Peripheral Analgesic Effects of Ketamine in Acute Inflammatory Pain

Juri L. Pedersen, M.D.,* Tina S. Galle,† Henrik Kehlet, M.D., Ph.D.‡

Background: This study examined the analgesic effect of local ketamine infiltration, compared with placebo and systemic ketamine, in a human model of inflammatory pain.

Methods: Inflammatory pain was induced by a burn (at 47°C for 7 min; wound size, 2.5 × 5 cm) on the calf in 15 volunteers on 3 separate days with 7-day intervals. They received either (1) subcutaneous infiltration with ketamine in the burn area (local treatment) and contralateral placebo injections, or (2) subcutaneous ketamine contralateral to the burn (systemic treatment) and placebo in the burn area, or (3) placebo on both sides. The study was double-blinded and the order of the treatments was randomized. Hyperalgesia to mechanical and heat stimuli was examined by von Frey hairs and contact thermodes (3.75 and 12.5°C), and pain was rated using a visual analog scale (0–100).

Results: The burns produced significant hyperalgesia. Local ketamine infiltration reduced pain during the burn injury compared with systemic treatment and placebo (P < 0.01). Heat pain thresholds were increased by local ketamine treatment compared with placebo immediately after injection (P = 0.03), and so were the mechanical pain thresholds (P = 0.02). Secondary hyperalgesia and suprathreshold pain responses to heat and mechanical stimuli were not significantly affected by local ketamine. No difference between local ketamine and placebo could be detected 1 h and 2 h after the burn.

Conclusions: Ketamine infiltration had brief local analgesic effects, but several measures of pain and hyperalgesia were unaffected. Therefore, a clinically relevant effect of peripheral ketamine in acute pain seems unlikely. (Key words: N-methyl-D-aspartate receptor antagonist; psychophysics; thermal injury.)

* Research Fellow.
† Graduate student.
‡ Professor of Surgical Gastroenterology.

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Address reprint requests to Dr. Pedersen. Hjortholms Allé 19b, DK-2400 Copenhagen NV, Denmark. Address electronic mail to: juri@dadi.net.dk

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familiar with the burn injury, the heat, and the von Frey hair stimuli, and they trained in ratings with the visual analog scale (VAS) before the study.

**Experimental Design and Medication**

A burn injury (2.5 × 5 cm) was produced on the medial part of the nondominant, distal leg on three separate days with 7-day intervals between each one. The three injuries were located in the same area with the longitudinal axis parallel to the leg. The top of the thermode was located 11 cm below the knee joint line and the front of the thermode 6 cm from the margo anterior tibiae. Assessments of pain and hyperalgesia were made 70 min and 40 min before the burn (baseline and postdrug assessment), and 0, 60, and 120 min after the burn injury ended. Time 0 was defined as the time when the burn was finished. Table 1 shows the timing and the order of the measurements. The study was double-blinded, and the order of the treatments was randomized, so all treatments were equally distributed over the 3 study days. On the 3 days the volunteers received either (1) subcutaneous infiltration with ketamine (7.5 mg in 5 ml; 6.3 mg) in the burn area (local treatment) and saline (0.9%, 5 ml) in a corresponding area contralateral to the burn, or (2) ketamine (7.5 mg in 5 ml) contralateral to the burn (systemic treatment) and saline in the burn area, or (3) saline on both sides. To evaluate the analgesic effects of local ketamine in both healthy and hyperalgesic skin, two doses were injected (total, 15 mg) because the half-life of the analgesic effect of locally applied ketamine may be shorter than 20 min in humans.\(^6\)\(^8\) Injections were performed immediately before the postdrug measurement (40 min before burn) and immediately before the burn (about 7 min before the 0 h measurement). Bilateral infiltrations lasted about 4 min. A person not involved in the testing administered the injections and prepared the ketamine and placebo.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Timing (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous pain from the burn</td>
<td>0.2</td>
</tr>
<tr>
<td>Area of mechanical allodynia</td>
<td>0–2</td>
</tr>
<tr>
<td>Area of secondary hyperalgesia</td>
<td>3–5</td>
</tr>
<tr>
<td>Pain threshold to mechanical stimuli</td>
<td>6–7</td>
</tr>
<tr>
<td>Pain response to mechanical stimuli</td>
<td></td>
</tr>
<tr>
<td>(5 stimuli of 462 mN) inside and</td>
<td></td>
</tr>
<tr>
<td>1–2 cm outside the burn</td>
<td>8</td>
</tr>
<tr>
<td>Warmth detection threshold</td>
<td>9–10</td>
</tr>
<tr>
<td>Pain threshold to heat</td>
<td>11–13</td>
</tr>
<tr>
<td>Pain responses to heat (45°C; 3.75 cm) in the burn</td>
<td>14</td>
</tr>
</tbody>
</table>

