Original Article

Drug challenge test and drip infusion of ketamine for post–stroke pain

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Abstract

Objective. To study the effect of ketamine on post–stroke pain, a drug challenge test was performed and the effects of a low–dose drip infusion of ketamine were examined in post– stroke pain patients.

Methods. In the drug challenge test, 5 mg of ketamine hydrochloride (i.v.) was given every 5 min up to a total of 25 mg in 120 post–stroke pain patients, and the pain reduction rate was assessed using a visual analogue scale (VAS). On the basis of the results of the drug challenge test, the effects of a low–dose ketamine drip infusion (LDKDI) were examined in 55 ketamine–sensitive post–stroke pain patients. For the LDKDI, 20 mg of ketamine hydrochloride added to 100 ml of saline was administered intravenously by 1-hour drip infusion.

Results. Fifty-five (45.8%) of 120 patients were evaluated as ketamine–sensitive with regard to their spontaneous pain. All of the 55 ketamine–sensitive patients treated with LDKDI could clearly experience pain reduction. The duration in which patients experienced pain reduction caused by LDKDI ranged from 1 to 6 hours in 27 patients (49%) and experienced in 38 patients (69.0%) up to 24 hours. In contrast, 17 (31%) of 55 patients experienced pain reduction lasting over 24 hours, and 4 (7.2%) of the 55 patients experienced pain reduction lasting about 1 week. In addition, 52 (94.5%) of the 55 patients were satisfied and expressed a desire to continue the LDKDI.

Conclusions. About half of the post–stroke pain patients were ketamine–sensitive, and LDKDI is useful for the treatment of post–stroke pain if candidates are selected on the basis of the results of a drug challenge test of ketamine.

Keywords: Post–stroke pain; Ketamine; Central sensitization; Drug–challenge test; NMDA receptor
INTRODUCTION

Although more than a century has passed since the 1906 report by Dejerine and Roussy describing post–stroke pain, such pain still remains one of the most difficult to treat clinically. The results of experimental studies on neuropathic pain have revealed the importance of excitatory amino acids (EAAs) in synaptic transmission and injury–induced neuroplasticity. The N–methyl–D–aspartate (NMDA) receptor is considered to be involved in sustained nociceptive transmission and in central sensitization, particularly after sensory input has been deafferented. Ketamine acts as a noncompetitive antagonist at the NMDA receptor, and NMDA receptors activated by the EAA glutamate are involved in central sensitization, the wind-up phenomenon, and allodynia of neuropathic pain.

Clinical studies have demonstrated that systematic administration of ketamine is an effective treatment for complex regional pain syndrome (CRPS), phantom limb pain, spinal cord injury pain, and orofacial pain; however, there had only been a limited number of studies on patients with post–stroke pain. In 1994, Backonja et al. reported that 2 patients suffering from post–stroke pain experienced an analgesic effect of ketamine. In 2001, Vick and Lamey described a case in which post–stroke pain was successfully treated with oral ketamine after an intravenous ketamine trial. In 1997, we reported the results of drug challenge tests with morphine, thiopental, and ketamine in post–stroke pain patients, and showed that 11 (47.3%) of 23 patients experienced a pain reduction of greater than 40% on a visual analogue scale (VAS).

In this study, we examined the effect of ketamine on post–stroke pain patients using the drug challenge test and low-dose ketamine drip infusion (LDKDI) method.

MATERIALS AND METHODS

Patients population

A total of 120 post–stroke pain patients, with hemorrhage or infarct in the thalamic area (thalamic lesions), the posterior limb of the internal capsule, the subcortical parietal area excluding the thalamus (supratralamic lesions), or the brainstem area, clearly identified by magnetic resonance imaging, were the subjects of the drug challenge test with ketamine. There were 67 males and 53 females, aged 25 – 79 years (mean, 59.2 years). All the patients had intractable pain associated with dysesthesia. They complained of spontaneous pain of great intensity, which they described as burning, tearing, or deep boring pain primarily in the upper and lower extremities (Table 1).

