

Topically Administered Ketamine Reduces Capsaicin-Evoked Mechanical Hyperalgesia

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Background: The n-methyl-d-aspartate receptor antagonists such as ketamine relieve chronic pain but their oral and parenteral use is limited by the adverse effects. Experimental studies indicate that the peripheral n-methyl-d-aspartate receptors are involved in nociception. Recent clinical findings suggest that ketamine gel alleviates neuropathic pain, but no placebo-controlled randomized studies are available on the neurosensory effects of ketamine gel in experimental neurogenic pain.

Objectives: The aim of this study was to assess the effects of topically applied ketamine using the intradermal capsaicin model in healthy volunteers.

Methods: Nine healthy subjects received ketamine and placebo gel on 3 occasions in a randomized, double-blind, and crossover manner. The concentration of ketamine was 50 mg/mL. One milliliter of gel was rubbed into the skin of both forearms 10 minutes before the intradermal injection of capsaicin (250 µg). Thereafter, the intensity and unpleasantness of spontaneous and evoked pain and dysesthesia was assessed up to 60 minutes using a 10-cm visual analog scale. Pain and dysesthesia were evoked using cotton gauze, a von Frey microfilament, and 38°C, 42°C, and 47°C heat. Side effects were recorded, and individuals' subjective experiences were assessed with a standard questionnaire.

Results: Ketamine gel had no effect on immediate burning pain followed by the capsaicin injection. Both the intensity and unpleasantness of mechanical hyperalgesia was statistically significantly reduced by ketamine gel applied both on the left and right side. Neither tactile allodynia evoked by a brush nor thermal hyperalgesia were observed in any volunteer. No local or systemic side effects were observed. No patient reported any drug effects.

Discussion: A significant reduction of mechanical hyperalgesia was produced by topically and pre-emptively applied ketamine in healthy patients. We propose that the mechanism of action would be the reduction of central sensitization caused by the absorption of ketamine in circulation.

Key Words: ketamine gel, capsaicin, hyperalgesia, allodynia, volunteer

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The activation of n-methyl-d-aspartate (NMDA) receptors is one of the predominant mechanisms for central sensitization of somatosensory nervous system after nociceptive stimulation and a key factor in the generation and maintenance of persistent pain states.¹ The NMDA receptor antagonists such as ketamine relieve chronic pain, but their oral and parenteral use is limited by the well-known adverse effects.^{2–4}

There is a growing amount of experimental evidence showing that NMDA receptors are found not only in the central nervous system (CNS) but also in the peripheral nerves.^{5,6} Furthermore, experimental studies indicate that peripherally administered NMDA receptor antagonists are involved with antinociception.^{7–9}

However, human data concerning the role of the peripheral NMDA receptors in the pathophysiology of clinical pain are inconclusive and contradictory. It has been shown that peripherally administered ketamine inhibits the development of secondary hyperalgesia in an experimental human burn model¹⁰ and reduces capsaicin-evoked hyperalgesia.¹¹ Other human studies using experimental inflammatory pain models have not been able to confirm the peripheral actions of ketamine.^{12,13} These experimental studies have also emphasized the local analgesic properties of ketamine.

Recently, 4 uncontrolled studies have been published to report good analgesia but no side effects after topical administration of ketamine gel in chronic unrelieved neuropathic pain,^{14,15} complex regional pain syndrome,¹⁶ and postoperative pain.¹⁷ Yet a recent double-blind placebo-controlled pilot study failed to demonstrate analgesic effects of topical ketamine in neuropathic pain.¹⁸ However, in this study, neurosensory testing during the gel application was not performed. In the absence of placebo-controlled studies of the effects of topically administered ketamine gel on skin sensitivity, we wanted to assess the neurosensory effects of ketamine gel using the experimental capsaicin model.

MATERIALS AND METHODS

The study was approved by the Institutional Ethics Committee and performed at McGill-MGH Pain Center. A written informed consent was received from 9 healthy volunteers. The mean (SD) age, height, and weight of the participants were 36 (8.6) years, 170 (15.2) cm, and 69 (16.1) kg, respectively.

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The volunteers participated in the study on 3 days with 1-week intervals. During each session, prior to the capsaicin injection, each subject received 1 of the following treatments in a randomized, double-blind, and crossover manner: 1) topical ketamine gel on the left lower forearm and placebo gel on the right forearm; 2) placebo gel on the left lower forearm and ketamine gel on the right forearm; or 3) placebo gel on both sides. The volume of each gel application was 1 mL and the concentration of ketamine 50 mg/mL. The gel was rubbed into the skin 10 minutes before the injection of capsaicin.

