

Meperidine-Ketorolac Combination Provides Better Analgesia than Meperidine Alone in Postoperative Patients

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Abstract

Background: Our study objective was to assess if multi-modal analgesia with meperidine-ketorolac combination provides superior analgesia or reduces opioid requirement following surgery compared to Meperidine alone.

Design: Double-blind randomized controlled trial.

Setting: Postoperative pain control in orthopedic ward after spinal anesthesia.

Patients: American Society of Anesthesiology (ASA) risk I or II (ASA I/II) patients who had lower limb implant surgery (88) at our center from September 2014 to July 2015.

Interventions: Patients were randomly assigned to receive either 1 mg/kg of intravenous (IV) meperidine and 30 mg of IV ketorolac (treatment group) or 1 mg/kg of IV meperidine (control group) post-surgery, administered every hour for the first 6 hours during the first 24 hours post-surgery. In addition, patients received intravenous meperidine on an 'as needed basis' during the first 24 hours of the postoperative period.

Measurements: Outcomes were time-to-first analgesia request postoperatively; cumulative opioid dose in first 24 hours post-surgery; frequency of side effects; and patient satisfaction with pain relief using a Likert scale. Numerical rating scale (NRS) pain scores hourly for the first 6 hours, then the 8th, 12th, 16th, 18th and 24th hour post-surgery were assessed.

Results: There was a significant delay in time of first request for analgesia (460 min vs 225 min; $P=0.03$) and a reduction in opioid consumption in 24 hours (299 mg vs 325 mg; $P=0.01$) in the meperidine/ketorolac group compared with the meperidine alone group which were both statistically significant. Patient satisfaction with pain relief was better in the treatment group ($P=0.01$). Additionally, there were fewer side effects in the treatment group than in the control group but this was not statistically significant.

Conclusions: Adding ketorolac to meperidine reduced postoperative pain, reduced patient daily opioid requirement, increased patient satisfaction with pain relief, without increasing the frequency of side effects. Therefore, IV ketorolac addition to opioids may be a reasonable option in multimodal analgesic protocol.

Keywords: Multimodal analgesia; Lower limb implant surgeries; Postoperative pain

Postoperative pain is the most common undesirable outcome for patients who undergo surgical procedures, besides causing patients to suffer, postoperative pain can delay recovery and prolong hospital stays.¹ Under-treatment and overtreatment of pain is a focus of growing concern to the medical community. Most orthopedic patients experience moderate to severe postoperative pain.² Poorly controlled postoperative pain leads to undesirable outcomes, including immobility, stiffness, myocardial ischemia, atelectasis, pneumonia, deep venous thrombosis, anxiety, depression, and chronic pain.³

High dose intravenous opioids have traditionally been used to manage postoperative pain.^{4,5} Opioids are associated with numerous dose dependent systemic side effects which can impair postoperative recovery and lead to serious medical complications.⁶ In addition, patients taking narcotics chronically, preoperatively, can become desensitized and tolerant, resulting in difficulty controlling surgical pain.⁶

The principle of multimodal pain therapy is to use interventions that target several different steps of the pain pathway, allowing therapeutic agents to act synergistically while requiring lower total doses of each drug.⁶ This promotes more effective pain control with fewer associated side effects.

The opioid-sparing effect of ketorolac can facilitate the recovery process by improving pain management and reducing opioid-related side effects (such as nausea, vomiting, constipation, urinary retention, cardiorespiratory depression, pruritus, and sleep disturbance).⁷ At our centre, meperidine is used for managing postoperative pain after major orthopedic lower limb surgery and its use is frequently associated with the aforementioned adverse effects. Our hypotheses were that the inclusion of ketorolac in multimodal pain management with intravenous meperidine may lead to superior analgesia compared with meperidine alone; and that this reduces opioid requirement following major orthopedic lower limb implant surgery.

Methods

Trial Design

This was a single center prospective, double-blind, randomized, controlled trial with balanced randomization of combined ketorolac and meperidine versus meperidine alone for multimodal pain management following lower limb implant surgery was conducted at our center from September 2014 through July 2015. This study was approved by the Institutional Review Board (IRB) Committee of the National Hospital of Abuja and was conducted in line with the Declaration of Helsinki.

