

The Effectiveness of Combining Intraoperative Ketamine with Postoperative Acetaminophen or Tramadol in Female Patients Undergoing Laparoscopic Cholecystectomy for Postoperative Pain Control: A Sample of Iraqi Patients

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Abstract

Background: Laparoscopic cholecystectomy is a frequently performed surgical procedure to treat cholecystitis. It is often accompanied by moderate to severe postoperative pain, which represents a significant concern. **Objectives:** To evaluate the efficacy of administering intraoperative ketamine along with acetaminophen or tramadol for controlling postoperative pain in female patients who have undergone laparoscopic cholecystectomy. **Materials and Methods:** A retrospective comparative study includes the records of 152 female patients who underwent elective laparoscopic cholecystectomy. Patients were divided into two groups of 76 patients, and both groups received intraoperative ketamine 0.5 mg/kg. The first group received acetaminophen intravenously and postoperatively at the end of the operation and every 8 h for 24 h, while the second group received tramadol intravenously at the end of the operation and every 8 h for 24 h. Numerical pain scores, intensity, and adverse effects were assessed and compared using SPSS statistical analysis. **Results:** No significant variation in pain scores was observed between groups treated with tramadol and acetaminophen during assessment periods ($P \geq 0.05$). The majority of patients who participated in this research experienced mild pain during the initial, 8th, 16th, and 24th hours. Nausea and vomiting were observed in five patients treated with tramadol, mainly during the first assessment hour. **Conclusion:** The combined administration of acetaminophen and intraoperative ketamine yields analgesic efficacy comparable with tramadol and ketamine. This suggests that female patients undergoing laparoscopic cholecystectomy may benefit from this alternative analgesic modality in favor of opioid medication.

Keywords: Acetaminophen, analgesics, cholecystectomy, ketamine, postoperative pain, tramadol

INTRODUCTION

Laparoscopic cholecystectomy is one of the common surgeries for acute and chronic cholecystitis. However, it is minimally invasive than open cholecystectomy, and postoperative pain is of considerable concern.^[1,2] Laparoscopic cholecystectomy is usually associated with moderate to severe pain originating from surgical trauma in addition to shoulder-referred pain. Although they vary in intensity and duration, the worst acute pain is experienced within the first 12 h postoperatively.^[1,3] Indeed, it is a great challenge for health professionals to provide the best available treatment and overcome the

hospital burden.^[1] Although multiple approaches have been proposed to reduce pain during the postoperative period, the optimal method remains difficult to determine. In fact, the intensity of postoperative pain is

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influenced by numerous factors, including gender, age, psychological state, and type of surgery, all of which should be taken into account when making appropriate treatment decisions.^[4,5]

Nonsteroidal anti-inflammatory drugs (NSAIDs), pregabalin, infiltration local anesthesia, ketamine, and opioids are familiar for postoperative pain management.^[6-8] Nevertheless, the exact dose, application timing (pre- or postoperative), and monotherapy or multiple therapy effectiveness are still indistinct. NSAIDs are known for their anti-inflammatory effect through the inhibition of cyclooxygenase enzymes (COX1 and COX2) that thought to be highly contribute to surgical site-associated postoperative inflammation and pain.^[9,10] NSAIDs vary in selectivity to COX enzymes; however, those with a high emphasis on COX2 inhibition seem more efficacious.^[11] Acetaminophen is one of the NSAIDs with uncertain mechanisms of action that lack apparent peripheral anti-inflammatory effects.^[12,13] Many studies declared the efficiency of acetaminophen for postoperative pain control of varied surgical procedures.^[14,15] However, its effectiveness for laparoscopic cholecystectomy-associated pain is under investigation. Fortunately, acetaminophen is part of a multimodal pain management method that represents a new technique for pain management and opioid-sparing.^[14,16]

Conversely, opioids are frequently efficacious as analgesics for pre- and postoperative pain. While the analgesic function of opioids is self-evident, their propensity to induce dependence, hyperalgesia, and other adverse reactions justify their limited utilization.^[6,7] Tramadol is an opioid with unique pain management mechanisms. Tramadol undergoes extensive metabolism to produce a metabolite that exhibits strong affinity and activity at mu receptors and its weak sympathetic reuptake inhibitory effect.^[17] Despite possessing opioid characteristics, tramadol exhibits a lower propensity for respiratory depression and dependence compared with morphine.^[18] Consequently, it is considered an effective analgesic for moderate to severe pain. Yet, it retains the adverse effects associated with opioids.

