The Effects of Small-Dose Ketamine on Morphine Consumption in Surgical Intensive Care Unit Patients After Major Abdominal Surgery

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In a randomized, double-blinded study, we evaluated the analgesic effect of ketamine in the management of pain in a surgical intensive care unit after major abdominal surgery. Patients received morphine patient-controlled analgesia with either placebo (Group M) or ketamine (Group K). Morphine was administered with initial loading doses of 2 mg until the visual analog scale (VAS) score was <30 and thereafter with bolus doses of 1 mg and a lockout time of 7 min. Ketamine was administered with an initial bolus of 0.5 mg/kg followed by a perfusion of 2 mg • kg^{-1} • min^{-1} during the first 24 h and 1 mg • kg^{-1} • min^{-1} during the following 24 h. The 4-h cumulative morphine doses were measured over 48 h. The VAS scores at rest and at mobilization were measured every 4 h during 48 h. A total of 101 patients were enrolled, and 93 were analyzed (41 in Group K and 52 in Group M). VAS scores at rest and at mobilization were similar. The cumulative consumption of morphine was significantly smaller in Group K (P < 0.05). We concluded that small doses of ketamine were a valuable adjunct to opioids in surgical intensive care unit patients after major abdominal surgery.

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Surgical intensive care unit (SICU) patients need effective and sustained pain relief without significant side effects, and IV morphine alone is not always successful in this context. Indeed, the nociceptive inputs of patients in the SICU have additional sources and severities beyond those created by tissue injuries. Pathologic pain states, mainly hyperalgesia and allodynia, can be induced. As a consequence, morphine may be less effective despite larger consumption. This tolerance to morphine is an early process favored by a paradoxical nociceptive stimulation; two studies have implicated N-methyl-D-aspartate (NMDA) receptors in these phenomena (1,2).

The anesthetic and analgesic effects of ketamine were first described 30 yr ago, but its use as an anesthetic has declined. However, because of research showing that NMDA receptors have a fundamental role as gates of perception, ketamine was reconsidered for clinical use. Indeed, ketamine is the most potent NMDA receptor inhibitor available, and it binds to a specific phenylcyclidine site in the NMDA receptor-gated channel, mainly when the channels are in the “open activated state” (3). Because NMDA receptors are also implicated in the development of tolerance to opioids, the vicious circle between pathologic pain and tolerance to opioids might be stopped with ketamine (1,4). With subanesthetic doses, a specific effect on postoperative hyperalgesia has been hypothesized (5). Previous clinical studies that have evaluated the use of ketamine in postoperative pain management have been limited to patients with uncomplicated postoperative courses after planned surgeries (6–15). Moreover, the routes and timing of administration have varied, and the results are controversial (6–15). No data are available about the use of ketamine for pain relief in the SICU. This prospective, randomized clinical trial was designed to determine whether the addition of small-dose ketamine could reduce the consumption of morphine and create fewer adverse effects in patients treated in the SICU after major abdominal surgery.

Methods

The protocol was approved by the IRB for human research of our hospital (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale.)

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de Rennes). The study was prospective, randomized, and double-blinded and was performed on two parallel groups in the SICU of a university hospital. Informed consent was obtained from each patient.

Adults older than 18 yr were included if they were scheduled to have major abdominal surgery and postoperative management and ventilation in a SICU. Pregnant women and patients who had severe cardiovascular disorders (ejection fraction <30%) or renal insufficiency (creatinine clearance <30 mL/min), or who were unable to understand the use of patient-controlled analgesia (PCA), were not included.

The following data were recorded at inclusion: 1) general characteristics (age and sex), 2) type of surgery, 3) the dose of sufentanil used during surgery, and 4) severity as assessed by the Simplified Acute Physiology Score II. The following variables were assessed: the 4-h cumulative morphine doses over the 48-h period; the visual analog scale (VAS) score (16) at rest and at mobilization, measured by a blinded observer every 4 h; and the Ramsay score for sedation. The occurrence of side effects (nausea, hallucination, confusion, and itching) was also measured.

After inclusion criteria were checked and informed consent was obtained, patients were instructed before surgery on the use of PCA and the VAS. Each patient was premedicated with oral midazolam 90 min before the operation. General anesthesia was induced with propofol (2 mg/kg) or thiopental (10 mg/kg). Anesthesia was maintained with nitrous oxide, isoflurane, sufentanil, and atracurium. A central venous catheter and an arterial radial catheter were inserted. Electrocardiogram, pulse oximetry, capnography, arterial blood pressure, and central venous pressure were continuously monitored. Crystalloids were infused during the surgical procedure if the central venous pressure decreased to less than 3 cm H2O, and packed red blood cells were administered if the patient's hemoglobin level decreased to less than 7.0 g/dL. At the end of the procedure, no antagonists were used. After the operation, patients were treated in the SICU for at least 48 h.