Participants

We enrolled 88 patients who were randomly assigned to either the treatment group (combined ketorolac and meperidine) or the control group (meperidine and normal saline). Our inclusion criteria were patients undergoing lower limb implant surgery at our center aged 18 to 65 years with American Society of Anesthesiology (ASA) risk I or II who had undergone spinal anesthesia. Lower limb surgeries included open reduction and internal fixation for tibiofibular fracture (47.7%), femoral fracture (40.9%), ankle fracture (9.1%), hip fracture (1.1%) and knee fracture/injuries (1.1%). Our exclusion criteria included patients who refused to participate in the study, chronic opioid use greater than 4 weeks in the immediate preoperative period, current use of anticoagulants or antiplatelet medications, age less than 18 or greater than 65, prior documented allergy to non-steroidal anti-inflammatory therapy, coagulopathy or bleeding disorders, gastric ulcers, chronic kidney disease stage IV or V, severe liver dysfunction with elevated liver enzymes up to 1.5 times upper limit of normal, asthma or pregnancy. All participating patients gave informed consent.

Anesthetic Protocol

A detailed preoperative review was done the night before surgery to identify patients who were eligible for the study. All eligible patients were given 150 mg of ranitidine and 10 mg of metoclopramide taken orally the night before surgery. Nil per oral was maintained after midnight. Ranitidine (50 mg) and metoclopramide (10 mg) were administered intravenously one hour before surgery. On arrival in the operating room, intravenous access was secured with a 16 gauge canula, monitors were attached to the patient and baseline pulse rate, blood pressure, mean arterial pressure (MAP), Oxygen saturation of hemoglobin (SpO₂), temperature and electrocardiography (ECG) were obtained and recorded using a Beneview T5 Mindray multiparameter monitor. Patient's circulation was preloaded with 15 ml/kg of Ringer's lactate. Spinal anaesthesia was performed under aseptic conditions with the patient in the sitting position at L3/L4 or L4/L5 intervertebral space. All patients received 3 ml of 0.5% hyperbaric bupivacaine (Marcaine spinal heavy 0.5%,) and 25 µg of fentanyl via a 26 gauge pencil point Whitacre spinal needle, into the subarachnoid space. On withdrawal of the needle dry gauze dressing was applied over the injection site and patient positioned supine with head up tilt. The level of sensory block was assessed; maximum block height of T8 was achieved before commencement of surgery.

There was continuous intraoperative monitoring and recording at 5 minutes interval of pulse rate, blood pressure, SpO₂, while maintaining continual verbal contact. Hemodynamic status was maintained with warm ringer's lactate and blood transfused if necessary. Hypotension (>25% drop from baseline blood pressure or MAP ≤60 mmHg) was treated with IV fluid bolus and 3 mg aliquots of ephedrine, while bradycardia (heart rate <60 beats/minute) was treated with 0.6 mg of atropine.

On placement of the last stitch which defined end of surgery, blood pressure, heart rate and SpO₂ were recorded and pain was assessed. The study medications were then administered at predetermined time

intervals. Local infiltration of analgesics was not done intraoperatively to prevent skewing pain scores in all patients.

Intervention

Patients were randomly assigned to receive either 1 mg/kg of intravenous (IV) meperidine and 30 mg of IV ketorolac (treatment group) or 1 mg/kg of IV meperidine (control group) post-surgery. The analgesia was administered hourly for the first 6 hours during the first 24-hours post-surgery beginning at time 0 from last stitch in surgery. We chose the six hourly administrations of analgesia based on the existing postoperative protocol for analgesia following major surgery. In addition patients received intravenous meperidine on an ‘as needed basis’ during the first 24 hours postoperative period.

Study Settings

This study took place in our center at the National Hospital Abuja, Nigeria between September 2014 and July 2015.

Outcomes

Outcomes were time to first analgesia request postoperatively; cumulative opioid dose in first 24 hours post-surgery; frequency of side effects; and patient satisfaction with pain relief using a Likert scale. Numerical rating scale (NRS) pain scores were done prior to time of request for first analgesia.

Data collection

The nurses and physicians who assessed study participants for pain levels helped the study team in collecting the data. The data was then compiled and sent to study team.