On each occasion, 25 μ L (250 μ g) of capsaicin was injected intradermally on the left volar forearm. The injection site was marked on the first testing day, and each subsequent injection was given 2 cm proximally to the previous one. Before the application of the gel and 5, 15, 30, 45, and 60 minutes after the capsaicin injection, spontaneous and evoked pain and skin sensitivity to heat were assessed. Allodynic pain or dysesthesia was evoked with a cotton gauze pad and hyperalgesia with a von Frey microfilament (164.32 g). The skin sensitivity on heat was evaluated using a 25 \times 50 mm rectangular Peltier contact thermode applied to the skin. Three temperatures, 38°C, 42°C, and 47°C, were tested in a random order. The intensity and unpleasantness of each sensation were assessed using a 10-cm visual analog scale. All tests were performed both on the left forearm injected with capsaicin and on the right arm, which served as a control. In addition, the area of allodynic/dysesthetic skin sensation was measured. The experiments were carried out in the morning in the temperature of 24°C.

At each time, to assess the possible central nervous system effects of ketamine, the volunteers were asked the following questions: Do you feel a drug effect? Do you feel the drug effect is unpleasant? Do you feel nauseated? Could you drive a car safely right now? Do you feel sleepy, woozy, or drunk? Do you feel dissociated? Do you have strange feelings? Do you feel alienated?

Ketamine gel was prepared by a private pharmacy using a commercially available ketamine hydrochloride (Ketalar®, Pfizer) and a plutonic lecithin organocream. In the open pre-

testing of ketamine concentrations 5, 10, 30, and 50 mg/mL, the concentration of 50 mg/mL appeared to be the most effective in the capsaicin test.

Tests for mechanical and tactile allodynia were repeated 3 times and the thermal test twice; the mean value of the tests was used for statistical analysis, which was performed using analysis of variance for repeated measurements (ANOVA; SPSS-8 for Windows). Significance was accepted as $P < 0.05$. The area under the curve (AUC) was calculated for the hyperalgesic and allodynic skin area versus time curve. The data is expressed as means \pm SD (figures) or means \pm 95% confidence intervals (CI).

RESULTS

Each time after capsaicin injection, intense pain was experienced by all subjects for 7 minutes. This spontaneous burning pain was unaffected by ketamine gel (Fig. 1). Moderate mechanical hyperalgesia was observed only in the left forearm after capsaicin injection in all subjects. The intensity of mechanical hyperalgesia was statistically significantly reduced by ketamine gel applied both on the left side and on the right side (Fig. 2). Both the intensity and the unpleasantness of pain were reduced in a similar way.

Neither tactile allodynia evoked by a brush nor thermal hyperalgesia were observed in any volunteer. However, a dysesthetic sensation to brush was reported by 7 subjects. The areas of dysesthetic skin and mechanical hyperalgesia were reduced by ketamine gel (not significant) (Table 1).

Ketamine gel had no effects on the sensitivity of skin in the right, control arm. We observed no local or systemic side effects after the application of ketamine gel. No subject reported of any drug-effects.

DISCUSSION

We choose to use intradermal capsaicin model for various reasons. First, capsaicin, when injected intradermally, produces an initial acute short-lasting neurogenic pain due to chemical inflammation in peripheral sensory fibers by acting on vanilloid receptors, which is followed by hyperalgesia and