In the same line, ketamine, a glutaminergic pathway inhibitor, performs its anesthetic and analgesic activity through the antagonism of *N*-methyl-D-aspartate receptors in the central nervous system (CNS) in addition to an opioid-like effect on mu receptors.^[19,20] Ketamine effectiveness in postoperative pain management established in many types of surgeries such as abdominal, otolaryngological, and gynecological surgeries. However, using ketamine as a sole analgesic was found to be associated with CNS-related adverse effects, especially in a dose exceeding 0.5 mg/kg.^[21]

In recent years, multimodal pain management has gained significant attention due to the synergistic and additive

effects of different medications that reduce adverse events. Logically, it represents the gold standard for implementing medications with variable mechanisms to manage acute pain effectively.^[10,22] Moreover, it is difficult to determine which medication set would be most effective in a given surgery.

Accordingly, the current study is designed to assess the efficiency of acetaminophen intravenous (IV) administration along with ketamine compared with tramadol and ketamine for postoperative pain control in laparoscopic cholecystectomy in female patients.

MATERIALS AND METHODS

A retrospective comparison study performed in Al-Hilla Teaching Hospital and Teba Private Hospital included the records of 152 female patients who underwent elective laparoscopic cholecystectomy in the period between October 2021 and November 2022. The aim of this study was to establish an opioid-free analgesia protocol in our hospitals. The ethical committee board of the Department of Surgery, College of Medicine, approved this study.

Sample

Patients who underwent elective laparoscopic cholecystectomy were included in this study according to the eligibility criteria that include the following: female, elective laparoscopic cholecystectomy, received the standard general anesthetic procedure, with no history of opioid dependence or other CNS depressants, comparable surgical procedure time, received either IV acetaminophen or IV tramadol postoperatively for pain management, and their records including complete numerical pain assessment scale (1—the lowest to 10—the worst) for 24 h. Patients with cardiac problems, elevated blood pressure during surgery, and any complication during surgery were excluded. Patients who received other analgesics in addition to the analgesics mentioned above or other opioid medications were also excluded.

Method

The current study included the records of 152 female patients, divided into two groups (76 patients for each). Both groups received 0.5 mg/kg of ketamine as a single IV dose before surgical incision. Then, the first group received 5 mg/kg IV acetaminophen at the end of surgery and every 8 up to 24 h. The second group received 1.5 mg/kg tramadol intravenously at the end of the operation and every 8 h.

The initial pain assessment was conducted at the first hour postoperatively, followed by subsequent assessments at 8, 16, and 24 h before administering analgesic medications. Assessment of pain was performed by resident doctors in the wards. Although numerous methods exist for pain assessment, each with its own drawbacks, the hospital opted for the numerical

pain assessment scale (1—the lowest to 10—the worst) due to its objectivity and reliance on strict clinical parameters that enhance reliability and minimize personal variation.^[16] If the patient experiences severe pain during the first and second assessments, extra dose of analgesic or other analgesic drug was administered according to pain management guidelines and the surgeon's decision.

Surgical procedure

Elective laparoscopic cholecystectomy is performed according to hospital protocols in which patients receive either opioid-free analgesia or opioid analgesia. The choice of a particular analgesic drug depends on the surgeon. Anesthesia was standard for both groups; intraoperative analgesia was provided by ketamine 0.5 mg/kg, and anesthesia was induced with thiopentone sodium 5 mg/kg; muscle relaxation was achieved exclusively with atropium; and anesthesia was maintained with halothane at a concentration of 1%–1.5%. At the end of the surgical procedure, muscle relaxation was reversed with atropine and neostigmine. Postoperative pain medication (acetaminophen or tramadol) was administered near the end of the operation. After that, patients were observed in the recovery room for an unspecified period until a satisfactory recovery was obtained. A patient was deemed well recovered when an Aldrete score of 10 was obtained.

Outcomes

Numerical pain assessment scale results for 1st, 8th, 16th, and 24th hours, age, number of patients required additional analgesia, and adverse drug effects such as sedation, confusion, nausea, and vomiting, were assessed for each group and compared.

Statistical method

The analysis of all the data was conducted using SPSS, version 22. Statistical tests included the independent single *t* test, Mann–Whitney *U* test, and Spearman's A correlation test. A significance level of $P < 0.05$ was established for each test.

Ethical statement

This study was approved by the Scientific Research Ethics Committee of College of Medicine, University of Babylon (Ref. No. 8-12, dated January 8, 2023). All procedures were

carried out in conformity with the applicable rules and regulations.

RESULTS

The present study observed no significant variation in pain assessment scores between groups treated with tramadol and acetaminophen during assessment periods ($P \geq 0.05$; [Table 1]). However, an evident decrease in pain scores was observed at 8 h postoperatively, and this reduction persisted in the subsequent observation periods for both treatment groups, with comparable results observed (see Table 1 and Figure 1).

The majority of patients who participated in this research experienced mild pain during the initial, 8th, 16th, and 24th hours. Conversely, moderate pain was reported by approximately 10% of patients during each observation period for both groups (see Table 2). Six patients in the tramadol-treated group and eight patients in the acetaminophen-treated group required additional analgesics during the initial observation period (see [Table 3]).