Ketamine hydrochloride (10 mg/ml; Parke-Davis, Morris Plains, NJ) was diluted in 4.25 ml 0.9% saline to 1.5 mg/ml (pH, 5 to 5.5). Saline 0.9% had a pH of 6.7. The injections were performed in the most superficial part of the subcutis with a 27-gauge needle (0.4 mm diameter) from two corners of marked areas in a fan-like manner, thus covering the area evenly.

All sensory testing was performed by the same experimenter at the same time of the day in a quiet room with the temperature set at 22–24°C. The volunteers were resting in a relaxed position during assessments and instructed to keep their eyes closed during all measurements.

**Burn Injury and Pain Rating**

Burn injuries were produced on the medial surface of the crura with a 5 × 2.5 cm thermode (Thermostest, Somedic A/B, Stockholm, Sweden). The thermode (47°C) was applied to the skin for 7 min under standardized pressure (4.5 kPa) and caused a first-degree or a mild second-degree burn injury. About 20% of the injuries evoked small blisters within 24 h, and 25% of the injuries induced slight color changes that persist 3 weeks after the injuries.\(^9\)

The pain induced by the burn was rated with a VAS (0–100) at the start and every minute after the start of the heat injury (7 min). After the burn, spontaneous pain from the injury was rated at the same times as other measures. The scale was anchored by the descriptors “no pain” (0%) and the “worst pain imaginable” (100%).

To make the scale more comprehensible, verbal descriptors were added (weak pain, 2%; mild pain, 8%; moderate pain, 18%; strong pain, 39%; and very intense pain, 74%) along the 10-cm line between the anchor points. The relative magnitudes for the sensory verbal descriptors were based on two studies in which 96 persons rated 15 sensory verbal descriptors by cross-modality matching to hand grip force and time duration.\(^10\)\(^11\)

The descriptors of sensory intensity on our scale are a subset of the descriptors used in these two studies, and the location of the descriptors was based on their results.

**Mechanical Hyperalgesia**

The mechanical pain threshold within the injured area was determined by mechanical stimuli with von Frey hairs (Senselab, Somedic A/B, Stockholm, Sweden). Nine different von Frey hairs were used that covered the range from 9–462 mN. Table 2 shows the force and the pressures produced by the von Frey hairs. The pain threshold was defined as the lowest force of me-
Table 2. Characteristics of the von Frey Hairs

<table>
<thead>
<tr>
<th>von Frey</th>
<th>Diameter (mm)</th>
<th>Force (mN)</th>
<th>Pressure (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.23</td>
<td>9</td>
<td>220</td>
</tr>
<tr>
<td>9</td>
<td>0.25</td>
<td>12</td>
<td>240</td>
</tr>
<tr>
<td>10</td>
<td>0.30</td>
<td>20</td>
<td>280</td>
</tr>
<tr>
<td>11</td>
<td>0.35</td>
<td>34</td>
<td>350</td>
</tr>
<tr>
<td>12</td>
<td>0.40</td>
<td>60</td>
<td>480</td>
</tr>
<tr>
<td>13</td>
<td>0.45</td>
<td>98</td>
<td>620</td>
</tr>
<tr>
<td>14</td>
<td>0.50</td>
<td>147</td>
<td>750</td>
</tr>
<tr>
<td>15</td>
<td>0.55</td>
<td>304</td>
<td>1,280</td>
</tr>
<tr>
<td>16</td>
<td>0.65</td>
<td>462</td>
<td>1,390</td>
</tr>
</tbody>
</table>

Mechanical stimulation that produced a sensation of pain or discomfort, and the volunteers were instructed to report the first trace of pain. Ten stimuli, covering the area of the injury, were made with each hair from the thinnest until at least one half of the stimuli with one hair caused pain or discomfort. The 10 stimuli were applied at a rate of about two per second. The threshold assessment was repeated three times at each measurement point, and the median was reported as the pain threshold. If hair 16 (462 mN) did not produce any pain or discomfort, we assigned the value 17 to that observation (the pain threshold not assessable).

