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Randomized comparison of effectiveness of unimodal opioid analgesia with multimodal analgesia in post–cesarean section pain management

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Background: Postoperative pain leads to patient discomfort, decreased level of satisfaction, prolonged recovery, and higher health costs. Acute pain control therefore improves the overall quality of life in patients undergoing cesarean section. Pain relief is a fundamental human right, but there is no gold standard for post–cesarean section pain management.

Objective: To compare the efficacy of pentazocine and tramadol used in unimodal and multimodal (in combination with piroxicam) approach, in the management of post–cesarean section pain.

Materials and methods: This study employed a random allocation design to compare the effectiveness of intramuscular pentazocine (60 mg) or tramadol (100 mg) as single analgesic agent and in combination with daily intramuscular piroxicam 20 mg, for the management of post–cesarean section pain during the immediate 12 hours after surgery. The primary outcome measure was control of postoperative pain, while the secondary outcome measures were the analgesic agent onset of action, duration of action, patient satisfaction, and maternal and neonatal adverse outcomes. Data obtained were entered into a predesigned sheet and analyzed with the Statistical Package for Social Sciences version 17. Means ± standard deviation (SD) were calculated for the quantitative variables, and the difference between two independent groups was compared using unpaired Student's *t*-test. The level of significance was set at 0.05.

Results: A total of 120 patients were equally and randomly allocated to four study groups – two that received unimodal analgesia (the pentazocine group and the tramadol group) and two that received multimodal analgesia (the pentazocine-piroxicam group and the tramadol-piroxicam group). Among the unimodal groups, tramadol had a faster onset of action, but pentazocine had a longer duration of action and provided better control of pain. Among the multimodal groups, the combination of pentazocine with piroxicam was superior to the tramadol with piroxicam combination, and it was also more effective than pentazocine alone.

Conclusion: The multimodal approach of combining pentazocine with piroxicam is a safe, effective, and an acceptable mode of analgesia for post–cesarean section pain management, especially in a resource-constrained setting.

Keyword: NSAID, opiods, piroxicam, tramadol, pentazocine

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Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[1,2] Postoperative pain leads to patient discomfort, decreased level of satisfaction, prolonged recovery, and higher health care costs. The International Association for the Study of Pain, in one of its publications, submitted

that uncontrolled acute pain not only leads to discomfort and suffering, but can also have unwanted consequences, such as delayed healing, an increased risk of morbidity, a prolonged hospital stay, and the risk of developing chronic persistent pain.[3] Specifically, in any post–cesarean section patient, poor pain control may interfere with ambulation, breastfeeding, and early maternal bonding with the infant.[2] Adequate postoperative analgesia hastens ambulation, decreases maternal morbidity, improves patient outcome, and facilitates care of the newborn. These therefore improve the overall quality of life in patients who have undergone cesarean deliveries.[4]

Surgical operations are associated with severe pain, especially in the first 6 hours of the postoperative period.[4] Adequate pain relief following cesarean section in women, using safe and effective analgesic combinations, is a universal concern because pain relief is a fundamental human right.[5] There is currently no gold standard for post–cesarean section pain management. The options are many, and the choices of the method of pain control are determined by drug availability, institutional protocols, individual preferences, available resources, and financial considerations.[6]

Many options are available for the treatment of postoperative pain, including systemic analgesics (ie, opioids and nonopioids) and regional analgesic techniques (ie, neuraxial and peripheral). However, multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system. This results in additive or synergistic analgesia, with lowered adverse effects, when compared with the administration of individual analgesics.[7] Several studies have investigated different protocols of postoperative pain management in women undergoing cesarean section, and some new technologies have been reported.[8] Among pain relieving agents, the opioids are the most commonly administered, either systemically or neuraxially.[4,8,9] Generally, opioids have important roles as postoperative analgesic agents, either as unimodal agents or as components of multimodal analgesia. Although multimodal analgesic combinations are well accepted, finding the right combination of analgesics remains the key challenge.[5]

In Nigeria and most centers in the developing world, the two most commonly used opioids are pentazocine and tramadol (as unimodal analgesics) due to resource constraint. However, limited studies are available in literature comparing these two opioids as unimodal or as components of multimodal analgesia in this context.

