INTRODUCTION

Although more than a century has passed since the 1906 report by Dejerine and Roussy [7] 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 [3, 23,30]. The N–methyl–D–aspartate (NMDA) receptor is considered to be involved in sustained nociceptive transmission and in central sensitization [28,33], particularly after sensory input has been deafferented [9, 12]. Ketamine acts as a noncompetitive antagonist at the NMDA receptor [26], and NMDA receptors activated by the EAA glutamate are involved in central sensitization, the wind-up phenomenon, and allodynia of neuropathic pain [4,6,8,10,14,28,33].

Clinical studies have demonstrated that systematic administration of ketamine is an effective treatment for complex regional pain syndrome (CRPS) [5,13], phantom limb pain [25], spinal cord injury pain [19], and orofacial pain [21]; however, there had only been a limited number of studies on patients with post–stroke pain. In 1994, Backonja et al. [1] reported that 2 patients suffering from post–stroke pain experienced an analgesic effect of ketamine. In 2001, Vick and Lamer [35] 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 [36], 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 (suprathalamic 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-

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)

	Drug challenge test with ketamine	LDKDI trial
Age (years)	25 – 79 (mean, 59.2)	46 – 75 (mean, 59.5)
Gender M	67	38
F	53	17
Total	120	55

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 [36].

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 $p<0.05$.

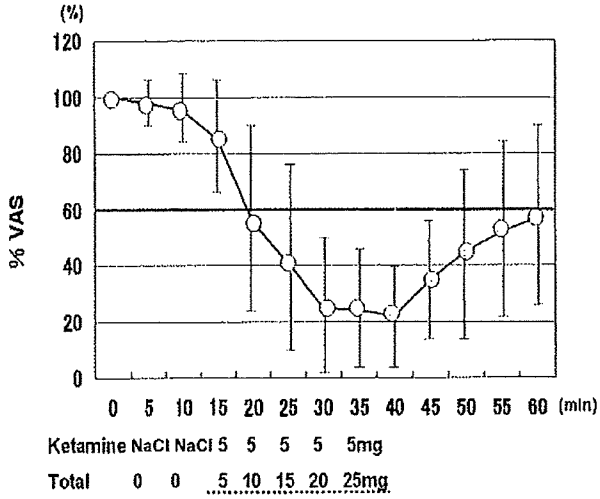

Fig.1 Changes in %VAS caused by the drug challenge test with ketamine.
Each calculated point of the %VAS is the average of 55 ketamine–sensitive patients with regard to spontaneous pain. Saline was first injected twice at an interval of 5 min to investigate the placebo effect. Subsequently, 5 mg of ketamine hydrochloride was given every 5 min until a total of 25 mg had been administered. Data are presented as the mean ± standard deviation.

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

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

Diagnosis		Drug challenge test with ketamine	
		ketamine–sensitive	ketamine–resistant
Supratentorial region	114	53	61
Thalamic region	75	37	38
Hemorrhage	50	22	28
Infarct	25	15	10
Suprathalamic region	39	16	23
Hemorrhage	29	11	18
Infarct	10	5	5
Infratentorial region	6	2	4
Hemorrhage	4	1	3
Infarct	2	1	1
Total	120	55	65

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.

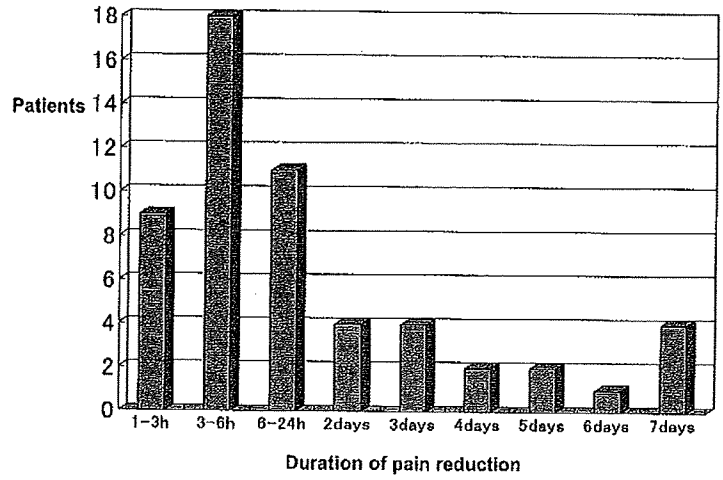

Fig.2 Duration of direct and obvious pain reduction experienced by each patient following low-dose ketamine drip infusion (LDKDI).

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-vesistant, 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-

Table 3 Adverse effects that appeared in drug challenge test

	Drug challenge test with ketamine for spontaneous pain	
	ketamine–sensitive	ketamine–resistant
Total cases	55	65
Adverse effects		
Severe unpleasant sensation and/or psychological reactions	0	17
Dizziness	2	5
Light headache	0	3
Fatigue	0	3
Nausea	1	2

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 [36]. 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 thiamylal 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 [3]. It is also reported that gabapentin can reduce excitatory neurotransmitter release at the nerve terminals and in the dorsal horn [15,27,31]. Such reduced release of EAA caused by

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

This work was supported by Grants-in-Aid for Scientific Research (No. C- 21591884) and Strategic Study of Fundamentals from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

The authors state that no conflict of interest is present.

References

1) Backonja, M., Arndt, G., Gombar, K.A., Check, B., Zimmerman, M., Response of chronic neuropathic pain syndrome to ketamine: a preliminary study, Pain, 56 (1994) 51-57.

2) Caroll, D., Joint, C., Masrtens, N., Shlugman, D., Aziz, T.Z., Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases, Pain, 84 (2000) 431-437.

3) Coderre, T.J., Melzack, R., Central neural mediators of secondary hyperalgesia following head injury in rats: neuropeptides and excitatory amino acids, Neurosci. Lett., 131 (1991) 71-74.

4) Coderre, T.J., Katz, J., Vaccarino, A.L., Melzack, R., Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence, Pain, 52 (1993) 259-285.

5) Correll, G.E., Maleki, J., Gracely, E.J., Muir, J.J., Harbut, R.E., Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome, Pain Med., 5 (2004) 263-275.

6) Davies, S.N., Lodge, D., Evidence for involvement of N-methyl-d-aspartate receptors in wind-up of class 2 neurones in the dorsal horn of the rat, Brain Res., 424 (1987) 402-406.

