Preemptive analgesia effects of Ketamine in patients undergoing surgery. A meta-analysis

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ABSTRACT
PURPOSE: To evaluate the preemptive analgesia effects of ketamine for postoperative pain.

METHODS: PubMed, EMBASE and Cochrane Library were searched to identify randomized controlled trials (RCTs) involved in ketamine for preemptive analgesic up to March 2013. The relative risk (RR) or mean difference (MD) as well as the confounding 95% confidence interval (CI) were calculated by the Revman 5.0 software.

RESULTS: A total of five studies including 266 patients were included in this meta-analysis. Overall, ketamine could reduce the postoperative morphine consumption and significantly prolong the time to first analgesic (p < 0.00001, MD = 0.91, 95% CI: 0.56 to 1.26). However, there was no significant difference in indicators of nausea and vomiting (p = 0.87, RR = 1.04, 95% CI: 0.67 to 1.60), surgical time (p = 0.41, MD = -2.13, 95% CI: -7.21 to 2.95) and anesthetic time (p = 0.53, MD = -1.54, 95% CI: -6.34 to -3.26) between ketamine and control group.

CONCLUSIONS: Ketamine was able to accomplish some preemptive analgesic effects of reducing postoperative morphine consumption and prolonging the time to first analgesic. Meanwhile, ketamine was as safe as physiological saline in side effects of nausea and vomiting.

Key words: Ketamine. Preemptive Analgesia. Pain, Postoperative. Meta-Analysis.
Introduction

Preemptive analgesia is considered as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input. By decreasing the altered central sensory processing, preemptive analgesia is thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery. Currently, the drugs for preemptive analgesia included such as opioids, N-methyl-D-aspartic acid (NMDA) receptor antagonists and non-steroidal anti-inflammatory drugs (NSAIDs).

Among them, NMDA receptor antagonists have been demonstrated as an effective treatment option in the management of chronic pain, particularly for pain which has been refractory to other treatment modalities. Ketamine, as a noncompetitive NMDA receptor antagonist, has a history of fifty years of pain management. Ketamine has served as a useful tool to provide a compelling rationale for developing other NMDA antagonists. It was reported that ketamine might disrupt dopaminergic neurotransmission in the prefrontal cortex as well as cognitive functions associated with this region, in part, by increasing the release of glutamate, thereby stimulating postsynaptic non-NMDA glutamate receptors.

Currently, the efficacy and safety of ketamine for the management of postoperative pain has been studied by many experts. However, the inconsistent conclusions of a beneficial effect and safety of ketamine for preemptive analgesic remains existed. Subramaniam et al. reported that the addition of epidural ketamine 1 mg/kg to morphine 50 μg/kg improved analgesia after major upper abdominal surgery without increasing side effects. While another recent studies found that the preoperative administration of 0.5 mg/kg ketamine in patients undergoing cesarean section did not elicit a preemptive analgesic effect. Moreover, Hala et al. reported that intranasal ketamine could enhance the postoperative analgesia after endoscopic nasal surgery, but the psychomimetic side effects of ketamine still occurred with intranasal administration. Thus, whether preemptive analgesic of ketamine is effective and safety in managing postoperative pain remains need more strong evidence to determine. In this study, the purpose of our meta-analysis was to assess the efficacy and safety of ketamine for preemptive analgesic by analyze the data from the randomized clinical trials (RCTs) and double-blind controlled trials.

Methods

Literature search

A literature search without language limitation was conducted for screening studies that reported the preemptive analgesic effects of ketamine. PubMed, EMBASE and Cochrane Library were searched to identify RCTs involved in the preoperative ketamine efficacy for preemptive analgesic up to March 2013. The key words used in this literature search included: “preemptive”, “ketamine”, “analgesic efficacy” and “randomized controlled trials”. Similarly, a manual search of the relevant references was performed.

Criteria for inclusion and exclusion

Articles that met the following criteria were included in this meta-analysis: (1) Studies had been published; (2) they should be RCTs; (3) the intervention was preoperative ketamine in ketamine group; (4) physiological saline instead of ketamine was used in control group; (5) the manner and dosage of anesthesia were same in two groups; (6) at least one of the following indicators were contained: postoperative pain score, postoperative morphine consumption, surgical time, anesthetic time, time to first analgesic and side effects. We excluded trials when there were less than 10 patients in each group or the studies were lack of available data or experimental results. In addition, animal studies and reviews were not considered.