On admission, when the patient was awake, the nurse in charge of the patient's care presented the VAS for pain. The nurse depressed the cursor of the 100-mm horizontal line from the point "no pain" to the point "worst pain imaginable," and the patient notified with his or her head, or hand, if possible, where the nurse should stop. The distance in millimeters was noted between "no pain" and the point designated by the patient. Next, participants were randomized to receive morphine PCA with either placebo (Group M) or ketamine (Group K). The PCA device contained morphine at a concentration of 1 mg/mL. All patients received initial loading doses of 2 mg of morphine until their VAS score was less than 30; they were then allowed to have bolus doses of morphine (1 mg every 7 min) without any limitation. In Group K, ketamine was administered separately with an initial bolus of 0.5 mg/kg followed by a perfusion of 2 µg·kg⁻¹·min⁻¹ during the first 24 h and 1 µg·kg⁻¹·min⁻¹ in the following 24 h. In Group M, ketamine was replaced by saline serum and was administered under the same conditions. Ketamine or placebo was administered simultaneously with the titration of morphine. A nurse not involved in the care of the patients prepared the syringes of ketamine or placebo. No additional analgesia or sedation was administered to patients during their SICU stay.

Data are presented as mean ± sd. Statistical analysis was performed with SAS statistical software (SAS Institute, Cary, NC). Analyses were performed with the Mann-Whitney U-test (quantitative variables) and χ² tests (qualitative variables). Forty patients were required in each group to detect a 25% difference in the amount of morphine consumption at the 0.05 level of significance with a power of 0.90. A P value <0.05 was considered significant. An analysis of variance (age, pathology, intraoperative opioid amount, and sex) was used to compare the cumulative dose of morphine.

Results

A total of 101 patients were enrolled in the study between March 1999 and March 2001. Eight patients could not be studied (six patients in Group K and two patients in Group M). Of these, four patients had inadequate data collection, two needed emergency re-operation, and two left the SICU before the completion of the study. Thus, 93 patients were included in the final results: 41 in Group K and 52 in Group M.

At baseline, there was no significant difference between the two groups in age, sex, type of operation performed, dose of sufentanil used during the operation, or severity (Table 1). During the period of study, despite localized differences, VAS scores were similar at rest and at mobilization (Figs. 1 and 2), whereas morphine consumption was significantly less at all times in Group K (Fig. 3). Before the start of the study (i.e., before the administration of the morphine or ketamine), the VAS score was similar in the two groups (point T0 of Figs. 1 and 2). It is noteworthy that the reduction of morphine consumption was larger during the first hours after admission to the SICU. The mean morphine consumption at 48 h was 80 ± 37 mg in Group M and 58 ± 35 mg in Group K, and the difference in the cumulative consumption of morphine between the two groups was 22 ± 8 mg (P < 0.05). The mean consumption of ketamine at 48 h was 367 ± 37 mg. The Ramsay score was not different between the two groups and was maintained between 2 and 3 during the study. The incidence of side effects was comparable in the two groups (Table 2).
Table 1. Demographic Data, Type of Surgery Performed, Intraoperative Dose of Sufentanil, and Severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine group (n = 41)</th>
<th>Morphine group (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>60 ± 16</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>27/14</td>
<td>41/11</td>
</tr>
<tr>
<td>Type of surgery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatectomy</td>
<td>54</td>
<td>44</td>
</tr>
<tr>
<td>Esophageal surgery</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Others</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Intraoperative sufentanil dose (µg)*</td>
<td>149 ± 64</td>
<td>144 ± 58</td>
</tr>
<tr>
<td>SAPS II*</td>
<td>30 ± 7</td>
<td>31 ± 8</td>
</tr>
</tbody>
</table>

SAPS = Simplified Acute Physiology Score.
* Values are expressed as mean ± sd.

Figure 1. Visual analog scale score at rest during the 48-h study. Black column = Ketamine group; white column = Morphine group; ICU = intensive care unit. *P < 0.05.

Figure 2. Visual analog scale score at mobilization during the 48-h study. Black column = Ketamine group; white column = Morphine group; ICU = intensive care unit. *P < 0.05.

Figure 3. Cumulative postoperative patient-controlled analgesia (PCA) morphine consumption. Black column = Ketamine group; white column = Morphine group; ICU = intensive care unit. *P < 0.05.

Table 2. Incidence of Side Effects in the Two Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine group (n = 41)</th>
<th>Morphine group (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Confusion</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Discussion

Pain management is a critical problem in SICU patients (17,18). IV PCA with morphine is convenient. However, prolonged exposure to large doses of opioids has side effects. Our study aimed to determine whether ketamine has a significant morphine-sparing effect. The main finding of this study was that a small dose of ketamine in combination with morphine allowed a significant reduction in morphine consumption in SICU patients after major abdominal surgery.

Many factors may account for this beneficial effect. SICU patients experience prolonged noxious stimuli caused by the inflammation reaction of damaged tissues and also created by the monitoring environment, therapeutic devices, and nursing care. In this context, central sensitization to pain may take place despite the use of adequate doses of opioids. The activation of NMDA receptors, marked by the development of hyperalgesia and allodynia, is critical in this evolution (1,2,19). In this context, ketamine, the most potent NMDA receptor inhibitor, has been used in the postoperative period. Stubhaug et al. (12) have shown that
small doses of ketamine administered before surgery (0.5 mg/kg) and until 72 hours after surgery (2 μg·kg⁻¹·min⁻¹ during the first 24 hours and 1 μg·kg⁻¹·min⁻¹ thereafter) significantly reduce the area of punctuate hyperalgesia surrounding the surgical incision compared with adequate opioid treatment alone. A larger consumption of morphine was observed in the placebo group. Some authors have found a more frequent incidence of nausea, vomiting, and use of antiemetics in placebo groups (6,10).