7) Dejerine, J., Roussy, J., Le syndrome thalamique, Rev. Neurol., 14 (1906) 521-531.

8) Dickenson, A.H., Sullivan, A.F., Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following C fiber stimulation, Neuropharmacology, 26 (1987) 1235-1238.

9) Dougherty, P.M., Palecek, J., Pleckova, V., Sorkin, L.S., Willis, W.D., The role of NMDA and non-NMDA excitatory amino acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, thermal and electrical stimuli, J. Neurosci., 12 (1992) 3025-3041.

10) Dubner, R., Neuronal plasticity in the spinal and medullary dorsal horns: a possible role in central pain mechanisms. In: K.L. Casey (editor), Pain and Central Nervous Disease: the Central Pain Syndromes, Raven Press, New York, 1991, pp.143-155.

11) Garcia-Larrea, L., Peyron, R., Mertens, P., Gregoire, M.C., Lavenne, F., Le Bars, D., Convers, P., Mauquière, F., Sindou, M., Lauret, B., Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study, Pain, 83 (1999) 259-273.

12) Gerber, G., Randic, M., Participation of excitatory amino acid receptors in the slow excitatory synaptic transmission in the rat spinal cord in vitro, Neurosci. Lett., 70 (1986) 143-147.

13) Goldber, M.E., Domsky, R., Scaringe, D., Hirsh, R., Dotson, J., Sharaf, I., Torjman, M.C., Schwarzman, R.J., Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome, Pain Physician, 8 (2005) 175-179.

14) Haley, J.E., Sullivan, A.F., Dickenson, A.H., Evidence for spinal NMDA receptor involvement in prolonged chemical nociception in the rat, Brain Res., 518 (1990) 218-226.

15) Kanai, A., Sarantopoulos, C., McCallum, B., Hogan, Q., Painful neuropathy alters the effect of gabapentin on sensory neuron excitability in rats, Acta Anaesthesiol. Scand., 48 (2004) 507-512.

16) Katayama, Y., Fukaya, C., Yamamoto, T., Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response, J. Neurosurg., 89 (1998) 585-591.

17) Kumar, K., Toth, C., Nath, R.K., Deep brain stimulation for intractable pain: a 15-year experience, Neurosurgery, 40 (1997) 736-746.

18) Kumar, K., Toth, C., Nath, R.K., Laing, P., Epidural spinal cord stimulation for treatment of chronic pain-some predictors of success: a 15-year experience, Surg. Neurol., 50 (1998) 110-120.

19) Kvarnstrom, A., Karlsten, R., Quiding, H., Gordh, T., The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury, Acta Anaesthesiol. Scand., 48 (2004) 498-506.

20) Leung, A., Wallace, M.S., Ridgeway, B., Yaksh, T., Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain, Pain, 91 (2001) 177-187.

21) Mathise, L.C., Skjelbred, P., Skoglund, L.A., Oye, I., Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain, Pain, 61 (1995) 215-220.

22) Myerson, B.A., Lindblom, U., Linderoth, B., Lind, D., Herregodts, P., Motor cortex stimulation as treatment of trigeminal neuropathic pain, Acta Neurochir. Suppl. (Wien), 58 (1993) 150-153.

23) Nestler, E.J., Greengard, P., Protein phosphorylation in the brain, Nature (Lond), 305 (1983) 583-588.

24) Nguyen, J.P., Lefaucheur, J.P., Decq, P., Uchiyama, T., Carpentier, A., Fontaine, D., Brugières, P., Pollin, B., Fève, A., Rostaing, S., Cesaro, P., Keravel, Y., Chronic motor cortex stimulation in the treatment of central and neuropathic pain: correlations between clinical, electrophysiological and anatomic data, Pain, 82 (1999) 245-251.

25) Nikolajsen, L., Hansen, C.L., Nielsen, J., Keller, J., Arendt-Nielsen, L., Jensen, T.S., The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input, Pain, 67 (1996) 69-77.

26) Oye, I., Paulsen, O., Maurset, A., Effects of ketamine on sensory perception: evidence for a role of N-methyl-d-aspartate receptors, J. Pharmacol. Exp. Ther., 260 (1992) 1209-1213.

27) Patel, M., Gonzales, M., Bramwell, S., Pinnock, R.D., Lee, K., Gabapentin inhibits excitatory transmission in the hyperalgesic spinal cord, Br. J. Pharmacol., 130 (2000) 1731-1734.

28) Persson, J., Axelson, G., Hallin, R.G., Gustafsson, L.L., Beneficial effects of ketamine in a chronic pain state with allodynia, possibly due to central sensitization, Pain, 60 (1995) 217-222.

29) Saitoh, Y., Shibata, M., Hirano, S., Hirata, M., Mashimo, T., Yoshimine, T., Motor cortex stimulation for central and peripheral deafferentation pain: report of 8 cases, J. Neurosurg., 92 (2000) 150-155.

30) Schaible, H.G., Grubb, B.D., Neugebauer, V., Opmann, M., The effects of NMDA antagonists on neuronal activity in cat spinal cord evoked by acute inflammation in the knee joint, Eur. J. Neurosci., 3 (1991) 981-991.

31) Shimoyama, M., Shinomiya, N., Hori, Y., Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn, Pain, 85 (2000) 405-414.

32) Stannard, C.F., Porter, G.E., Ketamine hydrochloride in the treatment of phantom limb pain, Pain, 54 (1993) 227-230.

33) Stubhaug, A., A new method to evaluate central sensitization to pain following surgery: effect of ketamine, Acta Anaesthesiol. Scand., 110 (1997) 154-155.

34) Tsubokawa, T, Katayama, Y., Yamamoto, T., Hirayama, T., Koyama, S., Chronic motor cortex stimulation in patients with thalamic pain, J. Neurosurg., 78 (1993) 393-401.

35) Vick, P.G., Lamer, T.J., Treatment of central post-stroke pain with oral ketamine, Pain, 92 (2001) 311-313.

36) Yamamoto, T., Katayama, Y., Hirayama, T., Tsubokawa, T., Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy, Pain, 72 (1997) 5-12.