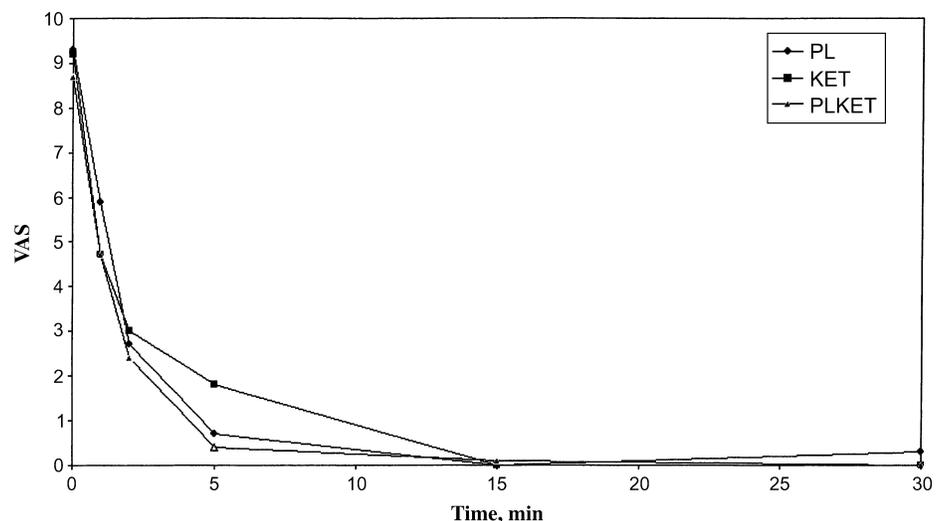


FIGURE 1. The mean intensity of spontaneously reported pain after capsaicin injection. PL, placebo; KET, ketamine gel on the capsaicin arm; PLKET, ketamine gel on the control arm.

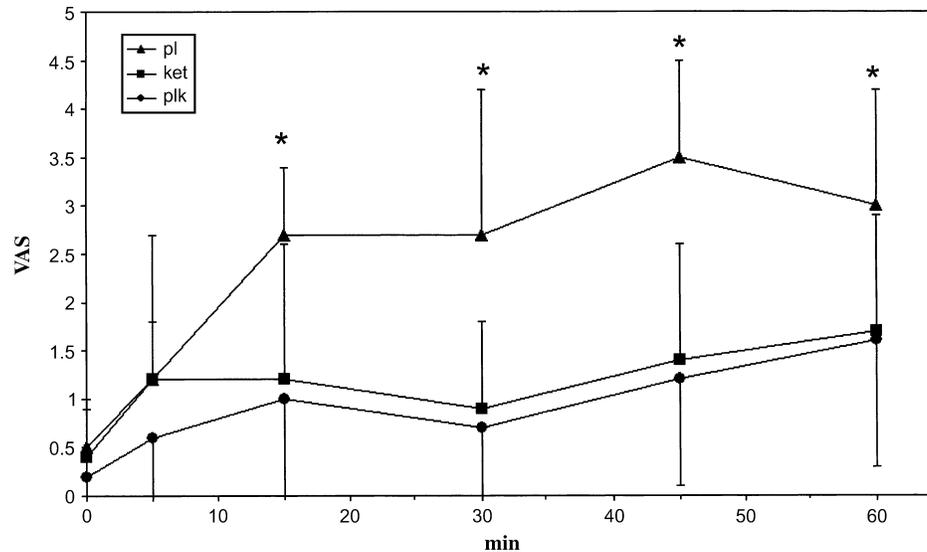


FIGURE 2. The mean (SD) intensity of capsaicin-evoked mechanical hyperalgesia. PL, placebo; KET, ketamine gel on the capsaicin arm; PLKET, ketamine gel on the control arm. Statistically significant differences between PL and KET and PL and PLKET are marked with * ($P < 0.05$, ANOVA).

allodynia due to central sensitizing.¹⁹ Secondly, experimental studies have indicated that there is an interaction between vanilloid and NMDA receptors in the CNS.^{20,21} Thirdly, in human studies, capsaicin-evoked hyperalgesia has been sensitive to intravenous ketamine.^{22,23}

Unfortunately, the capsaicin method has its drawbacks. High numbers of nonresponders and large coefficients of variance have been reported.^{22,24–26} Similarly, we failed to observe thermal hyperalgesia or allodynia (but only dysesthesia) due to capsaicin injection and thus could not assess the effects of ketamine in this respect. Whether rubbing the gel into the skin would have any effect on the skin sensitivity requires further studies.

The major finding of this study was the significant alleviation of intensity but not the area of capsaicin-evoked mechanical hyperalgesia by 50 mg of topically applied ketamine gel without any side effects. Also, the dysesthetic area was reduced, but not significantly. These observations are in accordance with the studies by Warncke et al¹⁰ and Koppert et al,¹¹ in which a moderate dose-related antihyperalgesic effect of intradermal ketamine was reported. However, 2 other studies^{12,13} failed to demonstrate analgesic effects of peripherally administered ketamine in the capsaicin and burn models. There are several differences between these previous studies and ours.