Sample Size

Our calculated sample size was 80 (and allowing for an attrition of 10%, became 88). This was derived from assumptions that ketorolac reducing opioid requirement was estimated to be 64%; as reported by Cassinelli et al⁴ who compared morphine requirement after primary multilevel lumbar decompression surgery between ketorolac and placebo and found 64% reduction in morphine requirement in the ketorolac group.

We assumed the probability of ketorolac when added to meperidine to reduce opioid requirement in this present study to be 90% assuming it was a superior combination. The study was stopped when the final sample size was reached.

Randomization

We used a computer randomly generated number that assigned odd numbers to the treatment group and even numbers to the control group to ensure 1:1 simple balanced randomization between groups.

Allocation concealment

Independent pharmacists dispensed either active or placebo medications according to a computer generated randomization list.

Implementation

Following randomization, the principal investigator informed independent pharmacists to dispense active study medications to administering physicians who were blinded to group of patient. Study medications were administered at time 0, 6, 12 and 18 hours.

Similarity of Interventions

Patients who were in the meperidine alone group also received 1 ml of saline to serve as a dummy ketorolac (placebo).

Statistical methods

Data analysis was done using SPSS (Statistical Package for Scientific Solutions) version 21.

Parametric data were summarized as means with standard deviation and categorical data presented as counts and frequencies.

Parametric data were analyzed using the unpaired student's t-test. The associations between categorical data were determined using either chi-square test or the Fisher's exact test. Level of significance was set at a probability of 0.05.

Results

Participants, Losses and Exclusions

During recruitment for our study, 156 patients were screened for eligibility. Of these, 58 were excluded because they had one or more exclusion criteria, 8 missed window of opportunity of enrollment and 2 refused consent or had no family member to provide consent during enrollment window. This left us with our final sample of 88 patients. All enrolled patients were followed until study conclusion, which was 24 hours postoperatively. No one was lost to follow up or died perioperatively.

Recruitment

Age-eligible participants who were planned for elective lower limb implant surgeries were screened using inclusion criteria. All those who met inclusion criteria were approached for recruitment and study was stopped when enrollment was complete.

Baseline data

Eighty-eight (88) ASA I or II participants aged between 18 and 65 years were enrolled in this study. Table 1 shows the demographics of study participants. The mean ages of patients in the treatment group (meperidine and ketorolac) and control group (meperidine and saline) were similar, 39.36 ± 11.25 and 36.00 ± 12.68 years, respectively ($P=0.192$, t test). There was no statistically significant difference between the two groups with regard to weight, height and body mass index (BMI) (Table 1).

The sex distribution was similar in both groups ($P=0.514$, X^2 test), with each group having more male patients. The ASA physical status classification of the patients was similar in both groups ($P=0.381$, X^2 test), both groups were mostly ASA 1 patients. The mean duration of surgery was 139.39 ± 25.81 and 136.93 ± 27.05 minutes in the treatment and control groups respectively ($P=0.664$, t test) (Table 1).

Numbers Analyzed

We analyzed all 88 patients in our final sample. We had complete data on all study participants.

Outcomes

The median NRS score at first request for analgesia was 5 (range 4-6) in both treatment and control groups ($P=0.188$) (Table 2).

The time from administration of study drugs to first request for analgesia was significantly greater in the treatment group (460 ± 229 minutes) compared to the control group (225 ± 127 minutes) ($P=0.034$, t test) (Table 2).

The mean opioid (meperidine) consumption in 24 hours was 299.14 ± 45.28 mg and 325.14 ± 46.11 mg in the treatment and control groups respectively ($P=0.009$, t test) (Table 2).

Side effects related to study drug administration are outlined in Table 3. Nausea was experienced by 22 (50%) and 28 (63.6%) patients ($P=0.282$); vomiting was in 7 (15.9%) and 15 (34.1%) patients ($P=0.084$); and sedation was experienced by 29 (65.9%) and 35 (79.5%) patients ($P=0.231$) in the treatment and control groups respectively. All nausea, vomiting, and sedation were grade 1; they resolved spontaneously and the patients did not require nor request treatment. There was no incidence of respiratory depression, urinary retention, increased surgical drain, gastrointestinal bleeding or evidence of post-operative renal or hepatic dysfunction.