Suprathereshold pain responses (VAS 0–100) to mechanical stimuli were assessed by five stimuli of 462 mN. The pain response was evaluated inside and 1–2 cm outside the proximal border of the burn.

The area of mechanical hyperalgesia that developed around the burn injury was assessed with a rigid von Frey hair (462 mN) (secondary hyperalgesia for punctate stimuli). In most cases, mechanical stimuli with this hair is painful on distinct points of the skin but not universally painful. Thus hyperalgesia, not allodynia, was measured with the von Frey hair. Allodynia was assessed by gently stroking the skin with a fingertip. Borders of hyperalgesia and allodynia were determined by stimulating along eight linear paths angled at 45°. Stimulation along each path began well outside the hyperalgesic area and continued slowly toward the burn injury, until the volunteers reported a definite change in sensation. With the von Frey hair, this was most often a change to a more intense pricking sensation with a burning aferosensation. Stroking was associated with a change from touch to a slight burning or smarting. The skin was stroked perpendicular to the stimulation path, for a distance of about 3 cm one time per second. The points of change were marked on the skin and later traced onto a transparent sheet. The areas of secondary hyperalgesia and allodynia were calculated from eight marks using software based on a vector algorithm (Meditec, Vanlose, Denmark).

**Thermal Hyperalgesia and Thermal Sensory Thresholds**

Thermal thresholds were determined using a computerized contact thermode (Somedic A/B). All thresholds were assessed using a 2.5 × 5.0 cm thermode, whereas heat pain responses were evaluated using a 1.5 × 2.5 cm thermode. The heat pain threshold was the lowest temperature perceived as painful, and the subjects were instructed to react to the first trace of pain. The warm detection threshold was defined as the smallest change from baseline that the volunteer could feel. The volunteer pressed a button as soon as he or she perceived the specified sensation. All thermal thresholds were determined as the average of three trials performed at 9-s intervals, from a baseline temperature of 32°C, and at a rate of change of 1°C/s. The upper cutoff limit was 52°C.

Pain responses (VAS) to heat were evaluated by a heat stimulus (5.75 cm²) of 45°C that lasted 5 s, preceded by a temperature increase from 40°C to 45°C in 5 s. The initial heating was necessary because the thermode cannot warm faster than 4°C/s. Heat pain responses were tested in the proximal part of the burn.

**Assessment of Side Effects**

The volunteers completed a questionnaire at the end of each day concerning the presence (yes/no responses) of drowsiness; dizziness; vertigo; anxiety; feeling drunk; hallucinations; paresthesia in the lips, tongue, or fingertips; feeling of muscular tension; nausea; and headache in relation to the injections. When side effects were present, they were rated as weak, moderate, or marked.

**Statistical Analysis**

Normality of data and differences between groups were evaluated using the Shapiro Wilk test. Data are presented as means or medians with standard deviations or interquartile ranges dependent on the distribution (normal or skewed), and comparisons were made using the Student’s t test for differences in a paired design, when the differences showed normal distribution, whereas differences showing non-normal distributions were analyzed using the Wilcoxon test for paired observations. Comparisons of more than two groups (changes over time) were done using parametric one-way analysis of variance (ANOVA) for repeated mea-
measurements or the Friedman ANOVA, as appropriate. The smallest differences between local ketamine and placebo detectable with the present variation, a power of 80% and a type 1 error of 5%, were calculated for all measures and time points. The calculations were based on the Student’s t test for differences in a paired design. The power of a study is the probability of detecting a real difference as statistically significant. Probability values < 0.05 were considered significant.

Interindividual variations are presented in the figures, and this may be misleading because all comparisons were based on intraindividual variations, which are smaller than the interindividual variations. The sensitivity of the study and the intraindividual variation are reflected in the smallest differences that can be detected between local ketamine and placebo.

