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Comparative Effects of Single Agent Rectal Diclofenac versus a Combination of Rectal Diclofenac and Intramuscular Pentazocine, on Post Caesarean Section Pain Relief in a Tertiary Institution in Southern Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author NJK designed the study, performed the statistical analyses and wrote the first draft of the manuscript as a dissertation in fulfilment of the award of fellow West African College of Surgeons. Authors DAM and PAA were supervising consultants for the dissertation and rewrote the manuscript for publication. Author DHJ assisted in data collection, managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Caesarean section commonly causes moderate to severe pain in the first 24 hours after surgery with associated discomfort, delayed ambulation, difficulty initiating breastfeeding and prolonged hospital stay. Receiving adequate analgesia after caesarean section is very important for the patient's comfort, overall wellbeing and recovery.
Objective: To compare the efficacy, time to rescue-analgesia and side effects of single agent rectal diclofenac versus its combination with intramuscular pentazocine for pain management after caesarean section in Rivers State University Teaching Hospital (RSUTH).

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Methodology: A randomized double-blind clinical trial was carried out at the RSUTH. A total of 120 patients scheduled for either elective or emergency caesarean section were recruited. Group 'A' received rectal diclofenac 100 mg and intramuscular placebo (unimodal group) while group 'B' received rectal diclofenac 100mg and intramuscular pentazocine 30 mg (multimodal group). Socio-demographic information was collected via structured proforma, while Visual Analog Scale (VAS) was used to assess the level of pain. Data were analyzed using SPSS version 20 and statistical significance was set at $p < 0.05$.

Results: The mean ages of respondents in unimodal and multimodal groups were 31.7 ± 4.3 years and 31.3 ± 5.2 years respectively. The difference in the median pain score and range was significant only at 8 hours between the groups, there was no significant difference before and after 8 hours. Although the mean time (in minutes) to first rescue-analgesia was shorter in the unimodal (147.5 ± 60.1) as compared to the multimodal group (170.0), this difference was not statistically significant. There was no side effect noticed in either of the two groups.

Conclusion: The combined agents (diclofenac and pentazocine) had a superior analgesic effect to the single agent (diclofenac alone) when given as used in the study.

Keywords: Analgesia; caesarean section; unimodal; multimodal; diclofenac; pentazocine.

1. INTRODUCTION

Caesarean section is one of the most common surgeries done globally in obstetrics. This operation commonly induces severe pain, hence reducing the pain after Caesarean section is very important. The International Association for the Study of Pain (IASP) has noted that uncontrolled acute pain not only leads to discomfort and suffering, but can also have unwanted consequences, such as delayed wound healing, increased risk of morbidity, prolonged hospital stay, and the risk of developing chronic persistent pain [1]. In fact, in any post-caesarean section patient, early ambulation, breastfeeding and maternal bonding with the infant may be disturbed by poor pain management [2].

Adequate pain management after caesarean section, using safe and effective analgesic drugs is a universal concern because pain relief is a fundamental human right [3]. Caesarean section patients have additional compelling reason to be provided with adequate pain relief, because thrombo-embolic diseases, which are increased during pregnancy could be prevented by early mobilization [4]. Besides, these patients need to be pain-free to care for their newborn and breastfeed them adequately.

There is currently no gold standard for post caesarean pain management [5]. However, opioid analgesic drugs were commonly used for pain relief, but none of them is ideal [6]. Morphine and other opioids have been administered either through neuraxial or systemic approach in post-operative pain management [7]. The neuraxial could be intrathecal or epidural while the systemic could be oral, intramuscular or intravenous routes. There is also infiltration of surgical wound with local anaesthetic agents [8]. Intramuscular pentazocine, a partial agonist opioid is widely used in low resource countries like Nigeria and most centers in the developing world for post-operative analgesia with limited side effects [9]. The two most commonly used opioids in such regions are pentazocine and tramadol [10].