Address for correspondence: Takamitsu Yamamoto
Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine
30-1 Ohyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
E-mail: nusmyama@med.nihon-u.ac.jp

Dual-lead SCS combined with low-dose ketamine drip infusion therapy for the treatment of neuropathic pain

**Takamitsu Yamamoto[1], Toshiki Obuchi[2], Toshikazu Kano[2]
Kazutaka Kobayashi[2], Hideki Oshima[2]
Chikashi Fukaya[1], and Yoichi Katayama[2]**

[1]Division of Applied System Neuroscience, Department of Advanced Medical Science and [2]Neurological Surgery, Nihon University School of Medicine

[Received 14 November 2008, Accepted 9 December 2008]

Abstract

Objective. Based on the results of a drug-challenge test with ketamine, we applied low-dose ketamine drip infusion (LDKI) therapy combined with dual-lead spinal cord stimulation therapy (Dual-SCS) for the treatment of various kinds of neuropathic pain. We report about benefits of this combined therapy.

Methods. In the drug-challenge test with ketamine, 5 mg of ketamine hydrochloride (i.v.) was given every 5 min up to 25 mg. Ketamine hydrochloride (0.33 mg/kg) added to 100 ml of saline was administered intravenously by 1-hour drip infusion every 2 weeks for LDKI therapy. Combined with this LDKI therapy, Dual-lead SCS therapy was applied for the treatment of various kinds of neuropathic pain.

Results. Comparing with single-lead SCS, Dual-lead SCS had obvious advantages to evoke paresthesia restricted only over the painful area. LDKI therapy directly and markedly reduced the intractable pain from 1 hour to 3 days, and also increased the effects of Dual-lead SCS for CRPS, failed-back syndrome, post-stroke pain, and phantom limb pain.

Conclusion. Dual-lead SCS combined with LDKI therapy is useful for the treatment of various kinds of neuropathic pain. Even if the direct effect of ketamine is transient, effects that provide release from central sensitization and the wind-up phenomenon may be important to increase the effects of Dual-lead SCS.

Key words: Spinal cord stimulation; Neuropathic pain; Ketamine; Dual-lead stimulation

PAIN RESEARCH 24 (2009) 9–15

神経障害性疼痛に対する Dual-lead を用いた脊髄刺激療法と low-dose ketamine 点滴療法の併用効果

山本 隆充[1]／大渕 敏樹[2]／加納 利和[2]／小林 一太[2]／大島 秀規[2]／深谷 親[1]／片山 容一[2]
日本大学医学部 [1]先端医学系 応用システム神経科学分野，[2]脳神経外科学系 神経外科学分野

はじめに

神経障害性疼痛 (neuropathic pain) の意味するところは神経の損傷後に出現する疼痛で，中枢神経の障害後に出現するものとしては，post-stroke pain，Wallenberg 症候群，脊髄損傷後疼痛などが代表例として挙げられ，末梢神経の障害後に出現するものとしては，幻肢痛，断端痛，腕神経叢損傷後疼痛，神経根損傷後疼痛，complex regional pain syndrome (CRPS) などが挙げられる。

脊髄刺激療法は，これまでに多くの神経障害性疼痛の治療に臨床応用されてきた[9]。脊髄刺激では，疼痛部には刺激による paresthesia を誘発し，非疼痛部には paresthesia を誘発しないように電極を留置するのが最良の方法である。しかし，脊髄硬膜外に留置した1本の刺激電極を用いる方法では限界があった[7]。近年，臨床応用が可能となったシナジー刺激装置を用いることによって，2本の刺激電極を用いた Dual-lead SCS が可能となり，電極間の刺激あるいは複数の刺激点を選択することによって，疼痛部位に限局した paresthesia を誘発するのも容易となった[16]。

知覚求心路の切断後に中枢側ニューロンに過剰活動が出現することが確認され[11]，この過剰活動が興奮性アミノ酸 NMDA レセプターのブロッカーであるケタミンによって抑制されることが確認されている[3,4,6,14,18]。また，臨床的にも求心路の遮断後に出現する central sensitization に対するケタミンの効果が報告されている[2,15,21]。

本研究では，ドラッグチャレンジテスト[23,24]の結果に基づいた low-dose ketamine 点滴療法と Dual-lead を用いた脊髄刺激療法の併用効果について各種の神経障害性疼痛において検討し，これまでの single-lead を用いた脊髄刺激療法[9]と比較した。

方　法

1. ドラッグチャレンジテスト (日本大学脳神経外科)

ケタラールテストは，5分間隔で生食を2回投与後，同様に5分間隔で ketamine hydrochloride を 5 mg，合計 25 mg まで静脈内投与する。モルヒネテストは，同様に5分間隔で morphine hydrochloride 3 mg を合計 18 mg まで静脈内投与し，サイオペンタールテストは，同様に 50 mg の thiopental sodium を，5分間隔で合計 250 mg まで静脈内投与している。途中で入眠した場合は，その時点で中止する[23,24]。Visual Analogue Scale (VAS) を連続的に測定し，(薬物投与後 VAS ÷ 薬物投与前の VAS) × 100 % = %VAS として，%VAS が 60 % 以下となったもの，すなわち薬物投与前と比較して，VAS が 40 % 以上減少したものを sensitive case，40 % 以下のものを resistant case としている。

サイオペンタールテストで入眠直前まで VAS が変化しない症例については，Dual-SCS の適応外としている。また，morphine-sensitive な症例については経口オピオイドの投与も考慮した。

2. Low-dose ketamine 点滴療法

ドラッグチャレンジテスト[23,24]で ketamine-sensitive な症例に対して，100 ml の生食に 20 mg のケタラール® (0.33 mg/kg) を加え，約1時間かけて点滴した。通常は2週間ごとに外来で点滴投与を行った。併用薬は塩酸マプロチニン (Ludiomil®) 30 mg/day，ブロマゼ

Table 1 Low-dose ketamine drip infusion (LDKI) therapy (Nihon Univ.)

