

# SINGLE-DOSE KETOROLAC AND PETHIDINE IN ACUTE POSTOPERATIVE PAIN: SYSTEMATIC REVIEW

Tasia Ma'bud\*

*\*Faculty of Medicine, Muslim University of Indonesia*

**\*Corresponding Author:**

[tasiambd0944@gmail.com](mailto:tasiambd0944@gmail.com)

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## Abstract

**Background:** According to the International Association for the Study of Pain (IASP), pain is a sensory and emotional condition associated with tissue damage. The effectiveness of postoperative pain management facilitates patients' recovery by minimizing acute pain while facilitating their transition back to normal activities. Severe and persistent postoperative pain is reported by 2-10% of adult patients. The lack of pain evaluating methods or intervention guidelines presents a challenge for managing pain. These procedures might be helpful in improving therapy to provide a better reduction of pain.

**Aim:** This study aims to determine whether single-dose ketorolac and pethidine effectively treat immediate postoperative pain.

**Methods:** The study met the PRISMA 2020 guidelines by self-evaluating to ensure compliance with the rules and regulations. The investigators' aimed to make the investigation using as recent information as feasible. Publications from 2013 to 2023 were included in the identification plans using various online reference databases, including Pubmed and SagePub. Paper reviews, previously published works, and incomplete articles are excluded from consideration.

**Result:** The PubMed record provided 43 articles, while SagePub retrieved 23 publications. In 2013, PubMed provided 14 research papers, and SagePub provided 3 papers. We collected 10 papers, 7 from PubMed and 3 from SagePub. We selected 5 research studies that fulfilled our requirements.

**Conclusion:** According to several studies, Ketorolac injection has shown to be an effective analgesic for patients undergoing various surgical procedures.

**Keyword:** Ketorolac; Pain; Pethidine; Postoperative pain

**INTRODUCTION**

Pain, as defined by the International Association for the Study of Pain (IASP), is an unpleasant sensory and emotional experience associated with actual or possibly damage to tissues.<sup>1</sup> Accurate diagnosis and treatment of chronic pain are crucial as they can increasingly interfere with daily activities with advancing age. Pain can be classified into three major categories: nociceptive, neuropathic, and mixed when the origin of the pain is unidentified. Postoperative pain is generally nociceptive in physical form.<sup>2,3</sup>

The objective of postoperative pain management is to minimize the adverse impacts of acute postoperative pain and facilitate patients' gentle response returning to their usual activity level.<sup>4</sup> Analgesics that contain opiates are the most common form of management of acute postoperative pain. Increased incidences of mortality and morbidity that are related to opioid abuse have driven an urgency for more investigative endeavors aimed at creating pain management techniques that give preference to a multimodal approach. This interest has resulted in a rise in opioid abuse.<sup>5</sup>

The challenge of this practice arises from the personal aspect of the perception of pain, which affects the accomplishing of adequate control over one's pain. Medical health conditions and social factors may increase patients' predisposition to experiencing high pain perception. Around 75% of individuals who undergo surgery experience acute discomfort following the operation, from mild to severe. Patients undergoing surgery indicate unsatisfactory postoperative pain management.<sup>4,6</sup>

Unsatisfactory pain control following surgery can result in unpleasant physiological impacts for patients over the immediate postoperative period, representing an important issue. Moreover, it increases the likelihood of patients developing treatment-related chronic pain. A range of 2 to 10 percent of adult patients report persistent and intense postoperative pain. The absence of pain monitoring protocols or intervention guidelines contributes to the challenge of pain management. Implementing protocols or guidelines could enhance the efficacy of treatment modifications for improved pain management.<sup>3,4,7,8</sup>