**Results**

**Pain Responses in Healthy Skin**

The baseline pain thresholds and pain responses were not significantly different among the three treatment groups, and systemic ketamine (subcutaneous infiltration contralateral to the burn) did not produce any significant sensory effects either in healthy or in burned skin compared with placebo. In the postdrug measurements, which were made in healthy skin before the burn injury, heat pain thresholds were significantly increased by local subcutaneous infiltration with ketamine compared with placebo (P = 0.03 by the Student’s t test; fig. 1A). In the postdrug measurements, local ketamine also reduced heat pain responses to 45°C compared with systemic ketamine (P = 0.003 by the Student’s t test; fig. 1B), but the responses were not reduced compared with placebo.

The average pain response (VAS 0–100) during the 7-min burn stimulus was significantly reduced by local ketamine (mean, 20; SD, 8) compared with placebo (mean, 25; SD, 7; P = 0.003 by the Wilcoxon test) and systemic ketamine (mean, 26; SD, 10; P = 0.01 by the Wilcoxon test, fig. 2). On the applied VAS, moderate pain is indicated at 18% and strong pain at 39%.

Ten volunteers experienced alldynia around the injury during the burn when they were tested 4–6 min after the start of the burn stimulus. The areas of alldynia were not affected by either local ketamine (median, 6.25 cm²; range, 0 to 42.5 cm²) or systemic ketamine (median, 2.5 cm²; range, 0 to 77.5 cm²) compared with placebo (median, 13.5 cm²; range, 0 to 49.5 cm²).

Injections of placebo (saline, 0.9%; pH, 6.7) caused no hyperalgesia; that is, no significant increase in pain responses or decrease in pain thresholds from baseline measurements to postdrug measurements. The injections of ketamine (pH, 5 to 5.5) were more painful (mean, 38; SD, 16) than the injections of saline (mean, 18; SD, 5; P = 0.004; n = 10; Student’s t test). Only 10 volunteers had data from both saline and ketamine injections, because pain ratings were not performed from the start of the study. The pain responses to ketamine injections were also more intense than the average pain response of the three burns (mean, 26; SD, 6; n = 10; P = 0.04; Student’s t test). The VAS rating of 38 corresponds to strong pain on the applied scale.

**Primary Mechanical Hyperalgesia**

The burn decreased mechanical pain thresholds (P < 10⁻³ by Friedman ANOVA) and increased pain re-
old pain responses compared with placebo, although pain was attenuated in the 0 h measurement compared with systemic ketamine ($P = 0.03$, by Student’s $t$ test).

**Secondary Mechanical Hyperalgesia**

For all treatments, the burn produced a significant area of secondary hyperalgesia to punctate mechanical stimuli ($P < 10^{-5}$ by Friedman ANOVA), and an increase in the pain response to mechanical stimuli in the area of secondary hyperalgesia ($P < 10^{-5}$ by Friedman ANOVA; figs. 4A, B). The area of secondary hyperalgesia and the pain response to mechanical stimuli within the zone were not inhibited by local or systemic ketamine in the present doses.

Only 3 of 15 volunteers experienced allodynia around the injury after the burn, and the changes over time were insignificant (Friedman ANOVA). Similarly, only 3 of the 15 volunteers expressed spontaneous pain from the burns after the injury (VAS 1-3, 5 positive ratings of 135). The combination of allodynia and spontaneous pain was found in one volunteer.

**Primary Thermal Hyperalgesia**

For all treatments, heat pain thresholds were decreased in the burned areas ($P < 10^{-6}$ by repeated measures one-way ANOVA), and pain responses to $45^\circ$C were increased ($P < 10^{-6}$ by repeated measures one-way ANOVA; figs. 1A, B). Heat pain thresholds were increased by local ketamine immediately after the burn.

Fig. 1. (A) Heat pain thresholds (means and SD) and (B) heat pain responses to $45^\circ$C (means and SD, B) in burns. Pain was assessed with a visual analog scale (VAS 0–100) on which verbal descriptors were added (weak pain, 2%; mild pain, 8%; moderate pain, 18%; strong pain, 39%; and intense pain, 74%) [10]. Heat pain thresholds in healthy and inflamed skin immediately after burn were significantly increased by local subcutaneous infiltration with ketamine compared with placebo (healthy skin, $P = 0.05$; inflamed skin, $P = 0.02$ by Student’s $t$ test). Suprathreshold heat pain responses were not reduced by local ketamine. The analgesia lasted <1 h.