We did not use any systemic analgesic as a positive control in our study, but chose a dose (250 μ g) of capsaicin for

which the effect has been shown to be sensitive for intravenous ketamine.²¹ In the studies by Koppert et al¹¹ and Gottrup et al,¹³ only 10 and 100 μ g of capsaicin, respectively, was used and ketamine was injected. To avoid possible erroneous subcutaneous administration, ketamine was not injected but was permitted to be absorbed through the entire skin in our study. The NMDA receptors are located in unmyelinated axons at the dermal-epidermal junction,²⁷ and thus they might be reached better with absorbed transdermal ketamine than with the injected type.

In addition to the NMDA receptor antagonism, ketamine in high concentrations (>11 μ M) blocks in vitro voltage-sensitive Na/K and Ca²⁺ channels, muscarinic receptors, and uptake of noradrenalin, dopamine, and serotonin.^{28–31} We believe that a direct local analgesic effect of ketamine is unlikely in our study, because ketamine did not reduce the acute intense pain evoked by capsaicin nor did it influence on the skin sensation of the control arm. Also, in our study, the antihyperalgesic effect was achieved with ketamine administered on both arms, meaning systemic absorption of ketamine. Because we did not observe any side effects by ketamine, the plasma concentration of ketamine most likely did not reach the level necessary^{28–31} for local anesthetic effect of ketamine.

Central nervous system effects have been found even with low concentration (50–100 ng/mL) of racemic ketamine,^{32,33} whereas 150 to 200 ng/mL would be sufficient for analgesia in acute nociceptive,³⁴ neuropathic,³⁵ and experimental pain³⁶ in man. These concentrations have been measured after intravenous doses of 0.5 to 2 mg/kg of ketamine. However, in the study of Wallace et al,³⁶ antihyperalgesic effects of ketamine were observed at lower plasma ketamine concentrations than those required for observable CNS effects. Azevedo et al suggested that the bioavailability of ketamine is 25% after transdermal application,¹⁷ but a recent study¹⁸ reported no detectable intravenous absorption of ketamine gel after topical application. In the latter study, the method of administration of the gel was not described in detail, and a comprehensive pharmacokinetic study was not performed.

TABLE 1. The AUC of the Areas of Hyperalgesic and Dysesthetic Skin

Treatment	Hyperalgesia	95% CI	Dysesthesia	95% CI
Placebo	1638	440	1944	1977
Ketamine	1348	737	649	310
Placebo/ketamine	1464	475	2374	495

Mean values \pm 95% CI are reported. Placebo/ketamine refers to the application of ketamine gel on the control arm.

Because placebo was used in the present crossover blind study, we were unfortunately not able to draw blood samples for measurements of plasma ketamine levels. The dose of 50 mg of ketamine appeared to be the lowest dose to produce analgesia in our preliminary tests. Compared with the doses (10–700 mg topically) used in patients,¹⁴ our dose was relatively low. Because we did not detect any typical CNS effects of ketamine, we—in the absence of the ketamine plasma levels—cannot rule out that the topically administered ketamine could have targeted the peripheral NMDA receptors after systemic absorption.

Although hyperalgesia may be due to sensitization of peripheral nociceptors,³⁷ capsaicin-induced hyperalgesia has been convincingly shown to be caused by the central sensitization.^{38,39} Nevertheless, a recent experimental study proposed a peripheral mechanism for ketamine-induced antihyperalgesic effect in a thermal injury model,⁹ we suggest rather a central mechanism or a combination of peripheral and central mechanisms in our study.

It is difficult to suggest any direct clinical implications of our findings and the previous studies published on the topical administration of ketamine.^{14–18} A very positive outcome has been noted in all open studies,^{14–17} but the recent double-blind and randomized pilot study could not find any analgesic effect of topical ketamine gel in neuropathic pain.¹⁸ Several possible explanations could account for why ketamine gel was ineffective in the pilot study. It is not known if the patients had received pain relief from systemic ketamine. In addition, the absorption of ketamine could be affected by the composition of the gel and the method of application. It would be interesting to find out how patients who receive pain relief from intravenous ketamine would respond to transdermal ketamine.

CONCLUSION

In conclusion, we observed a significant antihyperalgesic effect of topically applied ketamine in capsaicin model in man. We propose that the mechanism of this effect would be the reduction of central sensitization caused by the absorption of ketamine in circulation. The role of the possible block of peripheral NMDA receptors and other peripheral mechanisms remains to be studied. Also, studies on clinical pain and pharmacokinetics of transdermal ketamine in enriched patient populations are warranted.

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