ACUTE PAIN SECTION

Original Research Article
Pre-Incisional Analgesia with Intravenous or Subcutaneous Infiltration of Ketamine Reduces Postoperative Pain in Patients after Open Cholecystectomy: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

Background. In literature, there is controversy on the use of ketamine for management of postoperative pain. The aim of the present study was to evaluate the efficacy of pre-incisional intravenous or subcutaneous infiltration of ketamine on postoperative pain relief after open cholecystectomy.

Methods. One hundred twenty patients, aged 18–60 years, scheduled for open cholecystectomy was enrolled in this randomized, double-blind, placebo-controlled study. Patients were divided into four groups of 30 each and received subcutaneous infiltration of ketamine 1 mg/kg (group KS1), subcutaneous infiltration of ketamine 2 mg/kg (group KS2), intravenous ketamine 1 mg/kg (group KI), or subcutaneous infiltration of normal saline 20 mL (group C) before surgery. Visual analog scale (VAS) values and analgesic consumption were evaluated for 24 hours after operation.

Results. VAS scores were significantly lower at arrival to the postanesthesia care unit, 15 and 30 minutes in Group KS1, Group KS2, and Group KI compared with Group C (P < 0.05). Postoperative VAS scores were significantly lower at 1, 2, 3, 4, 8, 12, and 24 hours after operation in Group KS1, Group KS2, and Group KI compared with Group C (P < 0.05). In Group KS2, VAS scores were significantly lower than Group KS1 (P < 0.05).

Conclusion. A 2 mg/kg dose of subcutaneous infiltration ketamine or 1 mg/kg dose of intravenous ketamine given at approximately 15 minutes before surgery provides an adjunctive analgesia during 24 hours after surgery in patients undergoing cholecystectomy surgery.

Key Words. Pain; Acute; Postoperative; Preemptive; Ketamine; Open Cholecystectomy

Introduction

One of important factors in patient recovery is postoperative analgesia. Although many studies [1] confirmed that effective analgesia decreases postoperative complications, pain often is overlooked and its control unsatisfactory [2]. Releases of proteolytic and inflammatory mediators after surgical trauma generate powerful nociceptive impulses that trigger pain [3].

The most important phenomenon in transmission of inflammatory pain is sensitization of spinal cord with active contribution of glutamate and aspartate aminoacids on the N-methyl-dimethyl-aspartate receptors (NMDA) [4].

Ketamine, a non-competitive NMDA antagonist, prevents central sensitization of nociceptors at subanesthetic doses by elimination of peripheral afferent noxious stimulation [5–7]. Stubhaug et al. [8] showed that ketamine decreases acute postoperative pain by inhibiting C-fiber activity.

Moreover, Tan et al. [9] showed that the pre-incisional treatment with subcutaneous infiltration of ketamine...
prolongs the time to first analgesic requirement, decreases the total dosage of analgesics used and pain score after circumcision surgery.

Additionally, Aida et al. [10] showed that the pre-incisional administration of subanesthetic doses of intravenous (IV) ketamine significantly improved postoperative analgesia.

In view of the above conclusions, it seems reasonable to suggest that preemptive infiltration of ketamine into the intended line of surgical incision or IV administration of it may be a useful method for preventing postoperative somatic (wound) and visceral pain in some other surgeries such as open cholecystectomy. So, we designed this randomized, double-blind, placebo control study to evaluate the analgesic effect of pre-incisional IV or subcutaneous infiltration of two low doses of ketamine on visceral and wound pain after open cholecystectomy.

Materials and Methods

One hundred twenty American Society of Anesthesiologists (ASA) physical status I-II patients, aged 18–60 years old, scheduled for open cholecystectomy gave written informed consent to participate in the present study, which was approved by our institute Ethics Committee.