Table 4 shows patient satisfaction with pain relief. Twenty one (21; 47.7%) patients in the treatment group and 4 (9.1%) in the control group rated their satisfaction with pain relief as excellent or very good; whereas 23 (52.3%) patients in the treatment group and 40 (90.9%) in the control group rated post-operative pain relief as good, poor or very poor ($P<0.001$, X^2 test) (Figure 1).

Harms

There were similar side effect profile in both the treatment and control groups reported. There were no unintended consequences or harm on study participants.

Discussion

The goals of this study were to investigate if the addition of ketorolac to meperidine would reduce postoperative pain, reduce patient daily opioid requirement, and increase patient satisfaction with pain relief. Consistent with the study's hypotheses, addition of ketorolac to meperidine reduced postoperative pain scores, decreased patient opioid requirement in the first 24-hours post-surgery,

increased patient satisfaction with pain relief, and in addition increased time to request of first analgesia postoperatively. This study also showed that addition of ketorolac to meperidine during postoperative pain management did not significantly increase the side effects experienced by the patients. This implies that ketorolac may play a significant beneficial role in postoperative pain management following lower limb implant surgeries.

Preemptive administration of analgesics has been suggested to reduce postoperative pain therefore, resulting in less postoperative analgesic requirement.^{8,9} The administration of ketorolac as preemptive analgesia has been shown to reduce the degree of postoperative pain syndrome.⁹ It also, improved analgesic effect and postoperative clinical recovery after third molar surgery.^{10,11} Gopalraju and colleagues¹⁰ showed that preemptive use of ketorolac 30 mg intravenously significantly lowered pain intensity scores, prolonged time to rescue analgesics with less intake of postoperative analgesics and patients had good overall assessment as compared to the group that receive preemptive tramadol. Administering ketorolac as preemptive analgesia may have prevented central sensitization caused by surgical stimulus and consequently reduced the need for postoperative analgesia. In the present study, ketorolac was administered postoperatively, however, similar results were achieved because it was administered before the effect of spinal anesthetic wears off.

The American Society of Anesthesiologists Task Force on Acute Pain Management described “multimodal techniques for pain management as the administration of two or more drugs that act by different mechanisms for providing analgesia.”¹² Several studies showed that multimodal analgesia including ketorolac with opioid or non-opioid analgesics were superior to the control groups without ketorolac in treating moderate to severe pain in the postoperative period.^{5,13-17} Similarly, the findings of this study support the efficacy of ketorolac in the management of postoperative pain following lower limb implant surgery.

Breakthrough pain sometimes occurs in postoperative patients especially when they have inadequate pain control.⁴ This study compared the time of first request of analgesia as well as total opioid consumption in 24 hours. There were significant increases in the time of first request for analgesia by patients in the meperidine/ketorolac group compared to meperidine alone group. On the average, time of first request for analgesia was six hours later among patients in the treatment group compared with patients who received meperidine alone.

The opioid (meperidine) consumption in 24 hours was about 10% lower in the meperidine/ketorolac group than the meperidine alone group. This compares to ketorolac causing a 28% reduction in morphine requirement in 24 hours when administered as a local infiltrate in knee replacement surgery in the immediate postoperative period.¹⁸ Also, 18.3% less morphine requirement in 72 hours in colorectal surgery.¹⁹ It is significantly lower than the 64% reduction in morphine consumption following lumbar decompression surgery.²⁰ Morphine is a more potent opioid than meperidine, and therefore addition of ketorolac would cause a smaller reduction in meperidine requirement than morphine requirement. Hong and colleagues²¹ demonstrated a highly significant fentanyl sparing effect. These results also imply that ketorolac administered in the postoperative period will significantly reduce the need for large doses of opioid, which have addictive potential because of their dependence. This is a significant contribution to pain management in the postoperative period where there are no contraindications to the use of NSAIDs, as addition of a more cost-effective drug such as ketorolac would lead to use of lower doses of more expensive opioids with addictive potential.⁶