1. Saline 100 ml + ketamine 20 mg (0.33 mg/kg) 1 hour drip infusion, every 2 weeks
2. Antidepressant (Maprotiline p.o. 30 mg/day)
3. Benzodiazepine (Bromazepam p.o. 6 mg/day)
4. Anticonvulsant (Gabapentin p.o. 600 – 1200 mg/day)

パム（Lexotan®）6 mg/day，ガバペンチン（GABAPEN®）600～1200 mg/day を投与した。また morphine-sensitive で経口オピオイドを希望した症例には MS コンチン® 30 mg/day を投与した（**Table 1**）。本治療法については，日本大学医学部学術・臨床研究審査委員会の承認を得た。

3. シナジー刺激装置を用いた Dual-lead SCS

脊髄刺激電極は，レントゲン透視下に脊髄硬膜外針を用いて，経皮的に脊髄硬膜外腔に挿入した。2 本の電極の合計 8 ヵ所の刺激点から複数の刺激点を選択し，最適の刺激部位を決定した。

Dual-lead SCS を施行した神経障害性疼痛は，post-stroke pain 6 例，failed-back syndrome 4 例，CRPS 2 例，phantom limb pain 1 例で，術後に low-dose ketamine 点滴療法を併用した。

結　果

1. Dual-lead の留置方法

13 例全例で疼痛部位に限局した paresthesia を誘発することが可能であった。Dual-lead の留置部については，1) 右上肢の激しい疼痛を訴える post-stroke pain の症例では，頚胸椎移行部の正中部と右よりに平行に 2 本の電極を挿入し，選択的に右上肢の疼痛部に paresthesia を誘発することができた（**Fig.1-A**）。2) 両下肢痛を訴える failed-back pain の症例では，下位胸椎部に 2 本の電極を挿入し，両下四肢の疼痛部に paresthesia を誘発することができた（**Fig.1-B**）。3) 右上腕神経叢の引き抜き損傷による右上肢の幻肢痛症例では，脊髄を挟むように 2 本の電極を脊髄の前面と後面に挿入して電極間の刺激を行うことによって，幻肢の部位に paresthesia を誘発することができた（**Fig.1-C**）。4) 両下肢の CRPS と腰痛を訴える症例では，2 本の電極を第 8 胸椎から第 10 胸椎まで連続的に留置し，腰部と両下肢に paresthesia を誘発することができた（**Fig.1-D**）。5) 右下肢の激しい疼痛を主訴とする post-stroke pain 症例に対しては，脊髄硬膜外に 2 本の刺激電極を挿入し，両方の電極から最適の刺激点を選択することにより，下肢の前面と後面に paresthesia を誘発することができた（**Fig.1-E**）。

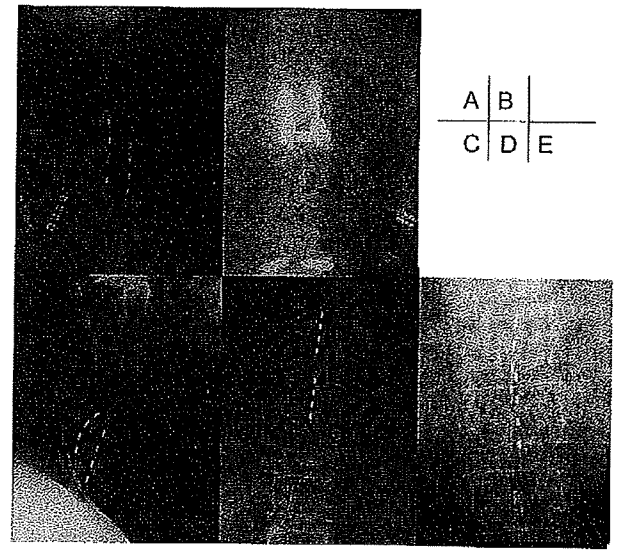

Fig.1 Various types of electrodes location.
A: Rt. upper extremity (Post-stroke pain), **B:** Bil. Lower extremities (Failed-back pain), **C:** Rt. upper extremity (Phantom limb pain), **D:** Bil. Lower extremities and waist (CRPS), **E:** Rt. lower extremity (Post-stroke pain).

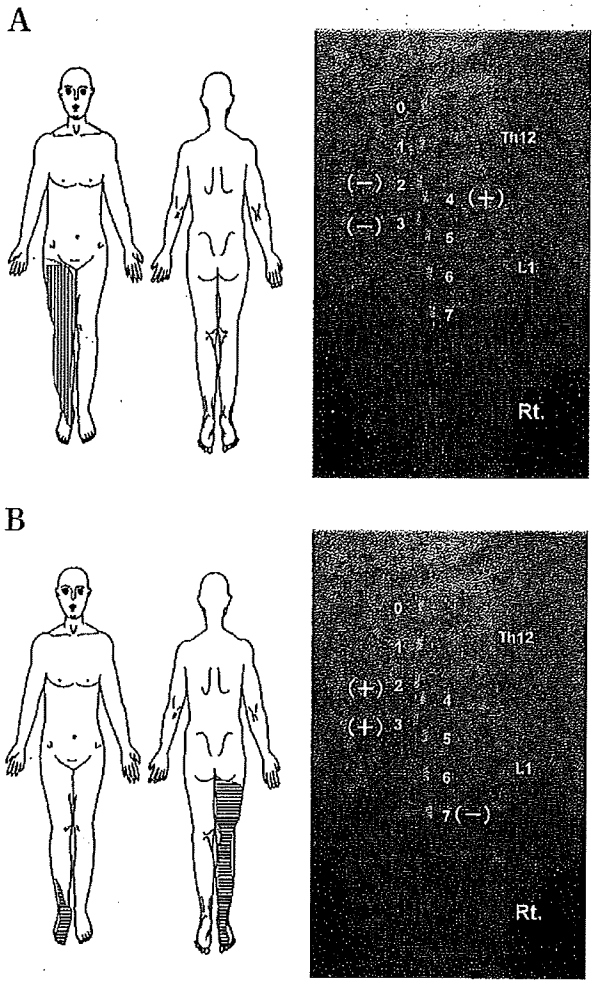

Fig.2 Dual-lead SCS for the treatment of post-stroke pain.
A: Combination of stimulation points with channel 1 (Right). Area of paresthesia evoked by channel 1 stimulation (Left)
B: Combination of stimulation points with channel 2 (Right). Area of paresthesia evoked by channel 2 stimulation (Left)
C: Employing Synergy stimulator, channel 1 and channel 2 can be used separately with different intensity and duration, and with same frequency.