Combination of parenteral opioid (eg, pentazocine/tramadol) with nonsteroidal anti-inflammatory drugs (NSAIDs) eg, piroxicam, provides a form of multimodal analgesia, with the benefits of both analgesia and additive anti-inflammatory actions. Its long-acting ability makes piroxicam especially suitable for short-term daily dosage in the immediate postoperative period.

This study was undertaken to compare the effectiveness and possible side effects of the single parenteral agents pentazocine and tramadol as well as the combinations of parenteral pentazocine or tramadol with a single daily dose of parenteral piroxicam, in the immediate 12 hours post–cesarean section, in our institution. We aimed to determine whether there were differences in the efficacy of these two drugs when administered as single analgesic agents (unimodal) and to compare these unimodal agents as component agents in multimodal analgesia with a long-acting NSAID (piroxicam), in order to suggest a local protocol for post–cesarean section pain relief in the Nigerian context.

Materials and method

This study compared the effectiveness of intramuscular pentazocine (60 mg) or tramadol (100 mg) as single-agent post–cesarean section analgesics and the combination of pentazocine (60 mg) or tramadol (100 mg) with daily intramuscular piroxicam (20 mg), in the immediate 12 hours after surgery. The study was conducted between March 2006 and February 2010 at Ladoke Akintola University of Technology Teaching Hospital, Osogbo, Nigeria. Patients with uncomplicated cesarean deliveries and live babies were recruited, after obtaining informed consent, and were allocated using computer-generated random numbers to pentazocine only (P), tramadol only (T), pentazocine + piroxicam (P-P) or tramadol + piroxicam (T-P) groups. All the patients had spinal anesthesia at surgery, using 2 mL of 0.5% hyperbaric (heavy) bupivacaine, the equivalent of 20 mg bupivacaine hydrochloride intrathecally. The study design was with intention to treat, with no crossover of patients between analgesic agents. Each patient served as her own standard with respect to request for analgesia, which was predetermined at not less than 4-hour intervals. All patients were blinded to the analgesic agents. The institutional Ethical Review Committee granted approval for the study.

Exclusion criteria were: inhalational general anesthesia, stillbirths, prolonged obstructed labor, delirium, history of preexisting opioid dependency, raised intracranial pressure, peptic ulcer disease, porphyria, or coagulation disorders.

In total, 120 patients were equally randomly allocated into the four study groups. Each analgesic agent of study was commenced 30 minutes after surgery.

The primary outcome measure was control of postoperative pain, while secondary outcome measures were analgesic agent onset of action (inferred from the time interval from drug administration to the onset of calmness in the patient), duration of action (determined from the interval between drug administration and the patient's request for repeat analgesia), patient satisfaction (determined by assessing patients' desire for the same treatment for the next surgery), and maternal and neonatal adverse outcomes.

Pain control was assessed using a visual analog scale (VAS).[10] Each patient received teaching on the VAS at enrolment into the study (before the surgery). This VAS technique uses a 10 cm–long scale marked from 0–10, where 0 represents "no pain" and 10 represents "worst possible pain." Scores of 1–4 were classified as mild pain, greater than 4–8 as moderate pain, and above 8 as severe pain. To assess for sedative effect of the agents, a sedation score was applied. The sedation score[11] was evaluated on a scale of 0 to 4; where 0 = asleep and not arousable, 1 = asleep but arousable, 2 = drowsy, 3 = awake and not alert, and 4 = awake and alert. Increased sedation score indicated a lesser sedative effect of the drug. Trained research assistants, who were also blinded to the agents of study, undertook assessments 1 hour after administration of the analgesic agents.