A possible caution to argue against the widespread use of NSAIDs as part of the multimodal pain management of patients in the postoperative period would be the incidence of side effects.^{1,7} In this study, major complications (epidural hematoma, excessive surgical drain output, gastrointestinal

bleeding, and evidence of postoperative renal or hepatic dysfunction) and minor complications (nausea, vomiting, urinary retention, sedation, respiratory depression) were examined in detail. There were no differences in incidence of side effects between both groups which were similar to what Singla and colleagues reported.¹⁴ In this study, no patient in the ketorolac/meperidine group had increased postoperative bleeding. Similar to what was observed in a study by Shende,²² there were reduced incidences of nausea, vomiting and sedation in the treatment group compared to the control group, though not statistically significant suggesting that combining ketorolac with meperidine may be reducing the side effects experienced by the patients on both drugs concurrently. Therefore, the nausea, vomiting, and sedation reported in this study may be attributed to meperidine since they are established side effects of opioid analgesics. Also, the postoperative opioid consumption was lower in the ketorolac/meperidine group which may have contributed to the reduced incidence of side effects compared to the meperidine only group.

This study showed a beneficial increase in patient satisfaction with pain relief with almost half of the patients in the meperidine/ketorolac group rating their satisfaction of pain relief as excellent or very good compared to less than 10% of patients in the meperidine only group. This may be attributed to the longer pain-free period before request of analgesia in the ketorolac/meperidine group. More so, they generally recorded lower NRS scores, this shows that addition of ketorolac would ensure greater patient satisfaction during postoperative management and ultimately results in quicker ambulation and better recovery. Other studies also reported high patient satisfaction with analgesia when ketorolac was used in multimodal technique.²³⁻²⁵ Soyannwo et al²⁶ reported that factors such as socio-economic status, patient care and expectations may affect response from patients regarding satisfaction with pain relief. However, Chang et al²⁷ have established that higher patient satisfaction with pain relief is closely tied to superior analgesic effect, an acceptable level of side effects and effectiveness of pain management.

This study has its limitations. Pain scores were analyzed using a numerical rating score (NRS), which is one of the best three available pain score ratings [NRS, Visual Analogue Scale (VAS), and Verbal Rating Scale (VRS)] and has been validated. Although this study did not set out to evaluate the individual-to-individual variation in the NRS pain score reporting, we noted that there might have been differences in individual reporting of scores. This may have resulted into some misclassification of the outcome (NRS pain scores) which would most likely be non-differential as patients were blinded to their status. This would tend to attenuate the effect size of any differences that may have existed between both groups implying that the true differences may even be greater than results reported in this study. There has been increasing research in the field of pain reporting comparing NRS, Visual Analogue Scale (VAS), and Verbal Rating Scale (VRS) and has shown great correlations ($r=0.88$) between all three but there is no consensus that they can be interchangeable during self-assessment of pain.^{28,29} However, there were no differences in the median pain scores of both groups as at the time of request for analgesia suggesting that they had similar pain threshold on average in the two groups.

Recent advances in pain management have encouraged the use of patient controlled analgesia for better pain control.^{19,25} However, in this study, study drugs were administered every hour for the first six hours, which is still the current protocol in our centre. The study also demonstrated improvement in prescription patterns for postoperative pain relief compared to an earlier study by Faponle and colleagues³⁰ which reported that postoperative analgesics were given only via the intramuscular route with limited range of drugs to choose from. Using patient controlled analgesia may therefore have resulted in even more significant differences between both groups.

This study has its strengths. This was a prospective, randomized, double-blind study, which help in reducing both bias and confounding variables. There was also no loss to follow up due to the short duration of follow up in the study and there were no dropouts from either group.

Both the investigator and patients were blinded to the status of their group assignment to eliminate any biases in assessing or reporting pain scores, respectively. Comparing the NRS pain scores during first request for analgesia showed no significant differences between the NRS pain scores in both patient groups. This suggests that the pain threshold for both patient groups were similar and reinforces that the main findings in this study are not confounded by differences in pain threshold of both patients.