Quality assessment

Two investigators independently assessed the quality of the included studies according to the descriptions provided by the authors of the included trials and the disagreement was subsequently resolved by discussion with each other or another investigator. Jadad scale was used to independently assess the methodological quality of selected clinical trial. Research with the score more than 3 was regarded as high quality study.

Data extraction

Original data were extracted independently by two investigators, including general information (first author name, year of publication and country, documents source), trial characteristics (surgery type, sample size, pain evaluation criteria and the dosage of ketamine), participant-related data (participant age and weight) and all the experimental results.

Statistical analysis

In this study, the relative risk (RR) and mean difference (MD) as well as the confounding 95% confidence interval (CI) were...
calculated to assess the categorical variables and continuous variables, respectively. Heterogeneity was explored using F statistic and Chi-square test with p<0.05. The fixed effects model was used if no heterogeneity was existed. Otherwise, random effects model was used.

The statistical analysis in this meta-analysis was performed by using Revman 5.0 software. When the data of the included studies could not be analyzed using software, the descriptively qualitative analysis was performed.

Results

Literature search

The initial literature search identified 142 potentially relevant studies. According to inclusion criteria in our analysis, a total of five English studies matched the selection criteria finally (Figure 1).

Characteristics of included studies

The characteristics of the included studies were shown in Table 1. The publication year of studies ranged from 2000 to 2012. The studies respectively come from Asia, Europe and America. Total 266 patients including 139 patients in ketamine group and 127 patients in control group were included in this meta-analysis. The surgeries in the included studies were all abdominal surgery. Visual analog scale (VAS) and verbal rating scale (VRS) were used to evaluate pain in two included studies, while the pain was accessed only based on the VAS in the other three studies. The range dosage of ketamine was 0.15 - 0.5 mg/kg. In addition, based on the Jadad score of the studies, all the included studies were high quality studies.

Postoperative pain score

All the included studies involved in the postoperative pain score. Kwok et al. and Nesek-Adam et al. accessed the postoperative pain score of ketamine at a dosage of 0.15 mg/kg. Among them, the study results of Kwok et al. indicated that the postoperative pain score during 0 - 6 h postoperatively was lower in ketamine group than in control group and there was no difference among the two groups for the postoperative pain score at 6 - 24 h postoperatively. Nesek-Adam et al. found the ketamine can decreased the postoperative pain at 12 h postoperatively in abdomen while the postoperative pain score during 12 - 24 h postoperatively was higher in ketamine group than that in control group. These study results of Nesek-Adam et al. were all no statistically significant. Lenzmeier et al. and Reza et al. assessed the postoperative pain scores of ketamine at a dosage of 0.50 mg/kg. Lenzmeier et al. reported that the postoperative pain

<table>
<thead>
<tr>
<th>Author year</th>
<th>Country</th>
<th>Procedure</th>
<th>Pain evaluation</th>
<th>Dose of ketamine (mg/kg)</th>
<th>Sample size (ketamine / control)</th>
<th>Age (ketamine / control)</th>
<th>Weight (ketamine / control)</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahl V 2000</td>
<td>USA</td>
<td>Hysterectomy</td>
<td>VAS, VRS</td>
<td>0.40</td>
<td>33 / 21</td>
<td>51 ± 6 / 48 ± 7</td>
<td>70 ± 11 / 66 ± 11</td>
<td>5</td>
</tr>
<tr>
<td>Kwok RF 2004</td>
<td>China</td>
<td>Gynecologic laparoscopic surgery</td>
<td>VAS</td>
<td>0.15</td>
<td>45 / 45</td>
<td>34 ± 7 / 34 ± 6</td>
<td>54 ± 9 / 52 ± 7</td>
<td>5</td>
</tr>
<tr>
<td>Lenzmeier B 2008</td>
<td>Netherlands</td>
<td>Laparoscopic abdominal procedure</td>
<td>VAS</td>
<td>0.50</td>
<td>11 / 11</td>
<td>29.72 ± 8.5 / 31.63 ± 6.68</td>
<td>71.36 ± 7.61 / 69.73 ± 9.67</td>
<td>4</td>
</tr>
<tr>
<td>Reza FM 2010</td>
<td>Iran</td>
<td>Cesarean section</td>
<td>VAS</td>
<td>0.50</td>
<td>30 / 30</td>
<td>26.96 ± 5.1 / 27.33 ± 4.54</td>
<td>71.54 ± 12.3 / 73.34 ± 13.4</td>
<td>5</td>
</tr>
<tr>
<td>Nesek-Adam V 2012</td>
<td>Croatia</td>
<td>Laparoscopic cholecystectomy</td>
<td>VAS, VRS</td>
<td>0.15</td>
<td>20 / 20</td>
<td>50.7 ± 11.9 / 53.6 ± 9.6</td>
<td>34.2 ± 4.1 / 32.9 ± 4.2</td>
<td>5</td>
</tr>
</tbody>
</table>