The written informed consent was obtained on the day of surgery by the anesthesiologist. The enrolled patients had contraindication for laparoscopic cholecystectomy (i.e., acute cholangitis, severe acute-cholecystitis, acute pancreatitis, peritonitis portal hypertension, and serious bleeding disorder as absolute contraindications and acute cholecystitis, prior upper abdominal operation, minor bleeding disorder, common duct stones, and morbid obesity as relative contraindications).

Exclusion criteria included patients with a known history of hypertension, hyperthyroidism, psychiatric disorders, allergy to ketamine, chronic pain syndrome, renal or hepatic insufficiency, history of seizure or intracranial hypertension, or drug or alcohol abuse in the preceding 6 months.

The patients were visited on the day before surgery and were informed how to evaluate their pain by a 10-cm visual analog scale (VAS), ranging from 0 (none) to 10 (worst possible pain). No premedication was given to the patients.

Noninvasive arterial blood pressure (systolic arterial pressure [SAP], diastolic arterial pressure [DAP], mean arterial blood pressure [MAP]), heart rate (HR), respiratory rate, and peripheral oxygen saturation (SpO2) level were monitored in the operation room.

Using random selection of sealed envelopes, patients were randomized into one of four test groups with 30 patients in each group.

Sealed envelopes were prepared by an anesthesia research nurse who did not involve in data collection. She prepared one envelope for each patient. The name of group was specified on each envelope. Then after, the envelopes were sealed and randomly ordered. These envelopes were stored in research nurse box in operating room. On the day of surgery, after taking informed consent, the first anesthesiologist who did not participate in data collection pull out one of the envelopes. He then prepared and labeled similar syringes containing either normal saline or the study medications for each subject according to the group that was specified in the envelope. All medications were 20 mL in volume.

Patients received either: subcutaneous infiltration of ketamine 1 mg/kg (group KS1) plus IV saline, subcutaneous infiltration of ketamine 2 mg/kg (group KS2) plus IV saline, IV ketamine 1 mg/kg (group KI) plus subcutaneous infiltration of saline, or subcutaneous infiltration of normal saline 20 mL (group C) plus IV saline before surgery. Subcutaneous infiltration of study drugs was at the actual site of the incision. All the cholecystectomy incisions were subcostal.

Induction of anesthesia was performed by second anesthesiologist who was not aware from the group allocation. After induction of anesthesia with 5 mg/kg of thiopental sodium, 3 μg/kg fentanyl and 0.6 mg/kg of atracurium for facilitation of tracheal intubation, the study drugs were administered by a surgeon who was not involved in the group assignment. All the surgical incisions were made only after 15 minutes had elapsed since study drug administration. Anesthesia was maintained with 1.2% isoflurane, nitrous oxide 50% in oxygen. Morphine 0.1 mg/kg was administered for intraoperative analgesia intravenously. At the end of the operation, neuromuscular blockade was reversed by IV neostigmine 0.04 mg/kg and IV atropine 0.02 mg/kg. Consequently, anesthesia was discontinued and the tracheal tube was removed in the operating room when airway reflexes had returned.

HR, SpO2, SAP, DAP, and MAP were recorded at 15-minute intervals during surgery, at the time of arrival to the PACU, at 15 minutes, and 30 minutes after that. These variables also were recorded at 1, 2, 3, 4, 8, 12, and 24 hours after operation at arrival to the ward. After extubation, the patients were transferred to the PACU where an anesthetist and nurse who were unaware of the study drug observed the patients. In the PACU, pain scores were assessed by a blinded observer physician at the time of arrival, 15, and 30 minutes using a VAS (0–10 cm: 0 = no pain, 10 = the worst pain possible).

During the postoperative period, pain score were evaluated by an investigator who was blinded to the treatment assignment, at 1, 2, 3, 4, 8, 12, and 24 hours. The pain that we asked was both somatic (incision) and visceral in origin. In addition, the sedation level of patients was evaluated with using a sedation scale (0, awake; 1, drowsy but responsive to verbal orders; 2, drowsy but responsive to
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Comparing between groups for nonparametric variables. Mann–Whitney U-test would be used to compare for pairs of groups. Sex, ASA physical status, and complication rates were assessed by Pearson chi-square test and by Fisher’s exact test when the anticipated number was <5. P < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA).