Data obtained were entered into a predesigned sheet and analyzed with Statistical Package for Social Sciences version 17 (SPSS Inc, Chicago, IL, USA). Means ± standard deviation (SD) were calculated for quantitative variables, and the difference between two independent groups was compared using unpaired Student's *t*-test. The level of significance was set at 0.05.

Results

The mean maternal age and parity was similar in the respective unimodal and multimodal analgesia groups.

Unimodal analgesia groups

The onset of action in the T group (7.90 minutes versus [vs] 14.80 minutes) was significantly shorter than in P group ($P < 0.0001$); however, the duration of action was longer in the P group (Table 1). In the first 6 hours post–cesarean section, the P group was also both significantly more effective as an analgesic agent and more associated with sedation than the T group (Table 2). However, in the second 6-hour postoperative period, the observed pain control effects in both the unimodal groups were not significantly different ($P = 0.154$), but the sedation effects persisted (Table 3).

Multimodal analgesia groups

In the multimodal groups, the onset of action was shorter when compared with the unimodal groups (6.24 minutes and 11.22 minutes for T and P, respectively vs 7.9 minutes and 14.8 minutes for T-P and P-P, respectively). The duration of action in the P-P group was significantly longer than in the T-P group (6.15 hours vs 4.80 hours) ($P = 0.0004$). In the immediate first 6-hour postoperative period, patients' assessment of pain control was superior in the P-P group ($P < 0.0001$) but was associated with more sedative effects ($P < 0.047$). In the second 6 hours after cesarean section, the comparative advantage in pain control in the P-P group was maintained ($P < 0.0001$), though the mean VAS scores were improved in both groups. However, the sedation score in the P-P group was further reduced from an initial score of 1.81 at 6 hours to 1.52 at 12 hours, indicating increased sedative effects in the P-P group, whereas improved alertness was recorded for the T-P group (in which the sedation score rose from 2.43 to 2.74).

Patient satisfaction was 68.4%, 60.2%, 89.2%, and 70.9% in the P, T, P-P, and T-P groups, respectively.

Table 1 Demographic characteristics of patients and mean onset/duration of action of analgesia

Factors	Unimodal analgesia groups				Multimodal analgesia groups			
	Pentazocine group n = 30 mean (SD)	Tramadol group n = 30 mean (SD)	*t*	*P*-value	Pentazocine + piroxicam group n = 30 mean (SD)	Tramadol + piroxicam group n = 30 mean (SD)	*t*	*P*-value
Maternal age (yrs)	29.20 (3.61)	30.12 (3.43)	1.012	0.316	29.64 (2.82)	29.23 (3.10)	0.536	0.594
Parity	1.89 (1.10)	1.76 (0.98)	0.483	0.631	1.82 (1.12)	1.94 (1.09)	0.421	0.676
Maternal weight (kg)	64.75 (8.92)	64.53 (9.10)	0.095	0.925	63.81 (8.63)	64.62 (8.48)	0.367	0.715
Onset of action (min)	14.80 (2.83)	7.90 (2.21)	10.525	<0.0001	11.22 (2.62)	6.24 (2.35)	7.750	<0.0001
Duration of action (hrs)	2.56 (0.38)	2.03 (0.52)	4.507	<0.0001	6.15 (1.72)	4.80 (0.94)	3.772	0.0004

Abbreviation: SD, standard deviation.

Table 2 Mean pain and sedation scores first 6 hours postsurgery

Scores	Unimodal analgesia groups				Multimodal analgesia groups			
	Pentazocine group n = 30 mean (SD)	Tramadol group n = 30 mean (SD)	*t*	*P*-value	Pentazocine + piroxicam group n = 30 mean (SD)	Tramadol + piroxicam group n = 30 mean (SD)	*t*	*P*-value
Mean pain score (VAS)	4.21 (0.60)	5.86 (0.67)	10.048	<0.0001	2.63 (0.48)	3.92 (1.23)	5.351	<0.0001
Sedation score	1.60 (0.80)	2.32 (1.04)	3.006	0.0039	1.81 (1.03)	2.43 (1.32)	2.028	0.047

Abbreviations: VAS, visual analog scale; SD, standard deviation.