The analgesic effect of opioid is dependent on continuous stimulation of opiate receptors, inhibiting nociceptive impulses and the effect of a single injection persists for 4-6 hours [11]. Opioid analgesia can have negative impact on breastfeeding outcome such as reduction of babies' alertness and suckling vigor [12]. Central and peripheral side effects of opioids such as pain, hypotension, pruritus, nausea and vomiting, sedation, respiratory depression, dizziness, ileus, flashing and tachycardia restrict their use [13]. High cost, the risk of abuse and unavailability are other reasons for limited use of these drugs as routine analgesic medication after surgery. These limitations of opioids have led to the introduction of non-opioid analgesia.

Some non-opioid analgesic medications such as non-steroidal anti-inflammatory drugs (NSAID) have been found to reduce pain of uterine contractions by inhibiting prostaglandin synthesis through the inhibition of cyclooxygenase. Apart from direct anti-inflammatory and analgesic effects, these drugs have an indirect effect on pain by reducing the chemical mediators of pain that make painful impulses leading to visceral pain relief. Diclofenac, a potent NSAID, in addition has an antipyretic property due to its direct depressant effect on the heat regulatory

center of the brain. It has been shown to provide effective pain relief in severe conditions such as dysmenorrhea and renal colic. It has also been shown to reduce opioid requirement in orthopedic, abdominal and gynecologic surgeries. Its onset of action is 30 minutes and the effect last for 6 hours [14].

Diclofenac does not interact with anesthetics, for example, it does not cause respiratory depression and it has been suggested that giving diclofenac (NSAIDs) before surgery begins may minimize the initiation of pain in the peripheral tissues and enhance their effectiveness as analgesics [15]. It is licensed for use during pregnancy and lactation [16]. When given on a regular basis, active substances have been detected in breast milk, but in such small quantities that it is not likely to cause undesirable effect [17]. Hence, diclofenac helps in early mobilization of the patient which reduces the risk of deep vein thrombosis and enhancing early postpartum recovery. In addition, a faster recovery post caesarean section means early establishment of breastfeeding which enhances maternal-infant bonding. Diclofenac could be administered parenterally, orally or as a suppository. Some side effects associated with diclofenac (NSAID) include: heartburn or dyspepsia and upper or lower gastrointestinal bleeding, ischemic colitis, proctitis, abdominal pain, local allergic reaction, itching and swelling [18].

Generally, analgesic agents are many and the choice of the method of pain control are determined by drug availability, surgeon's preference, institutional protocols, patient's preference, available resources and financial considerations [19]. In RSUTH, there is no written protocol for post caesarean section pain relief and different authorities manage post caesarean section pain differently. Some use single agent diclofenac, some use single agent pentazocine while others use a combination of diclofenac and pentazocine. This study seeks to compare the effectiveness of single agent rectal diclofenac 100 mg versus its combination with intramuscular pentazocine 30 mg for post caesarean section pain relief. This will enable us suggest a local protocol for our institution and possibly others in the country.

2. METHODOLOGY

This study was conducted in the RSUTH, a tertiary hospital owned and funded by the Government of Rivers State, and patients are expected to pay directly for services (except few that participate in National Health Insurance Scheme). It provides emergency obstetric services to women referred from other centers, as well as providing antenatal care and delivery services for low and high-risk pregnant women booked with the hospital. The hospital is well equipped and has round the clock availability of qualified team comprising of Obstetricians, Pediatricians and Anaesthetist. There is availability of laboratory and blood bank services in the hospital. Cases for elective caesarean operations are admitted from the clinic into the antenatal ward, prepared and operated on the managing team's theatre day. Cases for emergency caesarean sections are admitted and operated upon during the call duty. The department does an average of three caesarean sections (both elective and emergency) in a day.

The study was a prospective, double blind randomized clinical trial. The study population was pregnant women scheduled to undergo either elective or emergency caesarean section. Those who had elective or emergency caesarean section during the period of study, whose operative time lasted less than 90 minutes and who gave informed consent were included, while those with known drug allergy, those with medical co-morbidity, those with history of epigastric pain or gastrointestinal bleeding and those who had complications at surgery were excluded.