Results

One hundred twenty patients were enrolled in the study. No patient was withdrawn from the study due to any problem. There was no significant difference between four groups with respect to the demographic data, duration of surgery or anesthesia (Table 1).

VAS scores were significantly lower at arrival to the PACU, 15 and 30 minutes in Group KS1, Group KS2, and Group KI compared with Group C (P < 0.05) (Figure 1). In Group KS2, VAS scores were significantly lower than Group KS1 (P < 0.05). Also, the patients had significantly lower VAS scores in Group KI compared with Group KS1 (P < 0.05). VAS scores were not significantly different between Group KS2 and Group KI at these intervals.

Postoperative VAS scores were significantly lower at 1, 2, 3, 4, 8, 12, and 24 hours after operation in Group KS1, Group KS2, and Group KI compared with Group C (P < 0.05) (Figure 2). In Group KS2, VAS scores were significantly lower than Group KS1 (P < 0.05). Also, the patients had significantly lower VAS scores in Group KI compared with Group KS1 (P < 0.05). VAS scores were not significantly different between Group KS2 and Group KI at these intervals.

SpO2, HR, systolic, diastolic, and mean arterial pressure were not significantly different among four groups at any time intervals throughout surgery and in the postoperative period.

The sample size was based on a power calculation that showed that 30 patients per group were necessary to achieve 80% power to detect a 20% difference in the VAS scoring between group C with group KS1 and group KI, with a = 0.05. Data are presented as mean ± standard deviation or numbers. Differences among “groups means” were compared using one-way analysis of variance and post hoc comparisons at various points in time by using Bonferroni’s type I error rate correction for multiple tests of significance. Kruskal–Wallis test was used for nonparametric variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group KS1 (N = 30)</th>
<th>Group KS2 (N = 30)</th>
<th>Group KI (N = 30)</th>
<th>Group C (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.1 ± 12.1</td>
<td>50.6 ± 10.4</td>
<td>47.8 ± 11.8</td>
<td>54.1 ± 11.3</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>14/16</td>
<td>20/10</td>
<td>16/14</td>
<td>15/15</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>72.3 ± 9.2</td>
<td>70.8 ± 11.3</td>
<td>72.1 ± 8.9</td>
<td>73.7 ± 8.4</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>25/5</td>
<td>22/8</td>
<td>24/6</td>
<td>25/5</td>
</tr>
<tr>
<td>Duration of surgery (minutes)</td>
<td>85.1 ± 14.8</td>
<td>76.5 ± 13.9</td>
<td>78.7 ± 17.2</td>
<td>83.4 ± 12.9</td>
</tr>
<tr>
<td>Duration of anaesthesia (minutes)</td>
<td>130.0 ± 14.4</td>
<td>124.0 ± 10.4</td>
<td>129.0 ± 13.9</td>
<td>125.0 ± 11.4</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number.

Group KS1 = subcutaneous ketamine (1 mg/kg) group; Group KS2 = subcutaneous ketamine (2 mg/kg) group; Group KI = intravenous ketamine (1 mg/kg) group; Group C = control group. There were no significant differences between four groups. ASA = American Society of Anesthesiologists.
Also, median sedation values at any postoperative period were not statistically different between four groups. The time to first rescue analgesia in the postoperative period was significantly longer in Group KS1, Group KS2, and Group KI compared with Group C \( (P < 0.05) \) (Table 2). In Group KS2, this variable was significantly lower than Group KS1 \( (P < 0.05) \). Also, this variable was significantly lower in Group KI compared with Group KS1 \( (P < 0.05) \). There was no significantly different between Group KS2 and Group KI in this regard (Table 2).