Discussion

In the study, the maternal characteristics (age, parity, and weight) were similar at baseline in both the unimodal and multimodal study groups. This eliminated the possible confounding influence of these factors.

Limited studies exist in the literature comparing pentazocine and tramadol as post–cesarean section analgesic agents, either as unimodal or multimodal analgesia, though these drugs and other opioids are widely used for this purpose.

Both pentazocine and tramadol are synthetic opioids. While, pentazocine is a potent analgesic, with both agonist and antagonist action at opioid receptors, it has no anti-inflammatory or antipyretic function. Unlike morphine, it is a weak antagonist at μ opioid receptors. Its analgesic action is derived from an agonist action on κ receptors, which interrupts pain pathways in the spinal cord.[12] Alternately, tramadol is a centrally acting analgesic and is structurally related to codeine and morphine, consisting of two enantiomers, both of which contribute to its analgesic activity via different mechanisms. (+)-tramadol and the metabolite (+)-O-desmethyl-tramadol are agonists of the μ-opioid receptor. While (+)-tramadol inhibits serotonin reuptake, (−)-tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord.[13] On the other hand, piroxicam is an NSAID of the oxicam variety, unrelated to acetylsalicylic acid. It has different characteristics from other NSAIDS in that it has a longer half-life (30 hours), due to its extensive protein-binding ability. This allows for daily dosage and thus, provides a longer duration of analgesia compared with the other NSAIDS.[14] These were the individual characteristics that influenced the choice of these agents.

In this study, tramadol was found to have a faster onset of action, and this finding was consistent with some earlier reports.[15,16] This is a very crucial characteristic, which must be considered in the choice of the timing of the administration of the postoperative analgesic agent. When compared with pentazocine in this respect, it might be advisable to delay the administering of tramadol until after the conclusion of surgery, whereas it might be more beneficial to administer pentazocine during the latter end of surgery. Pentazocine achieved better pain control in the first 6 hours post–cesarean section and had a longer duration of action when compared with tramadol. This finding is consistent with the report of the study by Kuti et al, in which pentazocine was compared with tramadol for pain relief in the intrapartum period;[15] however, this finding was not supported by the reports from Magrini et al.[16] Yet another study suggested that the sedative effect of pentazocine could diminish the anxiety associated with the outcome and processes of labor and might be responsible for its observed better analgesic profile.[17] It is also possible that the better pain control seen with pentazocine might be related to its sedative effects on the postoperative anxieties often exhibited in many patients. In this study, the analgesic effect of both drugs at 12 hours post–cesarean section was similar. It is likely that the repeat administration of either pentazocine or tramadol does not translate into a remarkable stepwise increased analgesic effect. Consequently, it might stand to reason that either

Table 3 Mean pain and sedation scores second 6 hours postsurgery

Scores	Unimodal analgesia groups				Multimodal analgesia groups			
	Pentazocine group n = 30 mean (SD)	Tramadol group n = 30 mean (SD)	*t*	*P*-value	Pentazocine + piroxicam group n = 30 mean (SD)	Tramadol + piroxicam group n = 30 mean (SD)	*t*	*P*-value
Mean pain score (VAS)	3.82 (0.72)	4.11 (0.83)	1.446	0.154	1.73 (0.86)	2.80 (0.24)	6.564	<0.0001
Sedation score	1.33 (0.62)	2.16 (0.73)	4.747	<0.0001	1.52 (0.67)	2.74 (0.36)	8.786	<0.0001

Abbreviations: VAS, visual analog scale; SD, standard deviation.

agent, with optimal dosage, attains its possible near maximal analgesic effects in the first 6 hours during the immediate postoperative period, though marginal pain control, as evidenced by reduced VAS scores, was also recorded for both agents in the second 6-hour postoperative period. However, it is noteworthy that most reports in the literature have not extended the comparison of the efficacy of these two agents beyond the first 6-hour postoperative period.

