Small-Dose Ketamine Reduces the Pain of Propofol Injection

Seung-Woo Koo, MD
Sun-Jun Cho, MD
Young-Kug Kim, MD
Kyung-Don Ham, MD
Jai-Hyun Hwang, MD

BACKGROUND: IV injection of propofol during anesthetic induction induces pain. Ketamine has been shown to reduce injection pain. In this study, we established the optimal dose of ketamine to prevent the pain of injection with propofol.

METHODS: Two hundred forty patients presenting for elective surgery were randomly allocated into eight groups; five groups during the first part of the study and three groups during the second part. In Part 1, patients received saline (Group S), lidocaine (Group L), ketamine 10 μg/kg (Group K10), 50 μg/kg (Group K50), or 100 μg/kg (Group K100), respectively, immediately followed by propofol 2.5 mg/kg. In Part 2, the optimal dose of ketamine (100 μg/kg) was administered 3 min before propofol (Group Pre), mixed with propofol solution (Group KP), or after oral midazolam premedication (Group M). An anesthesiologist blinded to the study group monitored each patient’s pain score at 5-s intervals.

RESULTS: In Part 1, the incidence and intensity of pain were the lowest in the K100 and L groups (P < 0.001). In Part 2, the patients in the K100 and M groups had significantly lower pain scores compared with the KP and Pre groups (P < 0.05). During induction, there were no significant intergroup differences in mean arterial blood pressure and heart rate in all groups.

CONCLUSIONS: Administration of ketamine 100 μg/kg immediately before propofol injection provided the optimal dose and timing to reduce propofol-induced pain on injection.

(Anesth Analg 2006;103:1444–7)

Propofol is a popular IV anesthetic induction drug that causes pain when given. Several methods have been proposed to reduce injection pain. The incidence of pain on injection varies between 28% and 90% in adults during induction of anesthesia (1). Methods used to reduce this pain include the addition of lidocaine, cooling or warming, diluting the propofol solution, injection of propofol into a large vein, and previous injection of ephedrine, ondansetron, metoclopramide, opioids, thiopental, or ketamine (2–6). Although lidocaine is commonly used to decrease injection-related pain, its failure rate is between 13% and 32% (2,3).

Ketamine has potent analgesic and local anesthetic properties, but few studies have evaluated the utility of ketamine for reducing propofol-induced pain on injection (7,8), and none has defined the optimal dose and timing of ketamine to reduce the pain of injection with propofol.

We, therefore, performed a prospective, randomized, placebo-controlled, double-blind study to determine the optimal IV dose of ketamine and evaluated the appropriate timing for reducing pain on propofol injection during the induction sequence.

METHODS

The study population consisted of 240 patients (ASA physical status I or II, aged 19–59 yr) undergoing elective surgery. All patients provided written informed consent, and the study protocol was approved by the IRB of our hospital. Other than the midazolam group (see later), no patient received any premedication before arrival in the operating room or any opioid within 24 h before surgery. Patients taking sedatives or analgesics, and those with allergic, neurologic, or cardiovascular disease were excluded from this study. A 20-gauge Teflon catheter was inserted into a vein of the dorsum or wrist of the hand at approximately 120 min before the induction of anesthesia. The catheter was used for IV infusion of Ringer’s lactate solution.

In Part 1 of this study, patients were randomly allocated into one of the five groups to determine the optimal dose of ketamine. Each group consisted of 30 patients. Group S received 2 mL 0.9% normal saline, Group L received 2 mL 2% lidocaine, and Groups K10, K50, and K100 received 10 μg/kg, 50 μg/kg, and 100 μg/kg of a racemic mixture of ketamine, respectively. All were administered just before injection of 2.5 mg/kg propofol, which was slowly infused over 15 s.
In Part 2 of this study, the optimal dose of ketamine (100 μg/kg) was administered IV 3 min before injection of propofol (Group Pre, n = 30), mixed with the propofol solution and administered immediately after 2 mL saline (Group KP, n = 30), or administered just before injection of propofol in patients premedicated with midazolam (7.5 mg p.o.) 90 min before arrival in the operating room (Group M, n = 30), respectively. Thereafter, three groups were compared with Group K100. Except for Group KP, each dose of ketamine in each group was diluted with 0.9% normal saline to a volume of 2 mL. In Groups KP and M, 2 mL normal saline was given 3 min before injection of propofol; in Groups Pre and KP, 2 mL normal saline was administered just before injection of propofol to maintain blinding.