Moreover, neither the tramadol-treated nor the acetaminophen-treated groups exhibited a correlation between age and response to analgesic treatment. Furthermore, the mean age of patients in both groups did not differ significantly [Table 3]. Although it was found to be statistically not significant, numerical pain scores were lower in patients aged ≥ 45 years [Figure 2].

Nausea and vomiting were observed in five patients treated with tramadol, mainly during the first assessment hour, while in acetaminophen-treated group, adverse reactions were not found.

DISCUSSION

Elective laparoscopic cholecystectomy is a widely performed procedure, especially for female patients with cholecystitis. Accordingly, our study is designed to evaluate the pain of female patients as they are more prone to experience pain than male patients.^[23] The study findings revealed insignificant differences in patients' age between the two groups.

Nevertheless, according to patient records, pain scores were higher in patients younger than 45 years, especially in the acetaminophen-treated group. However, this variation

Table 1: Differences in pain perception scores between tramadol and acetaminophen groups during study observation periods

Observation periods (h)	Tramadol group 76 female patients	Acetaminophen group 76 female patients	Level of significance $P < 0.05$
1	1.761 ± 1.72	2.15 ± 1.90	0.591
8	1.89 ± 1.59	2.02 ± 1.77	0.488
16	1.76 ± 1.63	1.97 ± 1.73	0.108
24	1.25 ± 1.73	1.842 ± 1.840	0.517

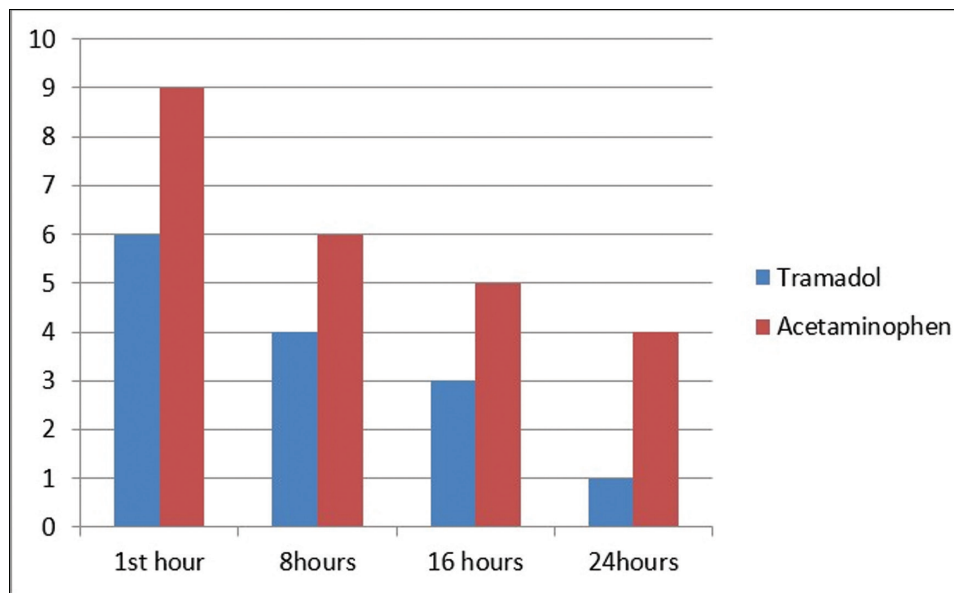


Figure 1: Variation in the number of patients with moderate pain treated with tramadol and acetaminophen during pain assessment periods

Table 2: Intensity of pain sensation among groups during observation periods

Observation periods (h)	Tramadol patients (n = 76)		Acetaminophen patients (n = 76)	
	Mild	Moderate	Mild	Moderate
1	64 (84.2%)	6 (7%)	58 (76.3%)	9 (11.7%)
8	66 (87%)	4 (5.3%)	62 (81.3%)	6 (7.7%)
16	67 (88.3%)	3 (4%)	63 (82.9%)	5 (6.7%)
24	69 (90.7%)	1 (1.3%)	64 (84.7%)	4 (5.3%)

Table 3: Patient-related data

Criteria	Tramadol group (n = 76)	Acetaminophen group (n = 76)	P value P < 0.05
Age	49.84 ± 10.47	50.12 ± 12.33	0.149
Body mass index (kg/m ²)	26.5 ± 3.5	25.7 ± 3.7	0.125
Operation time (min)	41.6 ± 10.8	40.8 ± 11.7	0.103
Adverse reaction	5 (1.5%)	None	Not applicable
Patients have severe pain and received additional analgesia	6 (7.8%)	8 (10.53%)	0.06

was statistically insignificant. This finding disagrees with the finding of Zheng *et al.*^[5] that age has an impact on postoperative pain perception in patients who underwent orthopedic surgery with lower pain relief in women older than 50 years. Yet, this could be explained by different types of surgeries and preoperative pain intensity and duration, which had further impact on postoperative pain.