![Chart](chart1.png)

![Chart](chart2.png)

Fig. 2. Pain during heat injury ($47^\circ$C for 7 min; means and SD). The legend to figure 1 explains the pain rating. The pain response to the burn was significantly reduced by local ketamine compared with placebo ($P = 0.003$ by the Wilcoxon test) and systemic ketamine ($P = 0.01$ by the Wilcoxon test).
PERIPHERAL ANALGESIC EFFECTS OF KETAMINE

Fig. 3. (A) Mechanical pain thresholds (medians and interquartile ranges) and (B) pain responses (medians and interquartile ranges) in the burn were evaluated using von Frey hairs (see Table 2 for diameters and force). The value 17 was assigned to pain thresholds >462 mN. The pain response was assessed by five stimuli of 462 mN. The legend to figure 1 explains the pain rating. Local ketamine increased the pain thresholds immediately after the burn (0 h) compared with placebo and systemic ketamine (placebo, P = 0.01; systemic ketamine, P = 0.02 by the Wilcoxon test). In contrast, local ketamine did not reduce the suprathreshold pain responses compared with placebo. The analgesia lasted <1 h.

compared with placebo (P = 0.02 by Student’s t test), but heat pain responses were not reduced by local ketamine.

Duration of Peripheral Analgesic Effects

No comparisons between local ketamine and placebo, or local and systemic ketamine, showed significant differences at any time after the 0 h postburn measurements (i.e., 1 h and 2 h after burn). Thus the analgesia lasted <1 h.

Warm Detection Thresholds

For all treatments, the thresholds were significantly increased by the burn (P < 10^{-3} by repeated measures one-way ANOVA), but no differences were found be-

Fig. 4. (A) Area of secondary hyperalgesia (means and SD) surrounding the burns and (B) pain responses (means and SD) in the area of secondary hyperalgesia were evaluated using von Frey hair stimuli (462 mN). The legend to figure 1 explains the pain rating. The area of secondary hyperalgesia and the pain response to mechanical stimuli within the zone of secondary hyperalgesia were not inhibited by local or systemic ketamine.

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Table 4. Smallest Detectable Differences between Placebo and Local Ketamine Infiltration

<table>
<thead>
<tr>
<th>Heat Pain Threshold (°C)</th>
<th>Heat Pain Response to 45°C in 5 s (VAS 0–100)</th>
<th>Mechanical Pain Threshold (von Frey no.)</th>
<th>Mechanical Pain Response to 462 mN (VAS 0–100)</th>
<th>Secondary Hyperalgesia (cm²)</th>
<th>Mechanical Pain Response to 462 mN in Zone with Secondary Hyperalgesia (VAS)</th>
<th>Warm Detection Threshold (°C)</th>
<th>Pain during the Burn (VAS 0–100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.3</td>
<td>7.7</td>
<td>1.0</td>
<td>5.5</td>
<td>35</td>
<td>6.5</td>
<td>1.2</td>
<td>4.6</td>
</tr>
</tbody>
</table>

between local ketamine and placebo or systemic ketamine.

Side Effects

Side effects (table 3) were generally mild, and all volunteers cooperated without problems. Side effects were present in 10 of 15 volunteers treated with ketamine, and in 2 of 15 volunteers treated with placebo.

Sensitivity of the Study

Table 4 shows the smallest differences between placebo and local ketamine that we could detect at single time points. The values shown are the mean of the five observation times (baseline; after drug 0, 1, and 2 h after burn).

Discussion

We examined the analgesic effect of local ketamine infiltration, compared with placebo and systemic ketamine, in a model of inflammatory pain based on a standardized burn in healthy volunteers. Subcutaneous ketamine infiltration had local analgesic effects in both healthy and hyperalgesic skin, but the effects on pain and hyperalgesia were brief and inconsistent.

Systemic ketamine in subanesthetic doses (0.15 to 0.30 mg/kg given intravenously) has analgesic effects in similar burn models. Thus establishment of a peripheral analgesic effect requires exclusion of systemic effects. We did not find any significant systemic effects of 15 mg ketamine administered subcutaneously within a 30-min period, although weak or moderate side effects were present in 10 of 15 volunteers. Thus the demonstrated analgesic effects were peripheral, and our study confirms the presence of peripheral analgesic effects of ketamine found in other human studies.