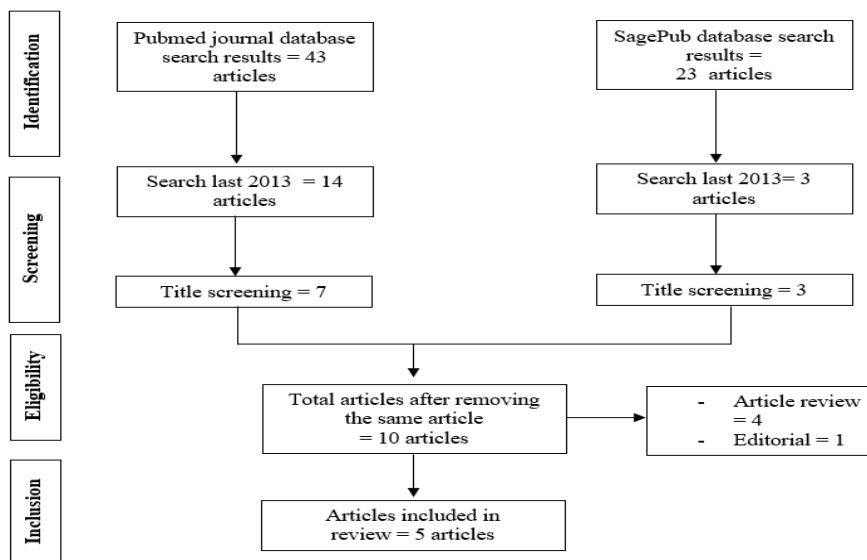
This study aims to determine whether single-dose ketorolac and pethidine effectively treat immediate postoperative pain.

**METHODS**

The author of this study ensured that it was up to date and followed all applicable rules by adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 criteria. This stage is critical since it ensures the investigation's findings are reliable. This investigation revealed that single-dose ketorolac and pethidine are in acute postoperative pain. The most efficient way to accomplish this goal on time is to evaluate previous research on the issue first. The significance of the issues raised will be demonstrated in this section as part of an effort to accomplish the goal of this essay.

To be permitted to participate in the investigation, researchers were required to provide proof that they met the following requirements: 1) In order to be considered for publication, the paper must be written in English, and its primary concentration must be on the single-dose ketorolac and pethidine in acute postoperative pain. 2) For this evaluation, works published after 2015 but before the evaluation period will be considered. Examples of research that cannot be published include editorials, applications lacking a DOI, previously published review articles, and entries nearly identical to those published journal articles.

We used "single-dose"; "ketorolac"; "pethidine" and "acute postoperative pain" as keywords. The search for studies to be included in the systematic review was carried out from June, 9<sup>th</sup> 2023 using the PubMed and SagePub databases by inputting the words: "single-dose" [All Fields] AND ("ketorolac" [MeSH Terms] OR "ketorolac" [All Fields]) AND ("meperidine" [MeSH Terms] OR "meperidine" [All Fields] OR "pethidine" [All Fields] OR "pethidine" [All Fields] OR "pethidine s" [All Fields]) AND ("pain, postoperative" [MeSH Terms] OR ("pain" [All Fields] AND "postoperative" [All Fields]) OR "postoperative pain" [All Fields] OR ("acute" [All Fields] AND "postoperative" [All Fields] AND "pain" [All Fields]) OR "acute postoperative pain" [All Fields]) used in searching the literature.



**Figure 1. Article search flowchart**

We considered each study's abstract and title when determining its credibility. They then examined additional historical documents. This conclusion is founded on synthesizing findings from multiple analyses employing the same methodology. The comment must be written in unpublished English. Only these works that meet a set of predetermined criteria were considered for inclusion in the systematic review.

Consequently, the purview of the search results is reduced. There is insufficient analysis of the research's findings. Who the subjects were, who penned the paper, when it was published, where the study was conducted, what it was about, and its parameters are described in the paper. The paper also includes information about the author and publication date. Endnote eliminated all instances of duplicate entries from the results list. Two sep rate evaluators analyzed the titles and abstracts of the articles.

Initially, their comprehensive papers were analyzed to determine if they were eligible for the study and to generate data. Last, GWG and numerous other health issues have been the subject of conference presentations and investigations. During deliberations, the justices reached a verdict. Before deciding which papers to analyze in greater detail, each author read all the papers' abstracts and titles. The following phase will investigate all of the papers that should be included in the review because they meet the inclusion criteria. After that, we will choose the review topics based on what we have learned about the numerous subjects. In this fashion, the research and review papers are selected.

**RESULT**

In the PubMed database, our search results included 43 articles, whereas our search on SagePub brought up 23 articles. The search results for the last year of 2013 yielded 14 articles for PubMed and 3 articles for SagePub. In the end, we compiled a total of 10 papers, seven of which came from PubMed and three of which came from SagePub. We included five research that met the criteria.