Using the formula for comparison of two groups, $n = \frac{(Z\alpha+Z\beta)^2(S1^2+S2)}{(\mu1-\mu2)^2}$, Where n - Minimum sample size; Zα - Significant level of 95%; corresponds to a value of 1.96, Zβ - Power of study, set at 90%; corresponds to a value of 1.28; S1 - Standard deviation of VAS scores from unimodal group in a similar study[1]=0.67; S2 - Standard deviation of VAS scores from multimodal group in a similarstudy[1]=0.48; μ1 = μ2 - Minimum mean difference detected between the two groups (the effect size) = 0.4, a sample size of 50 per group was calculated. However, 60 subjects per group were recruited for this study, making a total of 120 subjects.

An average of three caesarean sections were carried out daily (both elective and emergency) out of which one was randomized daily, giving a total of five per week. It therefore took twenty weeks to obtain the desired sample size. This study was carried out over a 5-month period (July to December 2017). The structured

proforma was used to collect the following, Socio-demographic information, Obstetrics Information such as parity and indications for the caesarean section, Visual Analog Scale (VAS), Time to rescue analgesia and observed side effects.

The Visual Analog Scale (VAS) is a psychometric response scale for assessing pain. It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points, for example, 0 – 10 where zero indicates 'no pain' and 10 indicates 'maximal pain'. VAS is the most common pain scale for quantification of pain [20].

The eligible subjects were randomized into groups using either 'A' or 'B'. 'A' represents the unimodal group while the 'B', multimodal group. The subjects were blinded to the type of drug being taken. The research assistants assessing the outcome in both groups were also blinded to the treatment received by the subjects. The drugs were administered by trained research assistants. The 'A' group had rectal diclofenac 100 mg 8 hourly for 24 hours and intramuscular placebo 6 hourly for 24 hours, while the 'B' group had rectal diclofenac 100 mg 8 hourly for 24 hours and intramuscular pentazocine 30 mg 6 hourly for 24 hours. The first dose commenced in the recovery room at time zero. Before each administration of rectal diclofenac, the level of pain was assessed by the research assistant who will administer the drugs, then after the administration of the last drug in the pack, the patient was asked about her satisfaction with respect to the pain relief. Those who received rescue analgesia for breakthrough pain and who had side effects to the drugs used were identified and noted.

Following the informed consent, their socio-demographic characteristics and other eligibility characteristics were documented in the structured proforma for each participant and their folder tagged for identification. The primary outcome variable was level of pain assessed using the Visual Analog Scale (VAS), scored 0 - 10. Zero being 'no pain' and 10 indicating 'maximal pain'. The secondary outcome variables were the duration of analgesia post-operatively expressed in hours, the frequency of breakthrough analgesia and the presence of side effects. Three research assistants, who were chosen from the junior residents in the department, were trained for 5 days on how to administer the consent form, questionnaire to obtain the socio-demographic information and indication for surgery, how to assess pain using Visual Analog Scale, how to administer the drugs and how to assess patient's satisfaction after the last drug has been administered.

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 20. The data were presented as tables and charts as appropriate. Qualitative variables were expressed as frequencies and projections. Kolmogorov-Smirnov statistics was used to check for normality at the $P<0.05$ significant level; this was not significant as the data were normally distributed, so we fail to reject the null hypothesis. Quantitative variables, that were normally distributed (parametric), were summarized as means and standard deviation; and the differences in means between the two groups was compared using the student's t-test, while non-normally distributed quantitative variables (non-parametric)were summarized using medians and ranges; and the Mann Whitney U test was applied to compare differences in median between the two groups; Chi square test and Fisher's Exact test were used as appropriate to determine statistically significant differences in proportions between the groups. Statistically significance was set at $p<0.05$.