All drugs were kept and prepared at room temperature and used within 10 min of preparation. All syringes of test solution were prepared by a doctor not involved in induction of anesthesia and covered so that the investigator who assessed the patient's behavior was unaware of the nature of the solution. Immediately after the administration of the test solution, 1% solution of propofol 2.5 mg/kg was injected slowly through a three-way tap directly connected to the IV catheter over 30 s, with the IV infusion line closed, after which crystalloids were administered at maximal gravity flow.

Before the administration of propofol, each patient was asked by an anesthesiologist, blinded to the dose of ketamine, to immediately rate any sensation of pain every 5 s during the propofol injection, using a 0–3 scale (verbal rating scale [VRS]) published by McCrerrick and Hunter (4). The highest pain score was recorded. The grading criteria of VRS were as follows: 0 = no pain, 1 = mild pain or soreness, 2 = moderate pain, and 3 = severe pain associated with grimacing, withdrawal movement of forearm, or both.

After the propofol was injected and the patient lost consciousness, vecuronium 0.15 mg/kg was administered to facilitate controlled ventilation, and 6 L/min oxygen with isoflurane 1.5–2.5 vol % was administered during ventilation via a facemask. Three to four minutes after vecuronium injection, the trachea was intubated, and anesthesia was maintained with isoflurane 1.0–2.0 vol % and N₂O 50% in oxygen. Noninvasive mean arterial blood pressure and heart rate were recorded at the start of monitoring, just before ketamine administration, just before intubation and 1, 2, 3, and 5 min after intubation. Peripheral oxygen saturation and esophageal temperature were also recorded. Experienced nurses assessed the state of patients during the recovery period. They did not use any special tool to quantify any emergence problems arising after ketamine administration but checked for abnormal behavioral response(s), including hallucinations, illusions or delirium and immediately reported any unusual responses.

Before beginning the study, a power analysis indicated that at least 25 patients in each group would be required to detect an improvement in injection pain of 25% with a power of 0.8 (α = 0.05). Data were expressed as mean ± SD. Statistical comparison among groups was made with one-way analysis of variance by using SigmaStat (version 2.03). Within group, comparisons were performed using repeated measures of analysis of variance. Post hoc testing was performed according to the Tukey’s method. For ordinal data of pain scores, medians were used. A P value <0.05 was considered statistically significant.

### RESULTS

Patient demographic characteristics including age, gender, height, and weight for the eight groups are presented in Table 1. There were no statistically significant differences among groups.

The patients in Groups L and K100 had significantly lower median pain scores (VRS) and significantly fewer incidences of pain than did patients in Group S (P < 0.001). Although the incidence of pain in Groups L (53.3%) and K100 (46.7%) did not differ significantly, the number of patients perceiving any pain or discomfort and the intensity of pain were less in Group K100 than in Group L (Table 2).

In Part 2 of the study, the patients in Group K100 had significantly lower median pain scores compared with Groups KP (P = 0.003) and Pre (P = 0.045). The percentage of any pain/discomfort in Group K100 and Group M, however, did not differ significantly (46.7% vs 40%; P = 0.888) (Table 3).

None of the doses of ketamine used increased arterial blood pressure or prevented the propofol-induced decrease in arterial blood pressure that occurs.