Shrestha et al. (2019)<sup>9</sup> found that ketorolac and pethidine had similar analgesic effects at 18 and 48 hours, according to the Visual Analogue Scale (VAS) score. In various experiment stages, pethidine had more significant analgesic efficacy than ketorolac. Ketorolac has a less effective sedation rate compared to pethidine. The research investigation demonstrated the efficacy of ketorolac or pethidine in managing postoperative pain within the initial 48-hour period. Ketorolac had been considered less harmful than pethidine; however, pethidine showed superior analgesic efficacy compared to ketorolac in postoperative pain management.

Hashem et al. (2019)<sup>10</sup> conducted a study with 132 patients. There was no significant difference between the ketorolac and pethidine groups at any time except at 10 minutes (p = 0.03) and a nearly significant difference at 30 minutes (p = 0.054) in ketorolac patients. The Numeric Pain Rating Scale (NPRS) scores were highest in the xylocaine group at 10, 20, and 30 minutes (p = 0.0001). Results for complete, partial, and none stone disintegration were as follows: 26 (89.7%), 3 (10.3%), and 0 (0.0%) for lidocaine (p=0.008); 25 (50.0%), 23 (46.0%), and 2 (4.0%) for pethidine. For ketorolac, the results were 19 (35.8%), 23 (43.4%), and 11 (20.8%).

**Table 1. The literature included in this study**

| Author                          | Origin | Method   | Sample                         | Result   |
|---------------------------------|--------|--|--------------------------------|--|
| Shrestha, 2019 <sup>9</sup>     | Nepal  | Comparative study  | 60 patients                    | Pethidine or ketorolac was equally effective at relieving postoperative pain during the first 48 hours after surgery by this research. Pethidi e found to be a more effective analgesic than ketorolac in the management of postoperative pain. On the other hand, ketorolac appeared to be a safer option than pethidine. |
| Hashem, 2019 <sup>10</sup>      | Egypt  | Single-blinded randomized controlled trial (RCT)           | 132 patients                   | When it comes to the treatment of SWL pain, ketorolac is a safer and more effective alternative to morphine derivatives. It is not recommended that lidocaine gel be used as the sole analgesic for SWL.   |
| Saryazdi, 2016 <sup>11</sup>    | Iran   | Comparative study  | Sixty-six children             | Because ketorolac is more successful than pethidine at relieving pain and reducing the risk of complications following surgery to repair an inguinal hernia, its usage is strongly encouraged because of these benefits.   |
| Eftekharian, 2017 <sup>12</sup> | Iran   | Prospective, randomized, placebo-controlled clinical trial | 50 patients                    | In the short-term therapy of mild to severe acute postoperative pain in mandibular fracture surgery, intravenous single-dose ketorolac is a safe and effective analgesic medication that can be used as an alternative to opioids. Ketorolac is also helpful in the management of postoperative pain in general.           |
| Khezri, 2018 <sup>13</sup>      | Iran   | Comparative study  | One hundred and fifty patients | Preemptively prescribing a single dose of intravenous meperidine and ketorolac can offer gratifying analgesia immediately after surgery while reducing the prevalence of shivering without causing any significant adverse effects.  |

Saryazdi et al. (2016)<sup>11</sup> Mean and standard deviations of postoperative pain 1 hour after surgery in the pethidine and ketorolac groups were 5.06 ± 1.41 and 3.88 ± 0.93, respectively. The scale was significantly lower in the ketorolac group

( $P < 0.001$ ). Postoperative pain intensity 2 hours after surgery in these two groups was  $4.48 \pm 1.52$  and  $3.55 \pm 1.15$ , respectively, and the difference between the two groups was significant ( $P = 0.006$ ). The variation in postoperative pain intensity in the ketorolac group was statistically lower than the pethidine group ( $P = 0.020$ ).

Eftekharian et al. (2017)<sup>12</sup> conducted a study with 50 patients (25 per group) who participated in this investigation. Two research groups had comparable baseline characteristics, including age, gender, weight, operation duration, anesthesia duration, and type of surgical procedure. Those who received the placebo required substantially more feeling pain relief by received analgesics than those who received ketorolac (72 vs. 28%;  $p=0.002$ ). Ketorolac significantly reduced the pain intensity 30-min after the operation ( $p < 0.001$ ). There were no significant adverse effects associated with ketorolac.