The results of this study may not only be applicable in the field of orthopedics but may be generalizable to other fields of surgery including general surgery, cardiothoracic surgery and pediatric surgery. NSAIDs are being increasingly used, in addition to morphine, as part of multimodal aspect of pain management in many parts of the world.^{4,18,19}

In conclusion, this study confirmed the proposed hypotheses, that the addition of ketorolac to meperidine will reduce postoperative pain scores, decrease patient opioid requirement in the first 24 hours after lower limb implant surgery, increase patient satisfaction with pain relief and in addition increase time-to-request of first analgesia post-operatively. This study also showed that addition of ketorolac to the postoperative pain management did not significantly increase the side effects experienced by the patients already on meperidine. This study therefore supports that ketorolac may play a significant beneficial role in postoperative pain management following lower limb implant surgeries.

References

1. De Oliveira GS Jr, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. *Anesth Analg*. 2012;114(2):424-433. [doi:10.1213/ANE.0b013e3182334d68](https://doi.org/10.1213/ANE.0b013e3182334d68). [Medline](#)
2. Wang ZQ, Zhan SY, Fransen M, Lin JH. Clinical attitudes towards pain treatment post-orthopedic surgery: a multicenter study in Beijing. *Chin Med J (Engl)*. 2012;125(14):2499-2504 [Medline](#).
3. Michelson JD, Addante RA, Charlson MD. Multimodal analgesia therapy reduces length of hospitalization in patients undergoing fusions of the ankle and hindfoot. *Foot Ankle Int*. 2013;34(11):1526-1534. [doi:10.1177/1071100713496224](https://doi.org/10.1177/1071100713496224). [Medline](#)
4. Cassinelli EH, Dean CL, Garcia RM, Furey CG, Bohlman HH. Ketorolac use for postoperative pain management following lumbar decompression surgery: a prospective, randomized, double-blinded, placebo-controlled trial. *Spine*. 2008;33(12):1313-1317. [doi:10.1097/BRS.0b013e31817329bd](https://doi.org/10.1097/BRS.0b013e31817329bd). [Medline](#)
5. White PF. The changing role of non-opioid analgesic techniques in the management of postoperative pain. *Anesth Analg*. 2005;101(5S)(Suppl):S5-S22. [doi:10.1213/01.ANE.0000177099.28914.A7](https://doi.org/10.1213/01.ANE.0000177099.28914.A7). [Medline](#)
6. Parvizi J, Bloomfield MR. Multimodal pain management in orthopedics: implications for joint arthroplasty surgery. *Orthopedics*. 2013;36(2)(Suppl):7-14. [doi:10.3928/01477447-20130122-51](https://doi.org/10.3928/01477447-20130122-51). [Medline](#)
7. White PF, Raeder J, Kehlet H. Ketorolac: its role as part of a multimodal analgesic regimen. *Anesth Analg*. 2012;114(2):250-254. [doi:10.1213/ANE.0b013e31823cd524](https://doi.org/10.1213/ANE.0b013e31823cd524). [Medline](#)
8. Dahl JB, Møiniche S. Pre-emptive analgesia. *Br Med Bull*. 2005;71(1):13-27. [doi:10.1093/bmb/ldh030](https://doi.org/10.1093/bmb/ldh030). [Medline](#)

9. Kokhno VN, Shmerko PS, Shakhtarin Iu. [Impact of preemptive analgesia on postoperative pain syndrome in laparoscopic surgery]. *Anesteziol Reanimatol*. 2009;(6):68-70 [Medline](#).
10. Gopalraju P, Lalitha RM, Prasad K, Ranganath K. Comparative study of intravenous Tramadol versus Ketorolac for preventing postoperative pain after third molar surgery – A prospective randomized study. *J Craniomaxillofac Surg*. 2014;42(5):629-633. [doi:10.1016/j.jcms.2013.09.004](https://doi.org/10.1016/j.jcms.2013.09.004). [Medline](#)
11. Ong KS, Seymour RA, Chen FG, Ho VCL. Preoperative ketorolac has a preemptive effect for postoperative third molar surgical pain. *Int J Oral Maxillofac Surg*. 2004;33(8):771-776. [doi:10.1016/j.ijom.2004.01.020](https://doi.org/10.1016/j.ijom.2004.01.020). [Medline](#)
12. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116(2):248-273. [doi:10.1097/ALN.0b013e31823c1030](https://doi.org/10.1097/ALN.0b013e31823c1030). [Medline](#)
13. Nett MP. Postoperative pain management. *Orthopedics*. 2010;33(9)(Suppl):23-26. [doi:10.3928/01477447-20100722-60](https://doi.org/10.3928/01477447-20100722-60). [Medline](#)
14. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. *Curr Med Res Opin*. 2010;26(8):1915-1923. [doi:10.1185/03007995.2010.495564](https://doi.org/10.1185/03007995.2010.495564). [Medline](#)
15. Cepeda MS, Carr DB, Miranda N, Diaz A, Silva C, Morales O. Comparison of morphine, ketorolac, and their combination for postoperative pain: results from a large, randomized, double-blind trial. *Anesthesiology*. 2005;103(6):1225-1232. [doi:10.1097/00000542-200512000-00018](https://doi.org/10.1097/00000542-200512000-00018). [Medline](#)