Also, postoperative analgesic requirement was significantly less in Group KI, Group K2, and Group KI compared with Group C \( (P < 0.05) \) (Table 2). There was no significant difference in duration of PACU stay and time to tracheal extubation among three groups (Table 2).

The median patient satisfaction was significantly more in Group KS1, Group KS2, and Group KI compared with Group C \( 2, 4, 4, \) and 1, respectively, \( P < 0.05 \). In Group KS2, this variable was significantly higher than Group KS1 \( 4 \) vs 2, \( P < 0.05 \). Also, this variable was significantly higher in Group KI compared with Group KS1 \( 4 \) vs 2, \( P < 0.05 \). There was no significantly different between Group KS2 and Group KI in this regard.

The incidence of adverse effects was not significantly different between four groups (Table 3). There was no hypotension (systolic blood pressure less than 90 mm Hg) or bradycardia (HR less than 50 beats per minute) throughout surgery and postoperatively in any four groups.

**Discussion**

Our results demonstrated that the pre-incisional treatment with IV or subcutaneous infiltration of the NMDA-receptor antagonist, ketamine, decreases postoperative pain scores compared with pre-incisional infiltration of normal saline solution in patients undergoing open cholecystectomy without significant side effects.

Additionally, our results confirmed that a single dose of ketamine administered by IV or subcutaneous infiltration delays the first request for analgesic and produces a significant meperidine-sparing effect during the first 24 hours after open cholecystectomy.

Elia et al. [12] showed that when ketamine administered intravenously during anesthesia in adults, it could reduce postoperative pain intensity up to 48 hours,
decreased cumulative 24 hours morphine use, and delayed the time to first demand for rescue analgesic [12].

In contrast to our study, they did not compare the analgesic effect of IV ketamine with subcutaneous administration. The dosage of IV ketamine (1.6 mg/kg) was less than our study (2 mg/kg). They could not conclude the prolonged effect of ketamine usage was due to systemic or peripheral effect of drug.

In addition, Hazama et al. [13] reported that pre-incisional administration of IV ketamine (100 mg) significantly decreased cumulative 24 hours morphine use, and delayed the time to first demand for rescue analgesic [12].

Table 2  Postoperative analgesics and antiemetic use and time to tracheal extubation and PACU stay in three groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group KS1 (N = 30)</th>
<th>Group KS2 (N = 30)</th>
<th>Group KI (N = 30)</th>
<th>Group C (N = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first analgesic demand (minutes)</td>
<td>34.8 ± 13.6†‡</td>
<td>170.0 ± 14.1*</td>
<td>170.0 ± 17.3*</td>
<td>17.5 ± 5.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative analgesic requirement (mg)</td>
<td>106.0 ± 65*</td>
<td>15.0 ± 7.1*</td>
<td>23.3 ± 5.8*</td>
<td>151.0 ± 52.8</td>
<td>0.000</td>
</tr>
<tr>
<td>Duration of PACU stay (minutes)</td>
<td>31.9 ± 4.9</td>
<td>32.0 ± 5.9</td>
<td>30.1 ± 3.4</td>
<td>31.2 ± 4.1</td>
<td>0.346</td>
</tr>
<tr>
<td>Time to tracheal extubation (minutes)</td>
<td>19.5 ± 2.9</td>
<td>20.4 ± 3.5</td>
<td>18.4 ± 2.7</td>
<td>19.1 ± 4.7</td>
<td>0.189</td>
</tr>
</tbody>
</table>

* P < 0.05 vs Group C; † P < 0.05 vs Group KI; ‡ P < 0.05 vs Group KS2.
Values are presented as mean ± standard deviation.
Group KS1 = subcutaneous ketamine (1 mg/kg) group; Group KS2 = subcutaneous ketamine (2 mg/kg) group; Group KI = intravenous ketamine (1 mg/kg) group; Group C = control group; PACU = postanesthesia care unit.
reduced the postoperative VAS score in patients who underwent abdominal hysterectomy compared with control group. They did not compare this effect of ketamine with its subcutaneous administration.