Khezri et al. (2018)<sup>13</sup> showed there was no significant difference between the meperidine and ketorolac groups in terms of shivering prevalence, while both groups were distinct from the placebo group ( $p < 0.04$ ). The mean time to first analgesic used in groups K ( $3.8 \pm 1.4$ ) and M ( $3.3 \pm 1.2$ ) hours was more prolonged than in group P ( $2.1 \pm 0.8$ ) hours ( $p < 0.001$ ). A single dose of intravenous meperidine and ketorolac can give satisfying analgesia immediately after surgery and reduce shivering prevalence without significant side effects.

## DISCUSSION

As defined by the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential damage to tissues.<sup>1</sup> Relevant evaluation and management of chronic pain are essential as it can increasingly challenge daily activities with age. Pain can be classified into four categories: nociceptive, neuropathic, mixed, and pain with an unknown origin.<sup>2</sup> Postoperative pain management is important. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids treat postoperative pain.<sup>12,14,15</sup>

Nociceptors, or pain receptors, may provoke somatic or visceral pain in response to noxious stimulation. Visceral pain results from internal organ inflammatory conditions, distension, and stretching, while somatic pain is related to bone, joint, or soft tissue damage, including fractures, cancer metastases, and arthritis.<sup>16,17</sup> Visceral pain may exhibit a higher intensity level than somatic pain. Neuropathic pain refers to pain caused by nervous system disorders or primary injury. Mixed pain is the combination of nociceptive and neuropathic pain.<sup>3,18</sup>

Based on patient conditions and social settings, personalized postoperative pain control is associated with a decrease in postoperative opioid administration, shorter lengths of stay in the hospital, reduced preoperative anxiety, and reduced demands for sedatives. Additional advantages comprise decreased preoperative anxiety and opioid usage. Patients with a history of allergic reactions to medications used for postoperative pain control should avoid their use due to the increased risk of anaphylaxis.<sup>19</sup>

Pain is caused by neurophysiological events in both the central and peripheral nervous systems. Peripheral nociceptors transduce noxious signals into electrical impulses in the peripheral nervous system.<sup>20</sup> Stimulation of peripheral nociceptive afferent signals results in the opening of channels and subsequent release of ions. Specific stimuli can cause depolarization and generate action potentials transmitted to the spine's dorsal horn through peripheral afferents. Excitatory neurotransmitters, neuropeptides, and neuromodulators are released from axon terminals into synapses in the dorsal horn. These include glutamate, substance P, and brain-derived neurotrophic factor (BDNF).<sup>21</sup>

Investigations have shown the administration of a single dose of intravenous meperidine plus ketorolac before a surgical procedure can provide adequate analgesia while decreasing the risk of shivering while avoiding any severe adverse reactions. Meperidine and ketorolac can be effectively recommended in a single dose to generate this analgesia.<sup>13</sup> Analgesia may decrease or completely eliminate pain before a strong stimulation. This theory has been investigated in multiple clinical investigations, although few studies have shown its effectiveness.<sup>17</sup>

To reduce nociceptor activation in pre-emptive analgesics, several pharmacological treatments block receptor activation and restrict the production of pain neurotransmitters. For example, local, epidural, or systemic analgesia can be administered before surgery. Non-steroidal anti-inflammatory drugs and proactive local anesthetic wound infiltration decreased the need for analgesics. A preventive local anesthetic injection around a small laparoscopic port incision does not reduce postoperative visceral discomfort. Pre-emptive analgesia gives short-term advantages in outpatient surgery.<sup>15</sup> Ketorolac is an injection of non-steroidal anti-inflammatory drug with analgesic properties. These COX-1 inhibitors can be used independently or with other medications to provide preemptive analgesia. In postoperative colorectal surgery protocols, ketorolac is used as an adjuvant and has been proven to reduce the amount of medicine taken by 25–45%. Ketorolac can be added to morphine PCA to produce an opioid-sparing effect, as demonstrated in a prospective randomized clinical trial with patients recently undergoing colorectal surgery. The result of this impact is a decrease in postoperative ileus.<sup>15</sup>

## CONCLUSION

According to multiple studies, Ketorolac injection is an effective analgesic for pain management in patients conducting various surgeries.

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