VAS: Visual Analog Scale; VRS: Verbal Rating Scale.
score (p<0.05) at post-anaesthesia care unit (PACU) were lower in ketamine group than that in control group but no significant difference were found among the two groups for the postoperative pain intensity when the patients discharged from hospital. Reza et al. did not find the difference among the two groups for the postoperative pain score at 2, 6, 12, 24 h postoperatively. Dahl et al. reported the postoperative pain score of ketamine at a dosage of 0.4 mg/kg. It indicated that the postoperative pain score (p = 0.02) at 0 - 6 h, 6 - 24 h and 24 - 96 h postoperatively was lower when compared ketamine group with control group. By observing these data, we did not find the evidence of the association between the dose of ketamine and its analgesic efficacy.

Postoperative morphine consumption

Three trials reported the morphine consumption after surgery. Kwok et al. reported that the overall postoperative morphine consumption (p<0.05) of patients in the ketamine group (1.5 ± 2.0 mg) was less than that in control group (3.4 ± 2.7 mg). Lenzmeier et al. found that the postoperative morphine consumption (p<0.05) in the postanaesthesia care unit (PACU) was reduced by ketamine group compared with control group. The study result of Reza et al. indicated that the postoperative morphine consumption (p<0.01) at 2h postoperatively was less in ketamine group than that in control group. There results suggested that ketamine could reduce the postoperative morphine consumption.

Surgical time

In this meta-analysis, all the included studies reported the data of surgical time. There was no significant heterogeneity (p = 0.21, I² = 32%) among the five studies. So a fixed effects model was used. Our results showed that there was no significant differences (p = 0.41, MD = -2.13, 95% CI: -7.21 to 2.95) among the two groups in the surgical time (Figure 2).

### (A) Surgical time

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ketamine</th>
<th>Control</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahle V 2000</td>
<td>74</td>
<td>22</td>
<td>52.3% (0.21; 0.01)</td>
</tr>
<tr>
<td>Kwok RF 2004</td>
<td>64</td>
<td>25</td>
<td>22.3% (-0.18; 0.75)</td>
</tr>
<tr>
<td>Lenzmeier B 2008</td>
<td>60.36</td>
<td>41.37</td>
<td>31.6% (0.21; 0.01)</td>
</tr>
<tr>
<td>Nessek-Adam V 2012</td>
<td>54</td>
<td>18</td>
<td>20.2% (0.21; 0.01)</td>
</tr>
<tr>
<td>Reza FM 2010</td>
<td>47.52</td>
<td>21.1</td>
<td>35.5% (-0.18; 0.75)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>139</td>
<td>135</td>
<td>100.0% (-2.13; 2.95)</td>
</tr>
</tbody>
</table>

FIGURE 2 - The forest plots of the evaluation indicators of preemptive analgesic effect (Surgical time).

RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.

### Anesthetic time

In our analysis, total out of the included studies assessed the anesthetic time between ketamine groups and controls. The fixed effects model was used because of no significant heterogeneity (p = 0.28, I² = 23%) among the studies. The results indicated that there was no significant difference (p = 0.53, MD = -1.54, 95% CI: -6.34 to 3.26) between ketamine and control group (Figure 3).

