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Changes in pain intensity of post-herpetic neuralgia following intravenous injections of ketamine hydrochloride

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Introduction

Hyperactivity of N-methyl-D-aspartate (NMDA) receptors has been proposed as a factor in the genesis of neuropathic pain [1,2]. Beneficial results have been achieved in several clinical studies in which ketamine hydrochloride, an antagonist of NMDA receptors, was given therapeutically to patients with post-herpetic neuralgia [3,4]. However, information on the value of long-term ketamine treatment for post-herpetic neuralgia [5] is limited.

The aim of this study was to clarify the outcome in patients with post-herpetic neuralgia treated with intravenous injections of ketamine hydrochloride.

Clinical report

Seven patients with post-herpetic neuralgia are included in this report. Their characteristics are shown in Table 1. They had suffered the post-herpetic pain for more than 1 year before they were referred to our pain clinic. Although we made several attempts to alleviate the post-herpetic neuralgia (by using agents such as antidepressants, opiates, or psychotropic agents), none of these produced a favorable result. Epidural analgesia or stellate ganglion block (SGB) were tried for several weeks, but pain relief was restricted to the duration of the treatment with the local anesthetic. Consequently, with approval from the Ethics Committee of Kagoshima University School of Medicine, and with the informed consent of the patients, we initiated a course of low-dose ketamine hydrochloride intravenous (i.v.) injections ($0.2\,mg \cdot kg^{-1}$). For the 2 days before the beginning of this trial and for the duration of the trial, the patients did not receive any systemic or local analgesic. A bolus intravenous injection of ketamine was given once a day for 4–24 days continuously (see below), and the patients were asked to rate the changes in their pain intensity. Pain relief was recorded as the change in pain intensity scored on a 100-mm visual analogue scale (VAS) (0 = no pain, 100 = most significant pain). On the first day of the course of injections, six patients were asked to provide a pain score every 2 h until 8 h after the injection (Fig. 1). The pain score was then checked once per day before each day's injection. The data were evaluated by non-parametric statistical analysis. Freidmann's two-way analysis by ranks was used to calculate significant differences between given timepoints. Significance was accepted at the 5% level.

The proportion of effective results was 85% (i.e., six of the seven patients rated ketamine as an effective treatment), while one patient (no. 7) reported no pain relief after the treatment. Immediately after the first injection of ketamine, adequate pain relief was obtained for at least 1 h, and VAS scores remained at low levels (i.e., around 5–20 mm) for the following 8 h in the six patients in whom treatment was rated as effective (Fig. 1). Twenty-four h after the first injection of ketamine, their pain had reverted almost to the level recorded prior to the injection, but the level gradually subsided day-by-day as the treatment was continued. The course of injections in these patients was tailored to each patient's needs and lasted from 4 to 24 days, with an average of 14.1 days (Table 1). The mean VAS score diminished significantly in the six patients, from 32.8 ± 7.5 before the beginning of the trial to 12.0 ± 4.6 before

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Table 1. Characteristics of patients with post-herpetic neuralgia treated with i.v. ketamine

Patient number	Sex	Age	Site of pain	Number of injections	VAS Score		
					Before first ketamine trial	Before final ketamine trial	1 Year after final trial
1	M	60	Left lower quadrant	18	32	5	10
2	F	60	Right lower thoracic	9	35	12	18
3	M	54	Left upper arm	20	30	10	0
4	F	62	Left lower thoracic	4	25	10	10
5	F	76	Left forehead	10	15	5	5
6	F	55	Left lower thoracic	24	60	30	40
7	F	53	Left forehead	1	10	—	—

VAS, Visual analogue scale (for scoring pain intensity; see text for details).