The use of perioperative ketamine for postoperative pain has been the subject of a quantitative and qualitative systematic review [14]. Twelve trials with 13 treatment arms compared a pre-incisional bolus of ketamine with placebo. Postoperative analgesic requirements were reduced by pre-incisional ketamine bolus in eight out of 13 treatment arms. However, in this systematic review, there were no studies that evaluated the pre-incisional subcutaneous administration of ketamine with IV ketamine injection. The authors of this systematic review emphasized that their data should be interpreted with caution as the retrieved studies were heterogenous, and the result of the meta-analysis could not be translated into any specific administration regimen with ketamine.

In a randomized, double-blind study done by Roytblat et al. [15], postoperative pain was assessed in 22 patients undergoing elective open cholecystectomy with two types of anesthesia: standardized general anesthesia (control group), and low-dose ketamine as an addition to the same method of general anesthesia, before surgical incision (ketamine group). They indicated that postoperative pain can be decreased when ketamine in low doses is added to general anesthesia before surgical stimulation. They did not investigate the effect of pre-incisional subcutaneous infiltration of ketamine on postoperative pain after open cholecystectomy. Also, they used low dose of ketamine (0.15 mg/kg), while we used two relative high dosage of ketamine (1 and 2 mg/kg).

Kianfar et al. [16] showed that preemptive administration of low dose (0.15 mg/kg) IV ketamine before surgical incision in open cholecystectomy provides clinicians with a tool to improve postoperative pain and to reduce anesthetic doses post surgery. Similar to the other previous studies, they did not use subcutaneous infiltration of high dose of ketamine.

We could not definitely conclude the ketamine in group KS working via a peripheral mechanism because we did not check subtherapeutic ketamine plasma level and infiltration of a peripheral ketamine antagonist. We administered high dosage of ketamine (2 mg/kg) subcutaneously so it is possible that the anti-nociceptive effects of ketamine occur as a result of a central blockage of NMDA receptors.

Carlton et al. [17] demonstrated that NMDA and non-NMDA glutamate receptors are present on primary afferent axons and are increased after the induction of inflammation. Furthermore, the release of glutamate into the peripheral tissue is increased after the injury and inflammation [18–20].

The stimulation of NMDA and non-NMDA glutamate receptor by glutamate may induce hyperalgesia and allodynia interpreted as pain [21–23]. Hence, the explanation for our results may be that ketamine binding to the NMDA receptors will possibly inhibit glutamate-induced activation of NMDA receptor on primary afferents in the skin, which consequently reduces peripheral nociceptive input into the spinal cord and central sensitization of the dorsal horn.

Our study showed that subcutaneous ketamine injection anywhere else probably would not have the same effect as subcutaneous ketamine injected into the intended line of the surgical incision. This decrease in pain noticed 24 hours after pre-incisional infiltration of ketamine, as evidenced by the high incidence of low pain scores and decreased use of analgesics in the present study, could be explained by the unusually long duration of ketamine’s direct peripheral pharmacologic action or by its preemptive effect on the inflammatory response to surgery.

The purposes of preemptive analgesia are: first, to inhibit or reduce the development of any “memory” of pain stimulus in the CNS, and second, to diminish analgesic requirements as a consequence [24,25]. NMDA antagonists have been shown to inhibit wind-up in a wide dynamic range of neurons as a consequence of long-lasting C-fiber stimulation. It is interesting to note that these drugs do not reduce the response to short-lasting C-fiber stimulation [26,27].

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group KS1 (N = 30)</th>
<th>Group KS2 (N = 30)</th>
<th>Group KI (N = 30)</th>
<th>Group C (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hallucination</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as number.