However, some aspects of the use of ketamine are controversial (5). Some authors advocate preemptive analgesia, and in this context the objective is to prevent a massive barrage of afferent impulses from reaching the spinal cord and causing a central sensitization (20). Others consider that an activated open state of NMDA receptors is required for an optimal effect of ketamine (3). Clinical trials can be broadly divided into those focusing on a preemptive effect and those using ketamine as a postoperative analgesic. In a nonrandomized study performed in patients undergoing abdominal surgery, these two strategies appeared to lead to differences in the amount of cumulative and incremental postoperative morphine, with a 40% larger opioid-sparing effect for preemptive analgesia (8). However, the amount of ketamine administered was different between the two groups (8). In our study, ketamine was started on arrival in the SICU and then administered as a continuous infusion over 48 hours. We found a 25% reduction in opioid consumption in patients who received ketamine. A 50% opioid-sparing effect was even reported by Adriaenssens et al. (6), who used a similar methodology in patients undergoing abdominal surgery. Such a discrepancy may be explained by the fact that in our study, analgesia was started regardless of VAS score; in Adriaenssens et al.'s (6) study, analgesia was not administered until a VAS score of 40 was reported by the patient.

Optimal dosage is another controversial area. In Adriaenssens et al.'s study, the infusion rate for patients allocated randomly to receive ketamine was calculated by using a pharmacokinetic-computed simulation and was set to produce a theoretical plasma analgesic concentration of 100 ng/mL. After the administration of an initial loading dose, an infusion rate of 2.5 μg·kg⁻¹·min⁻¹ was sustained for 48 hours. The affinity of ketamine for NMDA receptors is more than an order of magnitude higher than that for μ-receptors and is several-fold higher than that for monoamine transporter sites or other non-NMDA receptors. This suggests that the smaller the dose, the more selective the ketamine interaction with NMDA receptors. Our dosage schedule (2 μg·kg⁻¹·min⁻¹ for 24 hours and then 1 μg·kg⁻¹·min⁻¹ for another 24 hours) induces very small serum concentrations of ketamine without any sign of accumulation, such as that demonstrated by Stubhaug et al. (12). With these very small doses (i.e., <10 mg/h), a specific effect on allodynia and hyperalgesia is compatible with the absence of psychotic effects. In this context of very small doses, some authors have evaluated ketamine in PCA devices (13–15). Results are contradictory, and the analysis of these studies is made difficult by differences in the preoperative and postoperative management (13–15).

In our study, the profile of morphine consumption over time was as expected, i.e., an initial 50% smaller morphine consumption in Group K due to the initial loading dose of ketamine and then a sustained 25% to 30% opioid-sparing effect. We were unable to demonstrate a consistently increasing difference in morphine consumption between the two groups. Tolerance to opioids does not seem to be counterbalanced by ketamine.

The activation of NMDA receptors in the central nervous system is seen as a mechanism involved in the adaptive changes underlying both tolerance to opioids and delayed hyperalgesia. It has been suggested that activation of opioid receptors leads to protein kinase C-mediated activation of NMDA receptors. Rapid development of acute opioid tolerance is well established in animals, and the amount of tolerance that results from various opioids appears similar. However, tolerance develops faster in response to short-acting analgesics such as alfentanil or remifentanil (21,22). Attenuation of the development of acute tolerance to opioids by ketamine has received specific attention (23). This property has been demonstrated in clinical and experimental models when ketamine was administered before the opioid infusion. However, in most studies, patients received alfentanil. In our study, because of the extensive abdominal surgery with an immediate postoperative SICU admission, sufentanil was administered during the surgery.

Despite a stable reduction in morphine consumption, the patients in Group K showed a tendency for less pain at rest. Ketamine produced pain relief superior to that of placebo during mobilization from the supine to the sitting position; a significant level was obtained three times. Whether these differences are clinically relevant can be debated because of a low VAS score at these times (24).

An objective of our study was to determine whether ketamine was able to reduce the side effects of opioids, particularly nausea. Unlike some authors who reported a beneficial effect, we did not observe any significant difference between the two analgesic regimens. As demonstrated in many studies, the incidence of psychomimetic effects and cognitive impairment was negligible at small doses.

In conclusion, the administration of small doses of ketamine as an adjunct to morphine may be a valuable strategy for pain management in SICU patients. This
strategy may effectively circumvent some of the problems with the use of morphine. Moreover, in this context, a multimodal approach to pain control could provide increased activity against pathologic pain states. However, further investigations are warranted to determine the effect of ketamine on tolerance to opioids and to confirm a sustained action in case of prolonged exposure to opioid analgesics.

References