3. RESULTS

3.1 Socio-demographic Characteristics of Respondents

The study had a total of 120 women, 60 each were assigned to unimodal and multimodal groups. The mean ages of respondents in unimodal and multimodal groups were 31.72 ± 4.30 years and 31.30 ± 5.21 years respectively. The differences in the mean ages, mean Body Mass Index (BMI) and mean gestational age (GA) across the two groups were not significant as shown in Table 1.

The majority of respondents in unimodal group 44 (73.3%) and multimodal group 38 (63.4%) were aged 25 – 34 years, with a range of 15 – 44 years. The differences in proportions of the age categories across unimodal and multimodal groups were not significant (p = 0.401). The parity range for both groups was 1 – 6 and the median parity of the respondents was 2 in both groups. The majority of respondents in unimodal group 34 (56.7%) and multimodal group 33

Table 1. Comparison of mean characteristics between unimodal and multimodal groups

Variables	Unimodal (diclofenac only) Mean ± SD/n (%)	Multimodal (diclofenac +pentazocine) Mean ± SD/n (%)	Total n (%)	t	P-value
Age (years)	31.72±4.30	31.30±5.21		0.478	0.634
BMI (kg/m^2)	29.85±4.86	29.54±5.78		0.302	0.763
GA (weeks)	38.40±2.26	37.98±2.54		0.947	0.346
Age group					
15 – 24 years	2 (3.3)	5 (8.3)	7 (5.8)		
25 – 34 years	44 (73.3)	38 (63.4)	82 (68.3)		
35 – 44 years	14 (23.2)	17 (28.3)	31(25.9)		
	Fishers exact test = 1.951; p = 0.401				
Marital status					
Single	5 (8.3)	6 (10.0)	11 (9.2)		
Married	55 (91.7)	54 (90.0)	109 (90.8)		
	Chi square = 0.100; p 0.752				
Parity					
Primiparous (Para 1)	22 (36.7)	25 (41.7)	47 (39.2)		
Multiparous (Para 2-4)	34 (56.7)	33 (55.0)	67 (55.8)		
Grand multiparous (Para ≥5)	4 (6.6)	2 (3.3)	6 (5.0)		
	Fishers exact test = 0.875; p = 0.684				
Type of caesarean section					
Elective	21 (35.0)	25 (41.7)	46 (38.3)		
Emergency	39 (65.0)	35 (58.3)	74 (61.7)		
Total	**60 (100)**	**60 (100)**	**120 (100)**		

(55.0%) were multiparous women. The differences in the proportion of the categories of parity by group were not significant (p = 0.684) as shown in Table 1.

Emergency caesarean sections had higher proportion in both unimodal 39 (65.0%) and multimodal 35 (58.3%), while 21 (35.0%) and 25 (41.7%) of the unimodal and multimodal groups respectively were elective caesarean sections. The difference in proportion of the type of caesarean section across the groups was not significant (p = 0.453) as shown in Table 1.

3.2 Comparison of Analgesic Effect between the Unimodal and Multimodal Groups

At zero hour, the median pain score and ranges were 0 (0 – 10) and 0 (0 – 10) among respondents in unimodal and multimodal groups respectively. The difference in the median pain score across groups at zero hour was not significant (p = 0.118). At 8 hours, the median pain score and ranges were 0 (0 – 10) in the unimodal group and 0 (0 – 5) in the multimodal group, this difference in the median pain score was statistically significant (p = 0.033). At 16 and 24 hours, the differences in the median pain score and ranges across the groups were not statistically significant. The mean pain scores were consistently lower in the multimodal group in comparison to the unimodal group across the follow-up period as shown in Fig. 1.

3.3 Comparison of the Time to Rescue Analgesia between the Two Groups

The mean time to first rescue analgesia which was recorded within the first 8 hours post-operative period were 147.5 ± 60.1minutes and 170.0 minutes for unimodal and multimodal groups respectively. Although the mean time was shorter in the unimodal group in comparison to

the multimodal group, the difference was not statistically significant (p = 0.760). While the unimodal group had mean time to second rescue analgesia of 250.0 minutes (one patient), none of the respondents in the multimodal groups requested for second rescue analgesia. Third rescue analgesia was not requested by any of the respondents of the two groups as shown in Table 2.