Table 2 Results of Dual-lead stimulation therapy combined with low-dose ketamine drip infusion therapy

Excellent: 61 – 100% VAS reduction
Good: 31 – 60% VAS reduction
Fair: 0 – 30% VAS reduction

Cause of Pain	Number	Result
Post-stroke pain	6 cases	(Good 3, Fair 3)
Failed-back pain	4 cases	(Excellent 1, Good 2, Fair 1)
CRPS	2 cases	(Good 2)
Phantom limb pain	1 case	(Good 1)

シナジー刺激装置は，チャンネル1とチャンネル2の刺激を交互に連続して行うことができる。また，周波数は同じとなるが，チャンネル1と2でそれぞれ最適の刺激強度と刺激幅を選択することができる。**Fig.2-A** はチャンネル1の刺激部位と paresthesia が誘発される部位，**Fig.2-B** はチャンネル2の刺激部位と paresthesia が誘発される部位を示している。シナジー刺激装置を用いて Dual-SCS を行うことによって，これまでは困難であった下肢の前面と後面に同時に paresthesia を誘発することも可能となった（**Fig.2-C**）。

2. Dual-lead SCS と low-dose ketamine 点滴療法の併用効果

Dual-lead SCS の効果を VAS の減少率をもとに，Excellent(61％以上)，Good(60～31%)，Fair(30%以下）に分類した。low-dose ketamine の点滴目的に来院時のケタミン投与前の評価では，post-stroke pain では Good が3例，Fair 3例，failed-back pain では Excellent 1例，Good 2例，Fair 1例，CRPS では Good 2例，phantom limb pain では Good 1例であった（**Table 2**）。

13例の中で，VASの減少率からDual-lead SCSの効果がFairと判定されたものが4例存在したが，これらの症例も含めて全例でlow-dose ketamine点滴後には著しい疼痛の軽減を認め，Dual-lead SCSの効果増強も自覚することができた。

考　察

私どもの110例のpost-stroke painに対するケタラールテストの検討では，52例（47.3％）がketamine-sensitiveであった。また，自発痛の明らかな改善を認めない症例の中でも，8例ではアロデニアが著しく抑制されていた。これらの結果を総合すると，ケタラールは110例のpost-stroke painの中で，60例(54.5％)に有効であることが確認された。また，ketamine-sensitiveな群では，ケタラール20 mgの投与によってVASが70％以上減少し，それ以上の投与量を用いても明らかな変化を認めなかったので，low-dose ketamine点滴療法の量を20 mg (0.33 mg/kg)に決定した[25,26]。さらに，ketamine-sensitiveな症例は幻肢痛，神経根損傷など末梢神経に損傷を有する神経障害性疼痛に多く認められ，私どもの検討では約85％の症例がketamine-sensitiveであったことから，多くの症例に臨床応用することができるものと考える。

ドラッグチャレンジテストによってketamine-sensitiveな症例に対してpuncture trialによるDual-lead SCSを施行し，この結果で脊髄刺激の慢性植込みを行い，術後にはlow-dose ketamine点滴療法を併用した。長期的にlow-dose ketamine点滴療法を施行した26例の検討では，点滴後に明らかに疼痛が抑制される持続時間は1時間から6時間以内が最も多く，24時間以内が77％であったが，24時間以上持続するものも23％存在した[25,26]。長期投与によるケタミン耐性の有無についての検討では，20 mgで開始した26例中，6ヵ月後も20 mgが19例，21～30 mgが5例，10～19 mgが2例で，モルヒネのような耐性は認めなかった[25,26]。ケタミンの点滴によって情動面の変化を呈する症例が存在したが，投与量ならびに投与時間の調整によってコントロールが可能であった。

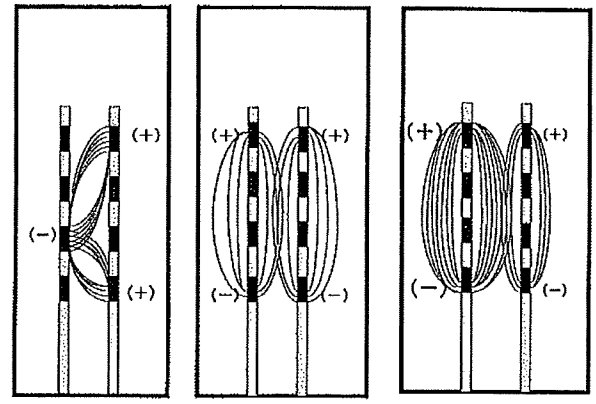

Fig.3 Schema of various kinds of Dual-lead stimulation method.

Low-dose ketamine点滴療法では，効果の持続時間が短い症例でも一度疼痛を軽減することが疼痛の管理には重要であり，これによって精神的な安定を得られるという症例が多い。また，central sensitizationの解除にも有効であると考えられている[15,21]。併用薬として，抗うつ薬，抗不安薬，抗てんかん薬を用いたが，本邦でも使用可能となったガバペンチンには，神経終末からの興奮性アミノ酸の遊離を抑制する作用が報告されており[8,19,20]，ケタミンとの相乗効果も期待される。

これまでの脊髄刺激装置はアイトレル3が用いられてきたが，アイトレス3では接続できる脊髄刺激電極は1本で，最高で4ヵ所の刺激点を選択することが可能であった。しかし，1本

の電極の上にある刺激点の中からのみの選択であるため，電極の走行に沿った刺激のみが可能であった。一方，シナジーニューロステイミュレータでは，2本の電極の合計8ヵ所の刺激点を自由に選択可能であり，陽極と陰極を選択すれば2本の電極間での刺激も可能となった。これまでは縦方向の刺激のみが可能であったが，2本の電極をパラレルに挿入することによって，横方向の通電も可能となった。また，2本の電極を用いて8ヵ所の刺激点をそれぞれ陽極または陰極で刺激することが可能であり，これまでは不可能であった各種の刺激部位の組み合わせパターンを脊髄刺激による痛みの治療に応用することが可能となった（**Fig.3**）。