On the other hand, our study finding agrees with the finding of Chae K *et al.*,^[24] who examined the relationship between age, gender, and postoperative pain in laparoscopic cholecystectomy, and they discovered that women aged 65 years and older had lower pain scores than younger patients. To our knowledge, age influences medication pharmacokinetics by reducing metabolism and excretion

rate in advance. Other variables, such as psychological state and cultural influences, may also disrupt the appropriate expression of pain.^[25] Nevertheless, further studies are required with large sample size to support that result.

The main findings of this research were that the pain scores of both treatment groups remained statistically insignificant throughout all observation periods, and the pain intensity was significantly mild in both groups treated with acetaminophen and tramadol. These results suggest that the combination of acetaminophen and intraoperative ketamine was effective in alleviating postoperative pain and was on par with tramadol. This finding is consistent with the conclusions drawn by Togrul *et al.*,^[26] who discovered that acetaminophen could serve as

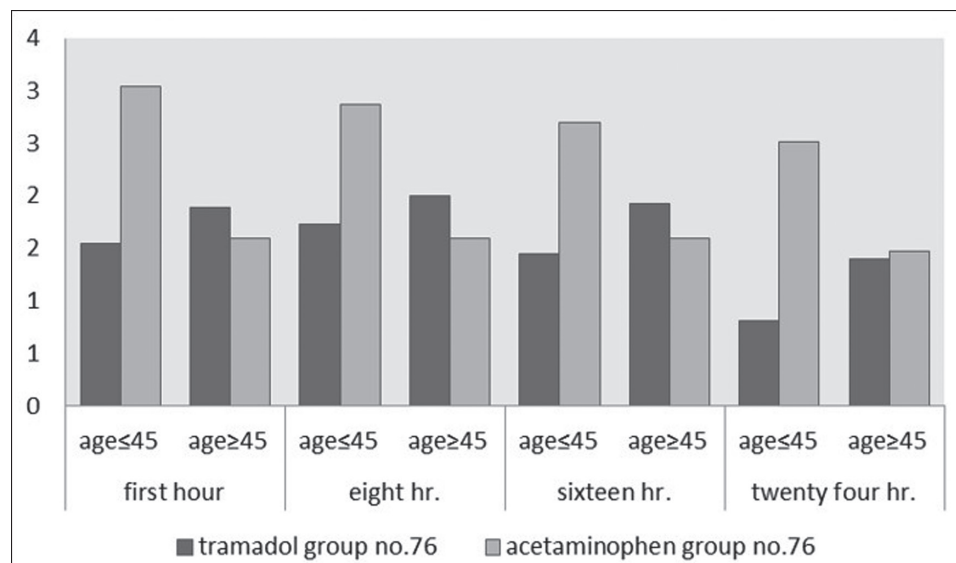


Figure 2: Correlation of age with the mean of numerical pain scores through observation periods in tramadol- and acetaminophen-treated groups ($P \geq 0.05$)

a viable substitute for opioids in the initial 6 h following surgery to alleviate mild to moderate pain. By contrast, our research demonstrated that IV acetaminophen could function as a convenient substitute for opioids for a duration of 24 h.

The concurrent efficacy of acetaminophen and ketamine may be attributed to the multitarget mechanism of ketamine in the subanesthetic dose administered in the present study, which reduced postoperative pain intensity when used with acetaminophen. Previous studies and meta-analyses by Talebi *et al.*^[27] and Zhu *et al.*^[28] highlighted the effectiveness of ketamine for postlaparoscopic cholecystectomy pain relief but as single analgesia or along with opioids, not with acetaminophen.

Despite the limited evidence regarding the effectiveness of ketamine and acetaminophen in managing pain after laparoscopic cholecystectomy, the findings of the present study offer encouraging support for their potential to alleviate pain for a duration of 24 h using a single preincisional subdissociative dose of ketamine and IV acetaminophen every 8 h in the absence of opioid additive therapy.

This study has the following limitations: The sample was obtained from a single hospital, so we cannot generalize the study conclusion; the small sample size and patient documents were deficient in certain information regarding adverse events and patients' socioeconomic status.

However, the present study endeavors to establish opioid-free post-operative analgesia for laparoscopic cholecystectomy pain by selecting safe, effective, and cost-effective multimodal analgesics.^[29,30] To the best of our knowledge, this is the first study of its kind in the country that specifically examines female patients in this regard.

CONCLUSION

In conclusion, the combined use of acetaminophen and intraoperative ketamine offers similar analgesic efficacy to that of tramadol; therefore, it may serve as a viable substitute for opioid analgesics in female patients undergoing laparoscopic cholecystectomy.

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Conflict of interest

There are no conflicts of interest.

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