Fig. 2 shows the proportion of those who requested rescue analgesia in both the unimodal and multimodal groups. Four respondents (6.7%) in the unimodal group and 1 respondent (1.7%) in the multimodal group requested for first rescue analgesia in the first 8 hours. A second rescue analgesia was requested by a respondent (1.7%) in the unimodal group while none (0.0%) in the multimodal requested a second rescue analgesia.

3.4 Comparison of the Level of Satisfaction between the Two Groups

A comparison of the level of participants' satisfaction experienced during the first 24 hours post operatively revealed that there was no statistically significant difference between the two groups (p = 0.224). A higher proportion of respondents 44 (73.3%) which was the same in both groups were satisfied. More of the respondents 14 (23.0%) in comparison to 9 (15.0%) in the multimodal and unimodal groups respectively were very satisfied. Only one respondent (1.7%) in the unimodal group was undecided and none (0.0%) in the multimodal group. The unimodal group had a higher number of respondents who were dissatisfied 6 (10.0%) in comparison to the multimodal group 2 (3.3%) as shown in Table 3.

3.5 Occurrence of Side Effects

Sedation, hypotension, pruritus, dizziness, nausea, vomiting, heartburn or dyspepsia, gastrointestinal bleeding and other side effects of pentazocine or diclofenac were not observed in any of the respondents in the two groups. Respiratory depression, poor suckling, excessive sleep or neonatal jaundice did not occur among the babies of the mothers in the two groups.

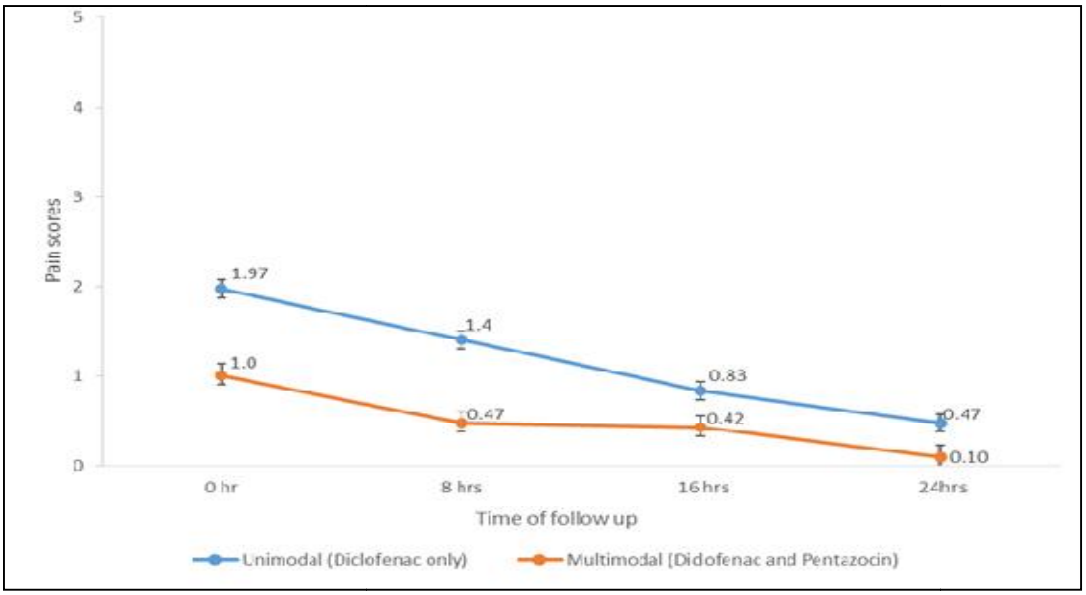

Fig. 1. Error bar showing the mean pain scores of unimodal and multimodal groups

Table 2. Comparison of mean time to request for analgesia between groups

Request for rescue analgesia*	Unimodal (diclofenac only) Mean ± SD	Multimodal (diclofenac + pentazocine) Mean ± SD	t	P-value
Time of first request (mins)	147.5±60.1	170.0±0.0	0.335	0.760
Time of second request (mins)	250.0±0.0	-	-	-