### (B) Anesthetic time

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ketamine</th>
<th>Control</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahle V 2000</td>
<td>103</td>
<td>33</td>
<td>11.0% (0.21; 0.01)</td>
</tr>
<tr>
<td>Kwok RF 2004</td>
<td>80</td>
<td>24</td>
<td>20.7% (-0.18; 0.75)</td>
</tr>
<tr>
<td>Nessek-Adam V 2012</td>
<td>63</td>
<td>18</td>
<td>15.7% (-0.18; 0.75)</td>
</tr>
<tr>
<td>Reza FM 2010</td>
<td>53.32</td>
<td>13.6</td>
<td>32.7% (-0.18; 0.75)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>128</td>
<td>124</td>
<td>100.0% (-1.54; 3.26)</td>
</tr>
</tbody>
</table>

FIGURE 3 - The forest plots of the evaluation indicators of preemptive analgesic effect (Anesthetic time).

RR; risk ratio; MD: mean difference; 95% CI: 95% confidence interval.
Preemptive analgesia effects of Ketamine in patients undergoing surgery. A meta-analysis

Time to first analgesic

Two included studies investigated the time to first analgesic of the patients after operation. The fixed effects model was used due to no heterogeneity \((p = 0.12, I^2 = 59\%)\) among the studies. Our results showed that the time to first analgesic was significantly longer in ketamine group than that in control group \((p < 0.00001, MD = 0.91, 95\% CI: 0.56 \text{ to } 1.26)\) (Figure 4).

Nausea and vomiting

Nausea and vomiting, as the side effects of ketamine, were reported in three included studies. The fixed effects model was used to pooled the data because of no significant heterogeneity \((p = 0.65, I^2 = 0\%)\). Our results showed that there was no significant difference between ketamine and control groups \((p = 0.87, RR = 1.04, 95\% CI: 0.67 \text{ to } 1.60)\). It indicated that the safety of ketamine for preemptive analgesia was equally with physiological saline (Figure 5).

Discussion

Preemptive analgesia is a treatment initiated before the surgical procedure in order to reduce this sensitization. In the present meta-analysis, we assessed the efficacy and safety of ketamine. For postoperative pain, we could not conclude that ketamine could decrease the pain intensity because of the inconsistent conditions and results of the included studies. For the indicators of postoperative morphine consumption and time to first analgesic, ketamine could reduce the postoperative morphine consumption and significantly prolong the time to first analgesic. It suggested that ketamine had some beneficially preemptive analgesic effects. However, the results demonstrated that ketamine didn’t play any role in reducing surgical time, anesthetic time. For nausea and vomiting, the result indicated that the ketamine for preemptive analgesia was as safe as physiological saline.

The mechanism of ketamine for preemptive analgesia is based on the induction and maintenance of central sensitization. Central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations. The proposed mechanism of this preemptive effect is that analgesia administered before a nociceptive stimulus reduces the degree of sensitization produced in the nervous system by the stimulus, and facilitates subsequent pain treatment. Therefore, there is reliable theory basis for ketamine as the drug of preemptive analgesia and further studies of ketamine for preemptive analgesia are worth doing.

It was reported that morphine administration after surgery carries a high risk of side-effects such as nausea, vomiting, pruritus, urinary retention and apnoea. Thus, the reduction of postoperative morphine consumption can decrease the postoperatively adverse reactions. It provided beneficial information for the clinical application of ketamine.
In addition, we did not find any difference between ketamine and control group for the incidence of nausea and vomiting in our analysis. However, it was reported that large doses of ketamine (> 2 mg/kg) can produce unpleasant side effects\(^\text{26}\). So for the safety of ketamine, more studies must be done to verify the conclusion of this study or find the other evidences for the side effects of ketamine.

This meta-analysis has some advantages compared with the previous review\(^\text{27}\). The first one is that the included studies were updated up to 2012. Second, the studies included in this meta-analysis were all high quality studies. Third, the control was only physiological saline and the intervention was only preoperative ketamine. It was benefit for the accuracy of the results in this study.

However, some limitations must be mentioned in this study. The first one is that the data of postoperative pain score could not be statistically analyzed. New methods must be established to evaluate the pain intensity. Second, the association of the dose of ketamine with the pain intensity was not found by the observation of the data from the included studies. More studies were needed to find the association of the dose of ketamine with the pain intensity and the preemptive analgesic effect. The second limitation is the small size of subjects. Third, the sensitivity analysis and evaluation of publication bias were not performed for lack of enough available data.

Conclusions

Ketamine was able to accomplish some preemptive analgesic effects of reducing postoperative morphine consumption and prolonging the time to first analgesic. For the safety of ketamine, ketamine for preemptive analgesia was as safe as physiological saline side effects of nausea and vomiting.

References


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