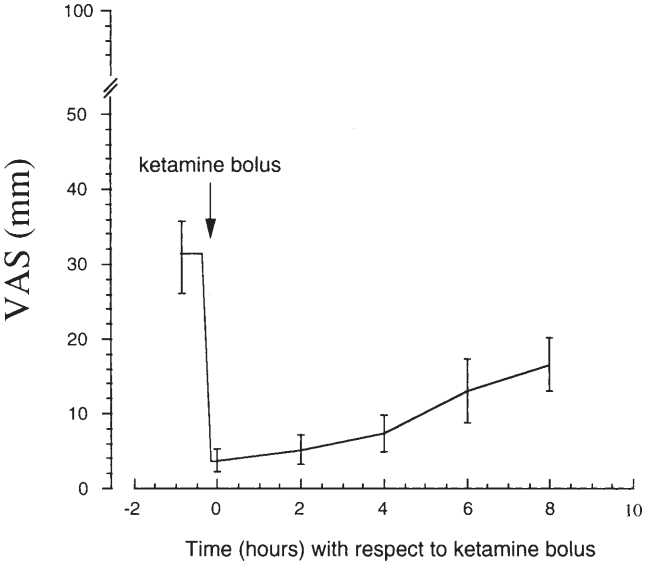

Fig. 1. Visual analogue scale (*VAS*) scores for pain experienced before and after injection of ketamine ($0.2\,mg{\cdot}kg^{-1}$) in the six patients in whom such treatment was effective. See text for details of the VAS

the final trial. During and after the infusion of ketamine, the patients were asked if they experienced specific side effects, such as dizziness, hallucinations, changes in hearing, or reduced visual acuity. They reported no side effects except for a slight feeling of unreality (in three patients) and transient blurring of vision for a few minutes (in one patient).

Our follow-up investigation 1 year after the final treatment with ketamine revealed that two of the six patients had experienced a resurgence of the pain, although it remained endurable (patients 1 and 2). One patient (patient 3) reported continuing pain relief. In two patients (patients 4 and 5), the pain remained the same as at the end of the treatment. However, one patient (patient 6) reported that the post-herpetic neuralgia had recurred soon after the ketamine treatment was discontinued and she had needed other treatment, such as capsicum ointment. No other patient in the group received medication of any sort for the residual post-herpetic pain in the follow-up year after the course of ketamine injections had been completed. The mean VAS scores in the six patients 1 year after the final treatment was 13.8 ± 7.1, significantly less than the score before the ketamine treatment.

Discussion

Six patients who had post-herpetic neuralgia after *Herpes zoster* infection, experienced a dramatic decrease in pain after the intravenous injection of low-dose ketamine hydrochloride. Although the mechanism behind such a beneficial effect is not at all clear, we speculate that this disorder may involve a sensitization of NMDA receptor-mediated transmission within the central nervous system (CNS) in pathways that convey pain sensation.

Our patients had received treatment with antidepressants, opiates, or psychotropic agents, but these were ineffective. Although neuronal blocking techniques such as epidural analgesia or SGB relieved the post-herpetic neuralgia to some extent, they still suffered malaise and pain in the affected regions, which they variously described as aching, itching, or squeezing. In contrast, as a result of the successive injections of ketamine, six of the seven patients reported that the pain was reduced to an endurable level, and they had a gratifying degree of relief from pain and discomfort. Moreover, five of these six patients had experienced no substantial resurgence in the pain 1 year after their final ketamine injection, suggesting that such treatment may provide a lasting effect.

In recent years, the hyperactivity of NMDA receptors has been implicated as a factor in the genesis of neuropathic pain [1]. Hyperalgesia and spontaneous

pain produced by nerve injury are reduced not only by local anesthesia of the responsible nerve, but also by NMDA antagonists, suggesting a central component as well [1,2]. Furthermore, it has been shown that the "wind-up" effect, which is a progressive increase in action potential discharge, is completely blocked by antagonists of the NMDA type of glutamate receptor, and also that most forms of long-term depression are dependent on the activation of NMDA receptors for their induction [6]. These results support the hypothesis that ketamine may act as an antagonist of NMDA receptors to induce the rapid normalization of some abnormality within the CNS that is related to post-herpetic neuralgia.

Recently, it was reported that a patient with severe post-herpetic pain resistant to conventional pain treatment experienced good pain relief when treated with ketamine and dextromethorphan for 4 years [4]. The authors recommended trying ketamine if other conventional treatment options failed. For patient no. 6 in our trials, the curative effect of ketamine was transient and far from satisfactory because of frequent relapses after the end of the ketamine treatment. It is conceivable that such patients with persistent post-herpetic neuralgia may need more long-lasting and aggressive treatment with ketamine to achieve a long-term analgesic effect. Further randomized controlled studies are necessary before the validity of ketamine treatment can be established.

In summary, intermittent therapy with low doses of ketamine resulted in adequate pain relief, lasting for at least 8 h after each injection, in five of seven patients with post-herpetic neuralgia. Daily injections were given for 4–24 days, and this tapered the patients' post-herpetic neuralgia to within endurable limits. Severe pain was not experienced by these five patients in the 1-year follow-up after their course of injections ended, although one patient with persistent post-herpetic neuralgia relapsed after an initially successful treatment with ketamine.

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