**None of the respondents in the multimodal group had second rescue analgesia*

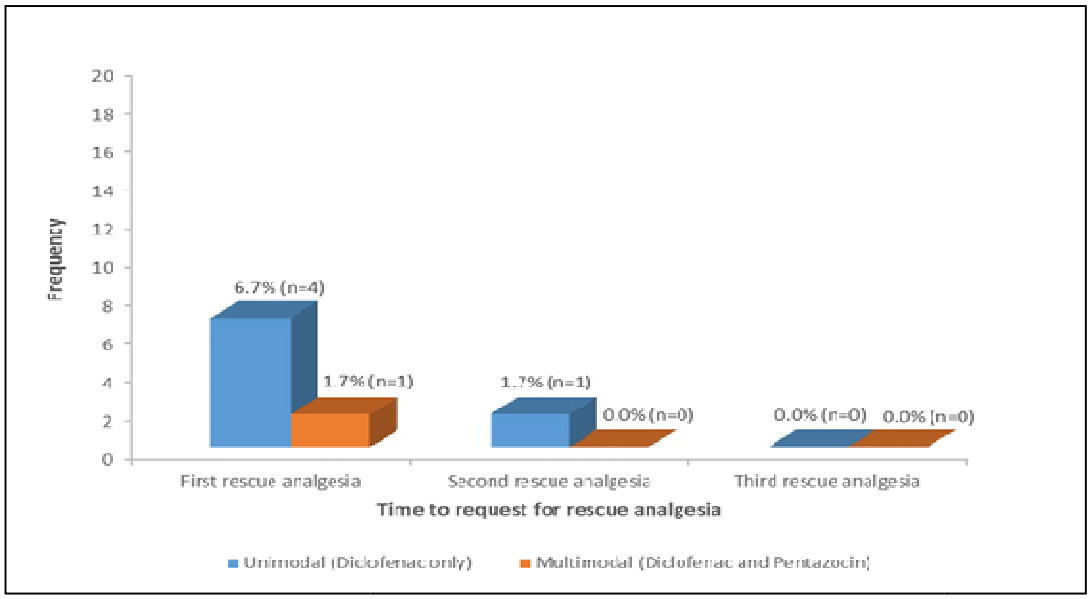

Fig. 2. Proportion of respondents that requested for rescue analgesia in the two groups

Table 3. Comparison of the level of satisfaction among respondents in the two groups

Level of satisfaction	Unimodal (diclofenac only) n(%)	Multimodal (diclofenac + pentazocine) n(%)	Total n (%)
Dissatisfied	6 (10.0)	2 (3.3)	8 (6.7)
Undecided	1 (1.7)	0 (0.0)	1 (0.8)
Satisfied	44 (73.3)	44 (73.3)	88 (73.3)
Very satisfied	9 (15.0)	14 (23.0)	23 (19.2)
Total	60 (100.0)	60 (100.0)	120 (100.0)

Fisher's exact test = 3.902; p = 0.224

4. DISCUSSION

Post caesarean section analgesia is indispensable for reducing post-operative stress, providing subjective comfort and facilitating post-operative recovery. This study compared the post caesarean analgesic effect between single agent diclofenac (unimodal) and its combination with pentazocine (multimodal). In this study, the maternal characteristics (age, parity and BMI) were similar at baseline in both the unimodal and multimodal groups. Hence, revealing that both groups were comparable, though they may not be at same baseline pain level.