The present study involving a drug challenge test and LDKDI for post–stroke pain patients was approved by the Committee for Clinical Trials and Research in Humans of Nihon University, Tokyo, Japan. Informed consent was obtained from all 120 patients in this study. Thus, this study conforms with the internationally adopted ethical standards for the performance of clinical treatment and research (Declaration of Helsinki).

Drug challenge test with ketamine

For a single blind test with ketamine, saline was first injected twice at an interval of 5 min to investigate the placebo effect. Subsequently, 5 mg of ketamine hydrochlo-
ride was given every 5 min until a total of 25 mg had been administered. The pain level was recorded on the VAS at intervals of 5 min, and the change in the VAS was expressed as a %VAS, calculated as (VAS after ketamine injection / VAS before ketamine injection) × 100%. The %VAS was plotted on the evaluation sheet. In addition, the examiner continued to talk with the individual patients about their sensation of pain and surroundings to monitor the level of consciousness and clarity of thought. For patients who displayed psychological reactions such as hallucinations or severe emotional expression during the test, detailed recordings were kept for further assessment. In these patients, only the results that were recorded before the appearance of such psychological reactions were used to estimate the pain level. A reduction of over 40% in the pain level, compared with that before ketamine injection, was judged to represent ketamine–sensitivity, and the others were judged as ketamine–resistant.

**Saline drip infusion and low–dose ketamine drip infusion**

Fifty-five patients who were sensitive to ketamine and showed reduction of spontaneous pain participated in the single-blind test of saline drip infusion and the LDKDI trial. For the LDKDI trial, about 20 mg of ketamine hydrochloride (0.31 mg/kg in each patient) added to 100 ml of saline was administered intravenously by 1-hour drip infusion.

On the first day, 100 ml of saline was administered intravenously by 1-hour drip infusion to investigate the placebo effect. On the second day, we first determined whether patients had experienced any obvious pain reduction from the previous day’s drip infusion. After that, LDKDI was performed intravenously by 1-hour drip infusion. On the third day, we first determined whether patients had experienced any obvious pain reduction from the previous day’s drip infusion. If patients had experienced obvious pain reduction from the previous day’s drip infusion, we recorded how long that pain reduction persisted. If obvious pain reduction continued for over 24 hours, we also recorded its duration. In addition, we also checked on all 55 patients whether they wished to continue second day’s drip infusion (LDKDI).

These 55 patients included individuals with post–stroke pain caused by cerebral hemorrhage (34 patients) and cerebral infarct (21 patients). There were 38 males and 17 females, aged 46 – 75 years (mean, 59.5 years) (**Table 1**).

**Statistical analysis**

Ketamine–sensitive and ketamine–resistant patients with comparable brain injury sites and causes of brain injury were examined using the chi-square test for independence and Fisher’s exact probability test, and the threshold for significance was set at p<0.05.

<table>
<thead>
<tr>
<th>Drug challenge test with ketamine</th>
<th>LDKDI trial</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td></td>
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<tr>
<td>25 – 79 (mean, 59.2)</td>
<td>46 – 75 (mean, 59.5)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>67</td>
</tr>
<tr>
<td>F</td>
<td>53</td>
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<tr>
<td>Total</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>55</td>
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</table>

**Table 1** Characteristics of 120 patients with post–stroke pain evaluated by the drug challenge test with ketamine, and 55 patients evaluated by low–dose ketamine drip infusion (LDKDI)**
**RESULTS**

**Drug challenge test**

Among the 120 patients with post–stroke pain, 55 (45.8%) were evaluated as ketamine–sensitive with regard to their spontaneous pain. In addition, 8 patients (6.7%) who did not experience a decrease in spontaneous pain revealed a marked reduction of allodynia in the extremities. In total, 63 cases (52.5%) out of the 120 post–stroke pain patients were thus evaluated as ketamine–sensitive. The changes in %VAS from the ketamine test are plotted in Fig.1, and each calculated point of the %VAS is the average of the 55 patients who were evaluated as ketamine–sensitive with regard to their spontaneous pain. In the drug challenge test of ketamine–sensitive patients with regard to their spontaneous pain, the %VAS was reduced by over 70% when a total of 20 mg of ketamine

![Graph showing changes in %VAS](image)

**Table 2** Comparison between ketamine–sensitive and ketamine–resistant patients with regard to lesion site and cause of lesion

