumulative dose of $MgSO_4$ used.

Seyhan et al. in comparing the effects of three different dose regimes of $MgSO_4$ on propofol requirements and postoperative pain relief among other outcomes, reported that a 40 mg/kg bolus of $MgSO_4$ reduced postoperative opioid consumption, and the effect was enhanced by a maintenance infusion of 10 mg/kg/hr.[21] Moreover, they stated that a 20 mg/kg/hr maintenance infusion provided no additional advantage and induced unwarranted hemodynamic effects. Helmy et al. considered 30 mg/kg bolus insufficient and conceded that this together with the failure to use continuous infusion after bolus may have affected their study outcome.[22] From findings in our study and others cited above, there is a suggestion that beyond the bolus and continuous infusion of $MgSO_4$, the cumulative dose used is also important to achieve an effective postoperative analgesia. However, the limit of safe use should be an important consideration.

Most of the women who received opioid-free analgesia in this study required rescue opioids in the 24 hours post-surgery. Conversely, women who were on opioid-based analgesia needed no further opioids. The difference was significant and suggests that opioid analgesics are required for the adequate and effective management of postoperative pain. However, mean opioid analgesic consumption was lower in women who received opioid-free analgesia. Only a single dose of rescue opioid analgesic was required by most of them, and the rest required two doses. It is noted that four of the women did not require rescue opioid analgesics at all. This is in keeping with the findings of Apan et al. that reported a reduction in total analgesic consumption in the magnesium group.[20] Hwang et al. also reported a lower cumulative postoperative opioid consumption in the magnesium group.[18] From the regimen point of view, this finding is also in line with that at the Cleveland Clinic, USA, that within the first month of introducing an opioid-free postoperative analgesia regimen for pain following CS, opioid use among post-CS patients fell substantially by 70%.[23] At Kirk Medicine in the University of Southern California, the practice of avoiding or limiting opioid use in the postoperative period achieved a drop in postoperative opioid usage ranging between 45 to 60%.[24]

$MgSO_4$ is the available form of magnesium most common in clinical use. Its analgesic effect may be related to its action at the N-methyl-D-aspartate receptors (NMDA-R). NMDA-R ion channel is susceptible to voltage-dependent block by extracellular magnesium ion (Mg^{2+}). When extracellular Mg^{2+} enter the NMDA-R pore, they bind tightly and prevent further ion permeation; including calcium ion (Ca^{2+}) influx.[25] $MgSO_4$ thus has an antagonist activity at the NMDA-R by which it alters the mechanism of hyperalgesia, which underlies its role in postoperative pain management.[8] High levels of magnesium in the body (hypermagnesemia) can cause hypotension, nausea and vomiting, bradycardia, and respiratory depression and toxic levels can lead to respiratory and cardiac arrest. Like in this study, the dose of $MgSO_4$ used in many studies on its role in postoperative pain management is guided largely by how $MgSO_4$ has been safely used in managing preeclampsia/eclampsia.[8] Using bolus 4g and a continuous infusion of 1 g/hr in this study, none of the women who received $MgSO_4$ had respiratory depression. There was no significant difference in number of women who had diastolic hypotension and bradycardia. Systolic hypotension was significantly higher among women who had $MgSO_4$. However, only one of the women (who had a systolic BP of 52 mmHg) manifested symptoms of hypotension which was not statistically significant. This suggests that spinal anesthesia alone may be associated with BP readings in the hypotension range, but a systolic BP<60 mmHg may be considered clinically relevant hypotension. This is in keeping with findings from previous studies that reported perioperative use of $MgSO_4$ with insignificant or no side effects at all.[7,12,18,19]

There was no significant difference in Apgar scores at 5 minutes of neonates born to women in both arms of the study. This is in keeping with the finding of Helmy et al., suggesting therefore that perioperative $MgSO_4$ administration does not affect the status of the neonate at birth.[22] Thus, with all necessary precautions in place, $MgSO_4$ is considered safe for perioperative use with spinal anesthesia.

Perioperative use of intravenous PCM has been shown to reduce opioid requirements in the postoperative period.[26] Studies that compared intraoperative intravenous PCM with $MgSO_4$ found that PCM produced more postoperative analgesia.[10,27,28] In this study, administering both intravenous PCM and $MgSO_4$ perioperatively, was to maximize the preventive use of both drugs. Despite the more frequent dosing of opioids in the control arm of this study, the combined preventive analgesic effect of intravenous PCM and $MgSO_4$ may have contributed to the lower postoperative pain scores and reduced opioid consumption recorded in the opioid-free analgesia arm.

This study set out as a non-inferiority RCT to establish whether opioid-free analgesia using intravenous $MgSO_4$, intravenous PCM, and postoperative rectal diclofenac was inferior to the control opioid-based analgesia in effectiveness. The non-inferiority limit was a difference in the mean pain score of NRS<1.3. From the results of this study, non-inferiority was established.

A randomized controlled design, outcome assessors blinding, intention-to-treat analysis, and ease of reproducibility are the strengths of this study. Limitations include the single-centre design which limits generalizability, the subjectivity of pain assessment, and the exclusion of women on $MgSO_4$ for another clinical indication-preeclamptic and eclamptic women-which means that the study result does not apply to this very important category of women who end up with CSs in many cases. These can be addressed by further studies.

CONCLUSION

The effectiveness of opioid-free analgesia using perioperative intravenous $MgSO_4$, intravenous PCM and postoperative rectal diclofenac is non-inferior to, and as safe as the opioid-based analgesia compared. The clinical implication of this is that the use of pentazocine in the postoperative period can be limited to only one dose in most cases or two doses in some patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Olakunle Ifeoluwa Makinde, Egbaname Obozegie Samuel Aigere;* ***Design:*** *Olakunle Ifeoluwa Makinde, Egbaname Obozegie Samuel Aigere, Nuvie Oyeyemi;* ***Control/Supervision:*** *Olakunle Ifeoluwa Makinde;* ***Data Collection and/or Processing:*** *Olakunle Ifeoluwa Makinde;* ***Analysis and/or Interpretation:*** *Olakunle Ifeoluwa Makinde, Adedotun Daniel Adesina, Nuvie Oyeyemi;* ***Literature Review:*** *Olakunle Ifeoluwa Makinde, Egbaname Obozegie Samuel Aigere;* ***Writing the Article:*** *Olakunle Ifeoluwa Makinde;* ***Critical Review:*** *Egbaname Obozegie Samuel Aigere, Nuvie Oyeyemi, Adedotun Daniel Adesina;* ***References and Fundings:*** *Olakunle Ifeoluwa Makinde.*

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