Noteworthy, limited studies exist in the literatures comparing diclofenac as a single agent analgesic after caesarean section and its combination with pentazocine even though these drugs and others are widely used for this purpose. Diclofenac was chosen as a single agent in this study because of its good analgesic properties, non-sedative and lack of the respiratory depressant effect seen in opioids. It has actually been found to be better when compared with paracetamol as was seen in the study by Munishanka et al. [21], where the analgesic effects of both drugs were compared in management of post caesarean pain. Similarly, diclofenac was also noted to have better analgesic property than pethidine in the study by Al-hakim et al. [22] and Shahraki et al. [23] where they were compared in post caesarean pain management. However, Mahapatra SJ et al. [24] found that Pentazocine was significantly better than Diclofenac for pain relief in Acute Pancreatitis.

Hence, the finding of a statistically significant difference in the mean pain score between group A (diclofenac only) and group B (diclofenac and pentazocine) within the first 8 hours post caesarean section in this study, reveals a better pain control in the multimodal group in comparison to the unimodal group. One plausible

explanation to this phenomenon could be the synergistic effect of combination of two different analgesics with different mechanisms of action, with the opioid acting on the central nervous system, while NSAIDs (e.g. diclofenac) inhibit prostaglandin synthesis from arachidonic acid by inhibiting cyclooxygenase, thus reducing inflammation [25]. Thus multimodal strategies help achieve better pain relief while using lower doses of opioids and potentially fewer adverse effects, by affecting pain through different mechanisms of action and pathways [26]. This finding is in keeping with similar studies by Adeniji et al. [1], Olateju et al. [10], Adamou et al [27] and Egede JO et al. [28] who in contrast to this study, compared multimodal (opioid and NSAID) with unimodal (opioid only) in post caesarean section pain relief. These studies, along with the present study demonstrated that combining two drugs of different mechanism of action had better analgesic effect than a single agent. However, unlike the present study, which used NSAID as a single agent, these studies used pentazocine.

Although, the mean time to first rescue analgesia in the unimodal group was not significantly different from the multimodal group, only the unimodal group sort and had a second rescue analgesia. This possibly connotes that the analgesic effects on both groups are comparable, however, the multimodal group appear to be superior. Also, the finding of no significant difference in the Mean Time to first rescue analgesia possibly exposes the usefulness of NSAIDs as a single analgesic agent in low resource settings.

The side effects of pentazocine or diclofenac were not noticed in this study population probably because the duration of the study was for only 24 hours or the use of low dose pentazocine in the multimodal group. The choice of rectal diclofenac when compared to other routes of administration is worthy of note as this rectal route avoids rare but hazardous complications of intramuscular diclofenac such as necrotizing fasciitis, anaphylactic shock and upper limb gangrene [29,30]. Contrary to some studies [31,32] where side effects of the drugs were noticed, this present study did not show any side effect in either the mothers or neonates possibly because the drugs were given for only 24 hours. This finding of no side effect agrees with the study by Adamou et al. [27].

5. CONCLUSION

The multimodal (diclofenac + pentazocine) group had a superior analgesic effect in comparison to the unimodal (diclofenac only) group. The time to first rescue analgesia between the two groups showed no significant difference, however none of the women in the multimodal group made second request for rescue analgesia. No side effect was observed in both groups within the period of study. Obstetricians should ensure that effective post caesarean section pain management is given to all patients. This research was a single-center study, hence the limiting extent of generalizability of the findings.

Government should support a prospective multicentered double blind controlled trial comparing the effectiveness, time to rescue analgesia and side effects of the agents used in this study and for longer period to derive a stronger evidence and generalization.

CONSENT AND ETHICAL APPROVAL

Ethical approval for the study was obtained from the Rivers State Health Research and Ethics Committee in Port Harcourt Nigeria. Participation was voluntary as Informed & written consent to participate and withdraw from the study was obtained and strict confidentiality was assured. No participant was made to pay for the analgesic drugs used for the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist. The drugs used in the study were provided by the first author with no aid from the manufacturers or distributors of diclofenac or pentazocine.

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