これまで疼痛に対する脊髄刺激療法の有効例は failed-back pain, CRPS, 四肢の血流障害などに限られることが多かった[9]。しかし，新たに使用可能となった Dual-lead SCS を用いることによって，post-stroke pain や幻肢痛症例においても疼痛部位を完全にカバーしながら非疼痛部位には paresthesia を誘発しない刺激を行うことができ，low-dose ketamine 点滴療法を併用することによって多くの症例で十分に満足できる結果が得られた。特に，これまで脊髄刺激の適応外と考えられていた post-stroke pain 症例においても半数で十分に満足結果が得られた事実は重要である。各種の神経障害性疼痛に対するケタミンの有効性も報告[1,5,10,12,13,17,22]されており，神経障害性疼痛に対する新たな治療法の開発に役立つものと期待されている。本研究で行った Dual-lead SCS と low-dose ketamine 点滴療法の併用は，新たな神経障害性疼痛の治療法として発展が期待され，今後の更なる症例の蓄積が必要と考える。

文　献

1) Backonja, M., Arndt, G., Gombar, K.A., et al., Response of chronic neuropathic pain syndrome to ketamine: a preliminary study, Pain, 56 (1994) 51-57.
2) Coderre, T.J., Katz, J., Vaccarino, A.L., et al., Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence, Pain, 52 (1993) 259-285.
3) Davies, S.N., Lodge, D., Evidence for involvement of N-methyl-D-aspartate receptors in wind-up of class 2 neurones in the dorsal horn of the rat, Brain Res., 424 (1987) 402-406.
4) Gerber, G., Randic, M., Participation of excitatory amino acid receptors in the slow excitatory synaptic transmission in the rat spinal cord in vitro, Neurosci. Lett., 70 (1986) 143-147
5) Goldberg, M.E., Domsky, R., Scaringe, D., et al., Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome, Pain Physician, 8 (2005) 175-179.
6) Haley, J.E., Sullivan, A.F., Dickenson, A.H., Evidence for spinal NMDA receptor involvement in prolonged chemical nociception in the rat, Brain Res., 518 (1990) 218-226.
7) Holsheimer, J., Nuttin, B., King, G.W., et al., Clinical evaluation of paresthesia steering with a new system for spinal cord stimulation, Neurosurgery, 42 (1998) 541-549.
8) Kanai, A., Sarantopoulos, C., McCallum, B., et al., Painful neuropathy alters the effect of gabapentin on sensory neuron excitability in rats, Acta Anaesthesiol. Scand., 48 (2004) 507-512.
9) Kumar, K., Toth, C., Nath, R.K., et al., Epidural spinal cord stimulation for treatment of chronic pain-some predictors of success: a 15-year experience, Surg. Neurol., 50 (1998) 110-120
10) Kvarnstrom, A., Karlsten, R., Quiding, H., et al., The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury, Acta Anaesthesiol. Scand., 48 (2004) 498-506.
11) Loeser, J.D., Ward, A.A., Some effects of deafferentation on neurons of the cat spinal cord, Arch. Neurol., 17 (1967) 48-50.
12) Mathisen, L.C., Skjelbred, P., Skoglund, L.A., et al., Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain, Pain, 61 (1995) 215-220.
13) Nikolajsen, L., Hansen, C.L., Nielsen, J., et al., The effect of ketamine on phantom pain: a central neuropathic disorder maintained by peripheral input, Pain, 67 (1996) 69-77.

14) Oye, I., Paulsen, O., Maurset, A., Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors, J. Pharmacol. Exp. Ther., 260 (1992) 1209-1213

15) Persson, J., Axelson, G., Hallin, R.G., et al., Beneficial effects of ketamine in a chronic pain state with allodynia, possibly due to central sensitization, Pain, 60 (1995) 217-222.

16) Rainov, N.G., Demmel, W., Heidecke, V., Dual electrode spinal cord stimulation in chronic leg and back pain, Acta Neurochir. Suppl., 97 (2007) 85-89.

17) Stannard, C.F., Porter, G.E., Ketamine hydrochloride in the treatment of phantom limb pain, Pain, 54 (1993) 227-230.

18) Schaible, H.G., Grubb, B.D., Neugebauer, V., et al., The effects of NMDA antagonists on neuronal activity in cat spinal cord evoked by acute inflammation in the knee joint, Eur. J. Neurosci., 3 (1991) 981-991.

19) Shimoyama, M., Shinomiya, N., Hori, Y., Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn, Pain, 85 (2000) 405-414.

20) Patel, M., Gonzales, M., Bramwell, S., et al., Gabapentin inhibits excitatory transmission in the hyperalgesic spinal cord, Br. J. Pharmacol., 130 (2000) 1731-1734.

21) Person, J., Axelsson, G., Hallin, R.G., et al., Beneficial effects of ketamine in a chronic pain state with allodynia, possibly due to central sensitization, Pain, 60 (1995) 217-222.

22) Vick, P.G., Lamer, T.J., Treatment of central post-stroke pain with oral ketamine, Pain, 92 (2001) 311-313.

23) Yamamoto, T., Katayama, Y., Tsubokawa, T., et al., Usefulness of the morphine/ thiamylal test for the treatment of deafferentation pain, Pain Res., 6 (1991) 143-146.

24) Yamamoto, T., Katayama, Y., Hirayama, T., et al., Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy, Pain, 72 (1997) 5-12.

25) 山本隆充, 大渕敏樹, 小林一太, 他, Post-stroke pain の特徴と治療, ペインクリニック別冊: 求心路遮断痛の診断と治療, 29 (2008) 119-126.

26) 山本隆充, 大渕敏樹, 片山容一, 中枢性疼痛に対するケタミン点滴療法, ペインクリニック, 28 (2007) 560-565.

Address for correspondence: Takiamitsu Yamamoto
Division of Applied System Neuroscience, Department of Advanced Medical Science
Nihon University School of Medicine
30-1 Ohyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan
TEL: 03-3972-8111 (ext. 2230) / FAX: 03-3972-8292
E-mail: nusmyama@med.nihon-u.ac.jp

doi: 10.1111/j.1525-1403.2009.00235.x
NEUROMODULATION: TECHNOLOGY AT THE NEURAL INTERFACE

Volume 13 • Number 1 • 2010
http://www.blackwell-synergy.com/loi/ner

CASE REPORT

Effects of Electrode Implantation Angle on Thalamic Stimulation for Treatment of Tremor

Kazutaka Kobayashi, MD, PhD*† • Yoichi Katayama, MD, PhD*† • Koichiro Sumi, MD*† • Toshiharu Otaka, MD*† • Toshiki Obuchi, MD*† • Toshikazu Kano, MD, PhD*† • Takafumi Nagaoka, MD, PhD*† • Hideki Oshima, MD, PhD*† • Chikashi Fukaya, MD, PhD*† • Takamitsu Yamamoto, MD, PhD*† • Hideki Atsumi, MD, PhD‡