Group KS1 = subcutaneous ketamine (1 mg/kg) group; Group KS2 = subcutaneous ketamine (2 mg/kg) group; Group KI = intravenous ketamine (1 mg/kg) group; Group C = control group. There were no significant differences between four groups.
Preemptive treatment with local anesthetics and NMDA inhibitors have all been proposed as methods of inhibiting transmission of noxious stimuli and consequently preventing stimulation of NMDA receptors in spinal cord and central sensitization [28,29].

The local anesthetic properties of ketamine have been explained in a previous report [30]. Tverskoy et al. [31] showed that the analgesic efficacy and duration of bupivacaine with ketamine infiltration was doubled during inguinal hemia incision. Moreover, it was shown that IV ketamine produced an adequate IV regional anesthesia in a sample of volunteers [32].

The preemptive blockade of initial nociceptive afferent input to the spinal cord may inhibit the development of long-term changes in the excitability of central neurons and, accordingly, prevent both peripheral and central nociceptive processing, then producing long-lasting antinociceptive effects [33,34]. The analgesic effect of the NMDA antagonist has been shown to be short-lived when administered after pain stimulation, possibly due to the failure to inhibit the maintenance of pain behavior because the peripheral or central sensitization has previously developed earlier [23]. Consequently, it is probable that prevention of the original neural activity by local infiltration of ketamine during the induction of pain behavior may inhibit the preservation of pain behavior.

Another theory to explain the analgesic effect of ketamine probably will be the synergistic or additive interaction among opioids that show activation of the NMDA receptors [35] and NMDA antagonists. One of the mechanisms of severe postoperative pain that leads to the need for progressively higher doses of opioids in postoperative patients is tolerance. It appears that ketamine act specifically to inhibit tolerance and pain sensitization [36].

In summary, the prolonged analgesic effect of 2 mg/kg subcutaneous infiltration of ketamine and 1 mg/kg IV ketamine in our study can be explained by several mechanisms: 1) the preemptive effect of ketamine administration by subcutaneous or IV route; 2) local anesthetic property of ketamine; 3) peripheral effect of ketamine by blockage of NMDA receptors located on primary afferent axons in the skin; 4) central effect of subcutaneous infiltration of ketamine by probable systemic absorption of drug; 5) synergistic effect of ketamine with opioids; 6) perhaps the 2 mg/kg subcutaneous ketamine was absorbed more slowly and really acts as a depot reservoir for the drug allowing longer duration of analgesia; and 7) less probably, ketamine is neurotoxic and this could potentially be from peripheral nerve destruction similar to capsaicin [37,38].

We used metoclopromide for treatment of postoperative nausea and vomiting because it was inexpensive. Also, its use was simple for nurses. The risk of extrapyramidal effects of metoclopromide is increased in young adults (<20 years) and children, and with high-dose or prolonged therapy [39,40].

Our patients were middle aged and we did not administer high-dose or prolonged therapy of metoclopromide. So, it was unexpected that postoperative hallucination, which developed in some patients, was due to metoclopromide administration.

In explaining limitation of our study, it is necessary to emphasize that we only recorded total consumption of meperidine on first postoperative days. Therefore, our results cannot document whether the meperidine sparing effect of ketamine was prolonged beyond the expected duration of action or was it limited merely during early postoperative period.

In our study, we evaluated the analgesic efficacy of ketamine as a single agent for postoperative pain management rather than in the setting of a multimodal analgesic protocol that would be considered current standard practice for this type of open abdominal surgery. However, we recommend investigating the effects of multimodal analgesia on postoperative pain improvement after open or laparoscopic cholecystectomy.

In conclusion, pre-incisional IV or subcutaneous infiltration of ketamine provides an adjunct analgesia during the 24 hours following surgery without significant side effects in patients who are candidate for the cholecystectomy surgery. Whether this is due to antagonism of the peripheral NMDA receptors, local anesthesia, or other undetermined effects of ketamine continues to be unknown.

References
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