A previous report rated tramadol as less efficacious in the control of acute pain and concluded that it is better suited for chronic pain.[18] This report might justify the findings in our study. Apart from this, pentazocine also had a greater sedative effect than tramadol at both 6 and 12 hours post–cesarean section, and this is similar to earlier reports.[15,16] However, both these agents showed less optimal pain control duration as single agent (unimodal) analgesia. A previous study by Kolawole and Fawole suggested improving the analgesic property of pentazocine and tramadol by using these drugs in combination with other drug(s) in multimodal analgesia.[19] Previous study has established that the multimodal approach, irrespective of whether systemic or neuraxial, reduces the total dose of opioids required in the postoperative phase, as well as its cumulative side effects.[20] Some of these studies have compared the use of opioids alone (unimodal) with combinations of opioids and NSAIDs or acetaminophen (multimodal) and found that the multimodal approach was more effective.[5,20–22]

Our findings support that the multimodal approach was better than the unimodal approach, when comparing groups taking pentazocine only and pentazocine-piroxicam or tramadol only and tramadol-piroxicam, both in onset and duration of action. This is similar to the findings of other studies.[5,20–23] In this study, piroxicam also showed a synergistic effect on the efficacy of both tramadol and pentazocine. Opioids are known to act upon only the subjective "hurt" associated with pain without affecting primary sensory modalities.[24] It stands to reason then, that in combination with piroxicam's anti-inflammatory action, the tissue swellings from handling at surgery and resultant nerve-endings stimulation were reduced. Further, the improvement in the efficacy was evident both in the shortening of the onset of action of P and T and also prolongation of the duration of action. These effects were more pronounced in the P-P group, possibly because pentazocine lacks any anti-inflammatory/antipyretic action,[12] thus the combination with an NSAID was synergistic. The analgesic effect of P and T were improved, as pain control was significantly better in the P-P and T-P groups; however, better effects were recorded in the P-P group than in the T-P group at both 6 hours and 12 hours. It was also observed that in the unimodal groups, pain control was not different between P and T at 12 hours post–cesarean section, whereas in the multimodal groups, the addition of piroxicam sustained the superior efficacy of pentazocine over tramadol, at 12 hours post–cesarean section.

The sedative effect of pentazocine was maintained across all groups and was greater in the P-P group than in the P-only and T-P groups, with no untoward adverse reaction. The main side effect recorded in this study was the occurrence of vomiting in the P (20%) and P-P (13.33%) groups. This was effectively managed with parenteral antiemetic (metoclopramide). No adverse reaction was recorded in any breastfed neonates, which is similar to the findings of another study.[16]

The limitation of this study is the possible confounding influence of the spinal analgesia agent (bupivacaine) on the observed analgesic effects of all agents studied; however, we reason that since all the patients had the same drug and dosage for the spinal analgesia, except for individual patient peculiarity, this effect should balance out. In this study, patients who had inhalational general anesthesia were excluded, and we advise further research in this group of patients.

In conclusion, in a resource-poor setting like Nigeria, where more potent opioids are not readily available and affordable, our study has shown that a multimodal approach combining pentazocine or tramadol with an NSAID, such as piroxicam, would achieve better pain relief and maternal satisfaction following cesarean section. Our findings indicate that in patients without the uncommon severe adverse drug reaction to pentazocine,[25] the combination of pentazocine with piroxicam is significantly better than that of tramadol with piroxicam, though a greater sedative effect should be expected. In our study, patient satisfaction was most outstanding in the P-P group, at 89.2%, and least in the tramadol-only group.

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Disclosure

The authors report no conflicts of interest in this work.

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