---

**Table 1. Characteristics of Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>S (n = 30)</th>
<th>L (n = 30)</th>
<th>K10 (n = 30)</th>
<th>K50 (n = 30)</th>
<th>K100 (n = 30)</th>
<th>KP (n = 30)</th>
<th>Pre (n = 30)</th>
<th>M (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.8 ± 11.2</td>
<td>41.3 ± 9.9</td>
<td>40.3 ± 11.3</td>
<td>45.0 ± 10.5</td>
<td>39.5 ± 11.7</td>
<td>43.4 ± 11.8</td>
<td>37.3 ± 11.8</td>
<td>40.4 ± 11.4</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/19</td>
<td>5/25</td>
<td>13/17</td>
<td>10/20</td>
<td>12/18</td>
<td>13/17</td>
<td>18/12</td>
<td>22/8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.7 ± 9.8</td>
<td>160.7 ± 6.5</td>
<td>163.4 ± 9.0</td>
<td>161.3 ± 8.5</td>
<td>163.2 ± 7.0</td>
<td>165.6 ± 7.6</td>
<td>164.2 ± 8.3</td>
<td>166.5 ± 7.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.9 ± 11.3</td>
<td>60.7 ± 10.2</td>
<td>62.7 ± 9.7</td>
<td>63.8 ± 9.7</td>
<td>60.7 ± 8.8</td>
<td>65.3 ± 11.5</td>
<td>60.5 ± 11.9</td>
<td>64.6 ± 11.5</td>
</tr>
</tbody>
</table>

L = lidocaine, K10 = ketamine 10 μg/kg, K50 = ketamine 50 μg/kg, K100 = ketamine 100 μg/kg, KP = ketamine 100 μg/kg in propofol solution after saline 2 ml injection, Pre = pretreatment with ketamine 100 μg/kg 3 min before injection of propofol, M = midazolam premedication.

Data are expressed mean ± SD.
before intubation. None of the patients developed profound hypotension or bradycardia that required treatment, and there were no adverse events, such as arrhythmias, severe hypertension, allergic reactions, or cardiovascular collapse, during induction and up to 5 min after intubation.

In Group Pre, pretreatment with 100 μg/kg ketamine induced a mild to moderate sedative effect in 11 patients before propofol injection. Five patients complained of mild injection pain, whereas six patients did not. None of these patients had postanesthesia emergence reactions during recovery. In Group M, most patients seemed to be asleep but responded well to oral commands. Although four patients who did not sleep well during the night before surgery because of anxiety showed a dull response, this did not affect the results.

Table 2. Incidence and Intensity of Pain on Injection of Propofol

<table>
<thead>
<tr>
<th>Intensity of pain</th>
<th>S (n = 30)</th>
<th>L (n = 30)</th>
<th>K100 (n = 30)</th>
<th>K50 (n = 30)</th>
<th>K10 (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (= 0)</td>
<td>4</td>
<td>14</td>
<td>16</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Mild (= 1)</td>
<td>13</td>
<td>13</td>
<td>11</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Moderate (= 2)</td>
<td>11</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Severe (= 3)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Any pain/discomfort</td>
<td>26</td>
<td>16</td>
<td>14</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>86.7</td>
<td>53.3</td>
<td>46.7</td>
<td>63.3</td>
<td>63.3</td>
</tr>
<tr>
<td>Median pain score</td>
<td>1</td>
<td>1*</td>
<td>0*</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

S = saline, L = lidocaine, K100 = ketamine 100 μg/kg, K50 = ketamine 50 μg/kg, K10 = ketamine 10 μg/kg.

Data are expressed in number of patients. The pain scores are shown in brackets.

* P < 0.001 when compared with Group S.

Table 3. Incidence and Intensity of Pain on Injection of Propofol

<table>
<thead>
<tr>
<th>Intensity of pain</th>
<th>K100 (n = 30)</th>
<th>M (n = 30)</th>
<th>KP (n = 30)</th>
<th>Pre (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (= 0)</td>
<td>16</td>
<td>18</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Mild (= 1)</td>
<td>11</td>
<td>7</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Moderate (= 2)</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Severe (= 3)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Any pain/discomfort</td>
<td>14</td>
<td>12</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>46.7</td>
<td>40</td>
<td>86.7</td>
<td>66.7</td>
</tr>
<tr>
<td>Median pain score</td>
<td>0</td>
<td>0</td>
<td>1*</td>
<td>1*</td>
</tr>
</tbody>
</table>

S = saline, K100 = ketamine 100 μg/kg, M = midazolam premedication, KP = ketamine 100 μg/kg in propofol solution following saline 2 mL, Pre = pretreatment with ketamine 100 μg/kg 3 min before injection of propofol.