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Drug challenge test with ketamine</th>
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<tbody>
<tr>
<td></td>
<td>ketamine–sensitive</td>
</tr>
<tr>
<td>Supratentorial region</td>
<td>114</td>
</tr>
<tr>
<td>Thalamic region</td>
<td>75</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>50</td>
</tr>
<tr>
<td>Infarct</td>
<td>25</td>
</tr>
<tr>
<td>Suprathalamic region</td>
<td>39</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>29</td>
</tr>
<tr>
<td>Infarct</td>
<td>10</td>
</tr>
<tr>
<td>Infratentorial region</td>
<td>6</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>Infarct</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
</tr>
</tbody>
</table>

Statistical analyses among supratentorial region and infratentorial region, thalamic region and suprathalamic region, and hemorrhage and infarct in each region were all determined to be nonsignificant by the chi-square test for independence and Fisher’s exact probability test.
was injected. However, increasing the amount of ketamine to 25 mg did not increase the %VAS reduction.

Statistical analyses among supratentorial region and infratentorial region, thalamic region and suprathalamic region, and hemorrhage and infarct in each region were all determined to be nonsignificant (Table 2).

**Saline drip infusion and low-dose ketamine drip infusion**

As mentioned, the 55 patients who participated in the trial of saline drip infusion and LDKDI were all ketamine-sensitive with regard to their spontaneous pain. None of the 55 patients reported clear pain reduction after saline drip infusion. On the other hand, all 55 patients reported obvious pain reduction by LDKDI. The duration in which patients experienced pain reduction caused by LDKDI ranged from 1 to 6 hours in 27 patients (49%) and experienced in 38 patients (69.0%) up to 24 hours. In contrast, 17 (31%) of 55 patients experienced pain reduction lasting over 24 hours, and 4 (7.2%) of the 55 patients experienced pain reduction lasting about 1 week (Fig.2). LDKDI induced few adverse effects in these patients, and 52 (94.5%) of the 55 patients wished to continue LDKDI for the treatment of post–stroke pain.

**Adverse effects**

Among the 120 patients with post–stroke pain, 65 (54.2%) were evaluated as ketamine–resistant, in which the %VAS reduction of spontaneous pain was under 40%. There were 17 ketamine–resistant patients who complained of an increase in the severity of pain. These 17 patients complained of severe unpleasant sensations and displayed psychological reactions such as hallucinations or emotional expression during the drug challenge test with ketamine. When such adverse effects were observed, the drug challenge test was discontinued. On the other hand, no ketamine–sensitive patients complained of unpleasant sensations or displayed psychological reactions. Thirteen patients complained of dizziness, light headache, fatigue, or nausea during the drug chal-
lenge test, but most of these cases were ketamine–resistant (Table 3). Of the 55 ketamine–sensitive patients, only 3 complained of dizziness or nausea caused by LDKDI. For these 3 patients, the speed of the drip infusion was decreased or stopped for a while, and all patients could continue the LDKDI.

**DISCUSSION**

In 1997, we performed morphine, thiopental and ketamine tests in an attempt to clarify the neurochemical background of post–stroke pain and to undertake a pharmacological analysis. Morphine is generally non–effective for neuropathic pain, but can be effective for nociceptive pain. The morphine test may thus be useful for assessing nociceptive pain, which is usually caused by joint dislocation, arthralgia and muscle contraction in post–stroke pain patients. Thiopental is an ultrashort–acting barbiturate, and patients usually fall asleep during the thiopental test. In our experience, 17% of post–stroke patients did not experience pain reduction at all, as assessed by VAS, even at the time immediately before falling asleep, and these patients also experienced no pain reduction following cerebrospinal stimulation therapy. Not only the ketamine test but also morphine and thiamyal tests are useful to clinically determine the mode of treatment. In the ketamine test, we intended to examine the effects of ketamine from a small dosage to a large dosage, and thus administered 5 mg of ketamine hydrochloride every 5 min until a total of 25 mg was reached. In the ketamine test for ketamine–sensitive patients, the %VAS was reduced by over 70% when a total of 20 mg of ketamine was administered, but 25 mg of ketamine did not further increase the %VAS reduction. On the basis of these results, we determined that the amount of ketamine hydrochloride to be used in the LDKDI trial would be 20 mg.