16. Kelley TC, Adams MJ, Mulliken BD, Dalury DF. Efficacy of multimodal perioperative analgesia protocol with periarticular medication injection in total knee arthroplasty: a randomized, double-blinded study. *J Arthroplasty*. 2013;28(8):1274-1277. [doi:10.1016/j.arth.2013.03.008](https://doi.org/10.1016/j.arth.2013.03.008). [Medline](#)
Erratum in *J Arthroplasty*. 2014;29(10):2057. Available at:
<http://dx.doi.org/10.1016/j.arth.2014.07.001>
17. Lamplot JD, Wagner ER, Manning DW. Multimodal pain management in total knee arthroplasty: a prospective randomized controlled trial. *J Arthroplasty*. 2014;29(2):329-334.
[doi:10.1016/j.arth.2013.06.005](https://doi.org/10.1016/j.arth.2013.06.005). [Medline](#)
18. Banerjee P. The efficacy of multimodal high-volume wound infiltration in primary total knee replacement in facilitating immediate post-operative pain relief and attainment of early rehabilitation milestones. *Eur J Orthop Surg Traumatol*. 2014;24(4):571-577. [doi:10.1007/s00590-013-1231-0](https://doi.org/10.1007/s00590-013-1231-0). [Medline](#)
19. Chen JY, Ko TL, Wen YR, et al. Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel function in colorectal surgery patients: a prospective randomized double-blinded study. *Clin J Pain*. 2009;25(6):485-489. [doi:10.1097/AJP.0b013e31819a506b](https://doi.org/10.1097/AJP.0b013e31819a506b).
[Medline](#)
20. Goodman SB. Multimodal analgesia for orthopedic procedures. *Anesth Analg*. 2007;105(1):19-20.
[doi:10.1213/01.ane.0000265444.73604.f0](https://doi.org/10.1213/01.ane.0000265444.73604.f0). [Medline](#)
21. Hong JY, Won Han S, Kim WO, Kil HK. Fentanyl sparing effects of combined ketorolac and acetaminophen for outpatient inguinal hernia repair in children. *J Urol*. 2010;183(4):1551-1555.
[doi:10.1016/j.juro.2009.12.043](https://doi.org/10.1016/j.juro.2009.12.043). [Medline](#)