Data are expressed in number of patients. The pain scores are shown in brackets.

* P < 0.05 when compared with Group K100.

The incidence of propofol injection pain has been reported to range between 28% and 90% in adults (1–3) and between 40% and 86% (86.7% in the present study) when injected into a hand vein during the induction of anesthesia (9). Even when small-dose propofol infusions are administered for sedation, the incidence of pain can vary from 33% to 50% (10,11).

Although the etiology of this pain remains obscure, numerous methods have been used to reduce its incidence and intensity. The most popular is the use of lidocaine either by mixing it with propofol or by pretreatment with a bolus injection of lidocaine (2,3,5). However, protection is not complete, with a failure rate of between 32% and 48% (3,12). Likewise, we found that 45%–55% of patients in Groups L and K100 experienced some pain. When mixed with propofol, lidocaine may act as a stabilizer for the kinin cascade (2), and 40 mg of lidocaine has been found to be more effective than 20 mg (13).

Although our comparison group was administered 40 mg lidocaine, we found that 53.3% of these patients experienced pain. Approximately 70% of all control patients have reported some degree of pain or discomfort on injection with propofol alone (5), whereas in our study, the incidence was somewhat higher (86.7%).

Pretreatment with 10 mg ketamine (approximately 100–150 μg/kg) in 1 mL normal saline 30 s before propofol injection was found to significantly reduce the incidence of pain during the latter from 84% to 26% (8). This may have been the result of a peripheral local anesthetic action, which attenuated the afferent pain pathway, rather than a central analgesic effect. Pain during propofol injection can be immediate or delayed, with the latter having a latency of between 10 and 20 s (14). To avoid even the possibility of immediate injection pain, we administered ketamine just before injection of propofol. We found that the reduction in the incidence of pain in Group K100 (46.7% vs 86.7% in Group S) was similar to that reported previously (8).

In Part 2 of this study, we evaluated the best method for ketamine administration. To eliminate the possibility of a systemic effect, 100 μg/kg ketamine was administered 3 min before injection of propofol in Group Pre.
This, however, was not as effective for reducing the pain incidence as that observed in Group K100, in which ketamine was given immediately before propofol. We also found that mixing the optimal dose of ketamine with propofol was not effective, perhaps because water soluble ketamine does not mix well with propofol, which is virtually insoluble in aqueous solution.

Our finding that smaller doses of ketamine (10 and 50 μg/kg) and mixing ketamine with propofol solution could not effectively relieve pain suggests that a minimum dose of 100 μg/kg ketamine is required for effective reduction of pain, and that a rapid, local vascular effect, rather than a systemic or central effect, is likely involved in the reduction of propofol-induced pain. Although the exact mechanism is not known, our results may suggest that ketamine acts peripherally, even in a setting without tissue injury, through an action on peripheral N-methyl-D-aspartate receptors.

One limitation of our study was that we did not investigate doses of ketamine larger than 100 μg/kg. We were concerned, however, that larger doses would cause sedation and thus bias the results. This criticism may also be true for Group M, although these patients were able to provide effective pain scores. In addition, it was difficult for Group M in Part 2 to be blinded, as it was easy to notice which patients were premedicated.

None of the doses of IV ketamine used in this study had a significant effect on mean arterial blood pressure or heart rate, compared with saline or lidocaine before or after intubation. The doses of ketamine we used were relatively small, even for relieving injection pain. Heart rate in Group L was slower than in other groups, but the difference was not significant, even at the lowest mean value.

In conclusion, our findings suggest that a dose of 100 μg/kg ketamine administered just before propofol can reduce the incidence and intensity of propofol-induced pain without significant adverse hemodynamic effects.

REFERENCES