Ketamine acts as a noncompetitive antagonist at the NMDA receptor site, and it has been suggested that analgesic effects are mediated at this site, particularly for intractable pain following sensory input deafferentation. It is also reported that gabapentin can reduce excitatory neurotransmitter release at the nerve terminals and in the dorsal horn. Such reduced release of EAA caused by

<table>
<thead>
<tr>
<th>Table 3 Adverse effects that appeared in drug challenge test</th>
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<tbody>
<tr>
<td>Drug challenge test with ketamine for spontaneous pain</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ketamine–sensitive</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Total cases</td>
</tr>
<tr>
<td>Adverse effects</td>
</tr>
<tr>
<td>Severe unpleasant sensation and/or psychological reactions</td>
</tr>
<tr>
<td>Dizziness</td>
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<tr>
<td>Light headache</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Nausea</td>
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gabapentin seems ideal with the combined effect of ketamine, which blocks the NMDA receptor of the EAA. Furthermore, recent reports have indicated satisfactory pain relief following intravenous and intrathecal injections of ketamine in patients with neuropathic pain \(^{20,32}\), CRPS \(^{5,13}\), phantom limb pain \(^{25}\), spinal cord injury pain \(^{19}\), and orofacial pain \(^{21}\). Although there had only been a limited number of investigations on patients with post–stroke pain, this study indicated that about half of post–stroke pain patients can be treated with LDKDI without serious adverse effects, if candidates are selected on the basis of the drug challenge test. In addition, we can expect more effective results using LDKDI in combination with gabapentin and antidepressant drugs. Such a new combined therapy has the possibility to increase the therapeutic effects on post–stroke pain.

In previous reports, adverse effects caused by ketamine infusion were found to be common, and included somnolence, dizziness, changes in vision, hallucinations, and balance difficulties \(^{19}\). When we performed the drug challenge test with ketamine, patients sometimes displayed psychological reactions such as hallucinations, severe emotional expression, or unpleasant sensations, but such patients were ketamine–resistant. For the LDKDI study, we selected only ketamine–sensitive patients, on the basis of the drug challenge test, and employed drip infusion therapy over a period of 60 min or longer while monitoring the patient’s responses. This may be the reason our LDKDI caused few adverse effects and 52 (94.5%) out of the 55 post–stroke pain patients wished to continue the LDKDI. Although the duration of clear pain reduction following LDKDI was generally several hours, most LDKDI patients were satisfied and hoped to continue the LDKDI. On the basis of these results, relief from central sensitization \(^{28,33}\) should be considered in ketamine–sensitive cases.

Following the pioneering publication of Dejerine and Roussy \(^{7}\), the thalamus has commonly been implicated in the pathogenesis of post–stroke pain. Although more than a century has already passed since their report, post–stroke pain still remains one of the most difficult types of pain to treat clinically. The finding that only about half of the post–stroke patients examined in this study were ketamine–sensitive reflects the complex pharmacological background and difficulties associated with treating post–stroke pain.

Cerebrospinal stimulation therapy, which includes spinal cord stimulation (SCS) \(^{18}\), deep brain stimulation (DBS) \(^{17}\), and motor cortex stimulation (MCS) \(^{16,22,24,29,34}\), has been utilized for the treatment of post–stroke pain. Usually, SCS and DBS therapies are not recommended for the treatment of patients with post–stroke pain. In contrast to SCS and DBS therapies, MCS was first reported for the treatment of post–stroke pain \(^{34}\), and numerous researchers have subsequently examined its effectiveness for post–stroke pain \(^{2,11,16,22,24,29}\). In most studies, the long–term success rate for pain alleviation was still about 50%. For ketamine–sensitive patients, we can apply LDKDI combined with cerebrospinal stimulation. On the basis of the results of the drug challenge test, we expect that LDKDI therapy can be used for the treatment of post–stroke pain, and that LDKDI can enhance the effects of SCS, DBS, and MCS in the treatment of post–stroke pain.
Acknowledgments

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The authors state that no conflict of interest is present.

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