22. Shende D, Das K. Comparative effects of intravenous ketorolac and pethidine on perioperative analgesia and postoperative nausea and vomiting (PONV) for paediatric strabismus surgery. *Acta Anaesthesiol Scand*. 1999;43(3):265-269. [doi:10.1034/j.1399-6576.1999.430305.x](https://doi.org/10.1034/j.1399-6576.1999.430305.x). [Medline](#)
23. Borgeat A, Ekatodramis G, Schenker CA. Postoperative nausea and vomiting in regional anesthesia: a review. *Anesthesiology*. 2003;98(2):530-547. [doi:10.1097/00000542-200302000-00036](https://doi.org/10.1097/00000542-200302000-00036). [Medline](#)
24. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97(2):534-540. [doi:10.1213/01.ANE.0000068822.10113.9E](https://doi.org/10.1213/01.ANE.0000068822.10113.9E). [Medline](#)
25. Kim JA, Kim TH, Yang M, et al. Is intravenous patient controlled analgesia enough for pain control in patients who underwent thoracoscopy? *J Korean Med Sci*. 2009;24(5):930-935. [doi:10.3346/jkms.2009.24.5.930](https://doi.org/10.3346/jkms.2009.24.5.930). [Medline](#)
26. Soyannwo OA. Post-operative pain control—prescription pattern and patients’ experience. *West Afr J Med*. 1999;18(3):207-210 [Medline](#).
27. Chang AM, Ip WY, Cheung TH. Patient-controlled analgesia versus conventional intramuscular injection: a cost effectiveness analysis. *J Adv Nurs*. 2004;46(5):531-541. [doi:10.1111/j.1365-2648.2004.03027.x](https://doi.org/10.1111/j.1365-2648.2004.03027.x). [Medline](#)
28. Myrvik MP, Drendel AL, Brandow AM, Yan K, Hoffmann RG, Panepinto JA. A comparison of pain assessment measures in pediatric Sickle Cell Disease: Visual analog scale versus numeric rating scale. *J Pediatr Hematol Oncol*. 2015;37(3):190-194. [doi:10.1097/MPH.0000000000000306](https://doi.org/10.1097/MPH.0000000000000306). [Medline](#)
29. Bahreini M, Jalili M, Moradi-Lakeh M. A comparison of three self-report pain scales in adults with acute pain. *J Emerg Med*. 2015;48(1):10-18. [doi:10.1016/j.jemermed.2014.07.039](https://doi.org/10.1016/j.jemermed.2014.07.039). [Medline](#)

30. Faponle AF, Soyannwo OA. Post-operative pain therapy: prescription patterns in two Nigerian teaching hospitals. Niger J Med. 2002;11(4):180-182 [Medline](#).

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Tables

Table 1: Demographic Characteristics of Study Participants

Parameter	Meperidine and Ketorolac (n=44)	Meperidine and Saline (n=44)	P value
Age (years) [Mean±SD]	39.36 ± 11.25	36.00 ± 12.68	0.192
Weight (kg) [Mean±SD]	70.41 ± 7.51	68.93 ± 8.59	0.393
Height (m) [Mean±SD]	1.71 ± 0.05	1.71 ± 0.03	1.000
BMI (kg/m ²) [Mean±SD]	24.02 ± 2.59	23.49 ± 2.92	0.379
Sex [n (%)]			
Male	26 (59.1)	29 (65.9)	0.514
Female	18 (40.9)	15 (34.1)	
ASA [n (%)]			
I	26 (59.1)	30 (68.2)	0.381
II	18 (40.9)	14 (31.8)	
Duration of Surgery (min) [Mean±SD]	139.39 ± 25.81	136.93 ± 27.05	0.664

Table 2: NRS Score and Time of First Request for Analgesia, and Total Opioid Consumption in 24 hours.

Parameter	Meperidine and Ketorolac (n=44)	Meperidine and Saline (n=44)	P value
NRS score at first request for analgesia [Median (IQR)]	5 (4-6)	5 (4-6)	0.188
Time of first request for analgesia (min) [Mean±SD]	460 ± 229	225 ± 127	0.034
Total opioid consumption in 24 hours (mg) [Mean±SD]	299.14 ± 45.28	325.14 ± 46.11	0.009

Table 3: Side Effects Resulting from Study Drugs

Side Effect n (%)	Meperidine and Ketorolac (n=44)	Meperidine and Saline (n=44)	P value
Nausea	22 (50.0)	28 (63.6)	0.282
Vomiting	7 (15.9)	15 (34.1)	0.084
Sedation	29 (65.9)	35 (79.5)	0.231
Rash	0 (0.0)	0 (0.0)	1.000
Urinary Retention	0 (0.0)	0 (0.0)	1.000
Increased Surgical Drain	0 (0.0)	0 (0.0)	1.000
Others	0 (0.0)	0 (0.0)	1.000

Table 4: Patient Satisfaction with Pain Relief

Pain Relief Satisfaction n (%)	Meperidine and Ketorolac (n=44)	Meperidine and Saline (n=44)	P value
Excellent/Very Good	21 (47.7)	4 (9.1)	<0.01
Good/Poor/Very Poor	23 (52.3)	40 (90.9)	< 0.01

Figure Legend

Figure 1: Patient satisfaction with pain relief