*Department of Neurological Surgery and †Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine, Tokyo, Japan; and ‡Department of Neurosurgery, Tokai University School of Medicine, Isehara, Kanagawa, Japan

ABSTRACT

Introduction. Chronic thalamic stimulation has been confirmed as an effective treatment for tremor. The optimal target has been commonly accepted to be situated within the ventral thalamus, but a standard trajectory of the deep brain stimulation (DBS) electrode has not yet been established. **Materials and Methods.** A 53-year-old man with an 11-year history of essential tremor was treated by DBS of the thalamus. In this patient, we had a chance to compare the effects of different trajectory angles of the DBS electrode on tremor. **Results.** Intraoperative stimulation with the DBS electrode temporarily inserted at a high angle to the horizontal plane of the anterior commissure–posterior commissure (AC–PC) line to cover only the nucleus ventralis intermedius (Vim) was not effective. In contrast, stimulation with the DBS electrode permanently implanted at a low angle, covering a wide area extending from the nucleus ventralis oralis (Vo) to the Vim, reduced the tremor. **Conclusion.** We report on the case of a patient who showed different effects on tremor depending on the trajectory angle of the DBS electrode to the AC–PC line. The insertion trajectory of the DBS electrode may be an important factor for the treatment of tremor.

KEY WORDS: *Deep brain stimulation, thalamus, tremor.*

Introduction

Deep brain stimulation (DBS) of the thalamus (thalamic DBS) is effective in reducing essential tremor, poststroke tremor, and Parkinsonian tremor (1–10). It is presumed that the optimal target for suppressing tremor with thalamic DBS is the nucleus ventralis intermedius (Vim), which also is the ideal thalamotomy target in the ventral thalamus. This association was derived from empirical observations made during ablation surgery. It was revealed that electrical stimulation was effective in controlling tremor and determined the optimal lesion site prior to radiofrequency ablation (11–13).

Because the electrode for therapeutic DBS (lead 3387; Medtronic, Minneapolis, MN, USA) has four contacts, each

Submitted: September 4, 2008; First revision: February 21, 2009; Accepted: March 28, 2009. Address correspondence and reprint requests to: Kazutaka Kobayashi MD, PhD, Department of Neurological Surgery, Nihon University School of Medicine, 30-1 Oyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. Email: kitta@med.nihon-u.ac.jp

1.5 mm long and spaced 1.5 mm apart (the span between the edges of the electrode is 10.5 mm), stimulation with the DBS electrode can cover an area wider than that covered by intraoperative stimulation during ablation surgery. Therapeutic DBS also has advantages over ablation surgery in terms of the reversibility of the treatment (2), the ability to adjust stimulus parameters (14), and fewer adverse effects (15). Moreover, the mechanisms by which DBS and thalamotomy produce effects differ (16,17). Because of this discrepancy, it is necessary to clarify the optimal stimulation site in the thalamus as well as the implantation trajectory of the DBS electrode, which passes through regions of the thalamus for the purpose of tremor control. Therefore, we report a case in which the effects of stimulation of the thalamus on tremor differed depending on the angle of the DBS electrode relative to the anterior commissure–posterior commissure (AC–PC) line.

Case Description

The patient was a 53-year-old, right-handed man with an 11-year history of action tremor in the right upper limb. He had no family history of a similar movement disorder. He underwent several medications previously to reduce the tremors without any noticeable change in his condition. His tremor had gradually worsened over the years and was affecting his activities of daily life; therefore, he was finally referred to our hospital for DBS surgery.

An examination revealed action tremors in the right hand, with no cerebellar signs such as hypotonia or ataxia or any other neurologic abnormalities. Electromyography (EMG) using surface electrodes showed no abnormal discharges at rest and rhythmic burst discharges of 4–5 Hz when performing any action, particularly writing. Magnetic resonance imaging (MRI) of the brain revealed no abnormalities.

He underwent surgery for implantation of a DBS electrode. A Leksell Series G head frame (Elekta Instruments AB; Stockholm, Sweden) was used. A 1-mm-thick section of tissue was used for MRI, and the AC and PC were identified with the aid of specialized software (Leksell SurgiPlan; Elekta Instruments AB). An X-ray indicator (Elekta Instruments AB) also was used to identify the AC and PC on plain X-ray films. A burr hole was made at the level of the coronal suture, approximately 2.5 cm from the midline.

Extracellular single- and multi-unit recordings were obtained using a semimicroelectrode (0.2–0.4 MΩ). Neuronal activity also was fed to an audio speaker. Neural and EMG activities of eight contralateral muscles, including the biceps, triceps, deltoid, wrist extensors, and flexors were displayed on an oscilloscope. Several aspects of neuronal activity were examined such as the relationship between spontaneous activity and tremor, and neuronal activity during somatic sensory stimulation and active movement. Intraoperative audio and oscilloscopic monitoring of tremor frequency and neural activity was performed to detect whether neuronal bursting and tremor frequency had same frequencies. Cells with neuronal activity in response to somatic sensory stimulation, that is, in response to the passive joint movement of the contralateral limbs without a response in skin deformation caused by stimuli, were classified as: 1) deep sensory cells and responding to light touch on the skin of the face and contralateral limbs were classified into 2) cutaneous sensory cells.