The study by Tverskoy et al. showed that ketamine enhanced the analgesic effect of bupivacaine by a peripheral mechanism. Ketamine was added to bupivacaine and used for wound infiltration performed after herniorrhaphy in 18 patients. The addition of ketamine nearly doubled the duration of analgesic (from 4 h to 7 h) and local anesthetic (from 3.5 h to 6 h) effects, and the pain threshold to pressure on the wound was significantly increased 24 h after the infiltration. The duration of the local anesthetic effects of ketamine alone ranged from 10–20 min, when tested with the same method and solution of ketamine (0.3%, 12.6 mm) in healthy skin of five volunteers. In our study, the duration of the analgesic effects of local ketamine was <1 h, which corresponds with other studies. Similar local anesthetic activity of ketamine in humans has been shown in studies of intravenous regional anesthesia, and the local anesthetic potency of ketamine is close to that of procaine.

In contrast to these findings, a recent human study found local analgesic effects of ketamine that lasted >90 min, and the authors suggested that the analgesic effects of ketamine may last even 1 week after the infiltration. This suggestion was based on the sizes of secondary hyperalgesic areas evoked by burns in saline-treated areas in six persons. These areas were smaller when ketamine was injected in the area 1 week before, compared with no previous ketamine infiltration. However, exact data were not shown and no statistical evaluation was performed. Further, the blinding of the study was questionable because saline-treated injuries were compared directly with ketamine- and lidocaine-treated injuries. In such comparisons, the volunteer would have little or no doubt about the type of treatment. In our study, only one treatment was evaluated per day, and assessments were made only on one side. Thus the treatment that the volunteer received, whether placebo, local, or systemic ketamine, was not obvious.

The peripheral analgesic effect of ketamine may be explained easily by blocking of sodium and potassium currents in peripheral nerves, but other possibilities exist. Ketamine blocks NMDA receptors, and the presence of ionotropic glutamate receptors such as NMDA, α-amino-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors has been demonstrated on unmyelinated axons of rat skin. Peripheral adminis-
Peripheral analgesic effects of ketamine

**Perusal of ligands to these receptors evoked nociceptive behaviors in rats.**

1. nociceptive reflexes,
2. and depolarization of primary afferents in neonatal rats. Glutamate and NMDA have also shown to produce strong excitation of C-fiber free nerve endings in the rabbit cornea, and ketamine blocked the glutamate effect. In accordance with these results, local cutaneous administration of the NMDA-antagonist, MK-801, and the non-NMDA glutamate receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), reduced nociceptive behaviors in rats induced by formalin and carrageenan injections in the paws. The effects lasted 10 min (from 20 - 30 min after the injections of the antagonists) in the formalin test, and assessments were ended 35 min after treatment. The local injections had no systemic effects. Similarly, combinations of intra-articular glutamate, aspartate, and arginine reduced paw-withdrawal latencies in rats to radiant heat and mechanical stimuli. The reduction of withdrawal thresholds to heat were attenuated by intra-articular injections of (±)-2-amino-7-phosphonohexanoic acid (AP-7) and CNQX up to 1 h after treatment, and the treatments prevented the reduction of thresholds to mechanical stimuli. Further, intra-articular AP-7, CNQX, and ketamine attenuated the nociceptive behavior produced by injection of a mixture of kaolin and carrageenan into the joint as long as 2 h after the treatment. Thus the peripheral analgesic effects of NMDA and non-NMDA receptor antagonists were relatively brief (20 – 120 min) although longer than the effects in our study. No human data exist to confirm the peripheral nociceptive effects of excitatory amino acids.

Contributions to the peripheral analgesic effects of ketamine may also be mediated by other mechanisms such as opioid receptor agonism, but the evidence for the analgesic efficacy of peripheral opioids is weak. Ketamine may also block voltage-sensitive calcium channels and acetylcholine receptors. Whether these mechanisms contribute to the peripheral analgesic effects is unclear.

Peripheral administration of ketamine in combination with other analgesics may be useful in humans, as shown by the combined effect of bupivacaine and ketamine on peripheral nerves, and of epidural ketamine and morphine, or caudal ketamine and bupivacaine in postoperative pain. The combination of ketamine or ketamine-like compounds with other peripheral-acting analgesics may produce synergistic pain relief and obviate the side effects that often result from systemic therapy with single drugs in higher doses. However, based on our findings, it seems unlikely that local ketamine alone will have a clinically relevant effect in acute inflammatory pain states.

**References**

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