The first trajectory of the semimicroelectrode for extracellular unit recording was directed toward the anterior aspect of the PC in the lateral view and at level with the AC–PC line, 17 mm lateral to the midline, with the intention of identifying the anterior border of the nucleus ventrocaudalis (the Vim–Vc border). Physiologic studies were initiated after the electrode had reached 12 mm above the intended target. In this study, the Vim–Vc border was physiologically defined as the most anterior neuron along a length of trajectory in which more than one-half the neurons located posteriorly were either deep or cutaneous sensory neurons (18). The Vim–Vc border was identified as a vertical line approximately 3 mm anterior to the PC, on the basis of the observations made during our initial trajectory assessment (Fig. 1). This identification was consistent with the Vim–Vc border determined on the basis of the Schaltenbrand–Wahren atlas. The second trajectory of the semimicroelectrode was directed toward a position 1 mm anterior to the Vim–Vc border at the level of the AC–PC line, 17 mm lateral to the midline. The target was approached through the burr hole at an angle of 77° to the horizontal plane of the AC–PC line and at an angle of 10° to the sagittal plane. The second trajectory included some deep sensory cells of the wrist and/or the elbow and the tremor-frequency activities were the same as those exhibited at the Vim (Fig. 1). Therefore, on the basis of these classifications, the second trajectory was regarded as the optimal stimulation site. Following this, the first DBS electrode (model 3387; Medtronic, Inc.) was implanted through an identical trajectory using stereotactic instruments and then a test stimulation with the DBS electrode was conducted. These four contacts of the DBS electrode were primarily located in the Vim (Fig. 1a). The stimulation was performed in the bipolar mode, with contact 0 as the cathode (−) and contact 3 as the anode (+). The stimulation generated muscle contraction without having an effect on tremor. It was assumed that the muscle contraction caused the current to spread to the internal capsule. To prevent muscle contraction, a second DBS electrode was introduced more medially through another trajectory at the level of the AC–PC line, 14 mm lateral to the midline, and at the same angle as the first DBS electrode to the horizontal plane of the AC–PC line (Fig. 2). We then conducted a test stimulation in the bipolar mode with the second DBS electrode. The stimulation also did not have an

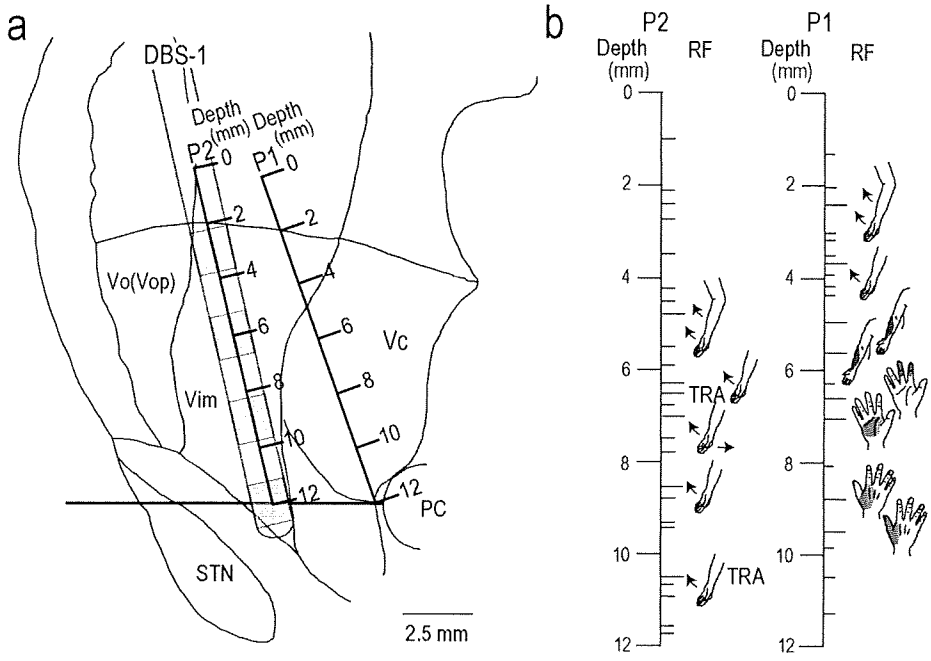

FIGURE 1. Receptive field (RF) maps of trajectories in the region of the ventral thalamus in the described patient. (a) The 17-mm lateral section from the Schaltenbrand–Wahren human brain atlas with the anterior commissure–posterior commissure (AC–PC) length is stretched to fit the coordinates obtained from the patient's stereotactic magnetic resonance imaging. The trajectories used (P1 and P2) are shown by the oblique lines. DBS-1, the first electrode of deep brain stimulation, was temporarily implanted through the same track as P2. (b) Details of the recordings. The labels P1 and P2 indicate sagittal trajectories shown as 1 and 2 on the brain map in a. Locations of neurons are indicated by tick marks to the right of the trajectory. RF maps are shown on the right. The label "TRA" indicates that neuronal activity was subjectively related to tremor, as assessed in the operating room. PC, posterior commissure; STN, subthalamic nucleus; Vc, nucleus ventrocaudalis; Vim, nucleus ventralis intermedius; Vo, nucleus ventralis oralis; Voa, nucleus ventralis oralis anterior; Vop, nucleus ventralis oralis posterior.

effect on tremor. To form another trajectory, a second burr hole was made approximately 3 cm anterior to the coronal suture, approximately 2 cm from the midline. The trajectory was directed toward a position 1 mm anterior to the Vim–Vc border at the level of the AC–PC line, 14 mm lateral to the midline. The target was approached through the burr hole at an angle of 44° to the horizontal plane of the AC–PC line and at an angle of 5° to the sagittal plane. A microthalamotomy effect was observed immediately after implantation of the third DBS electrode and the tremor disappeared completely without electrical stimulation. The microthalamotomy effect indicates that the location in which the third DBS electrode was implanted was the optimal therapeutic site (19,20). Therefore, only adverse effects of stimulation were examined and the third DBS electrode was permanently implanted into the patient.

After the postoperative disappearance of the microthalamotomy effect, stimulation with various combinations of bipolar mode was examined. Stimulation with contact 0 as the cathode (−) and contact 1 as the anode (+) stimulated mainly Vim and had some effect on tremor. However, the strongest effect was produced when contact 0 was the cathode (−) and contact 3 was the anode (+), covering a wide area extending from the nucleus ventralis oralis (Vo) to the Vim (Fig. 2).

Discussion

Ohye and Narabayashi (12) and Nagaseki et al. (11) emphasized that a small area (40 mm^3) that includes movement-related cells is the best site of lesion for thalamotomy to have an effect on tremor. In both studies, the lesions were made within 1 to 2 mm of the Vc, and therefore, did not include the region with cells responding to cutaneous sensory stimuli. It is commonly accepted that the optimal target for chronic thalamic stimulation for treatment for tremor is the Vim, close to the border of the sensory thalamus (Vim–Vc border) (11–13). In the present case, deep sensory cells and cells with tremor-frequency activity were recorded in the second trajectory (Fig. 1). Although the site including these cells is considered the optimal target for tremor control (11,12,21,22), electrical stimulation of this region was not effective in suppressing tremor.

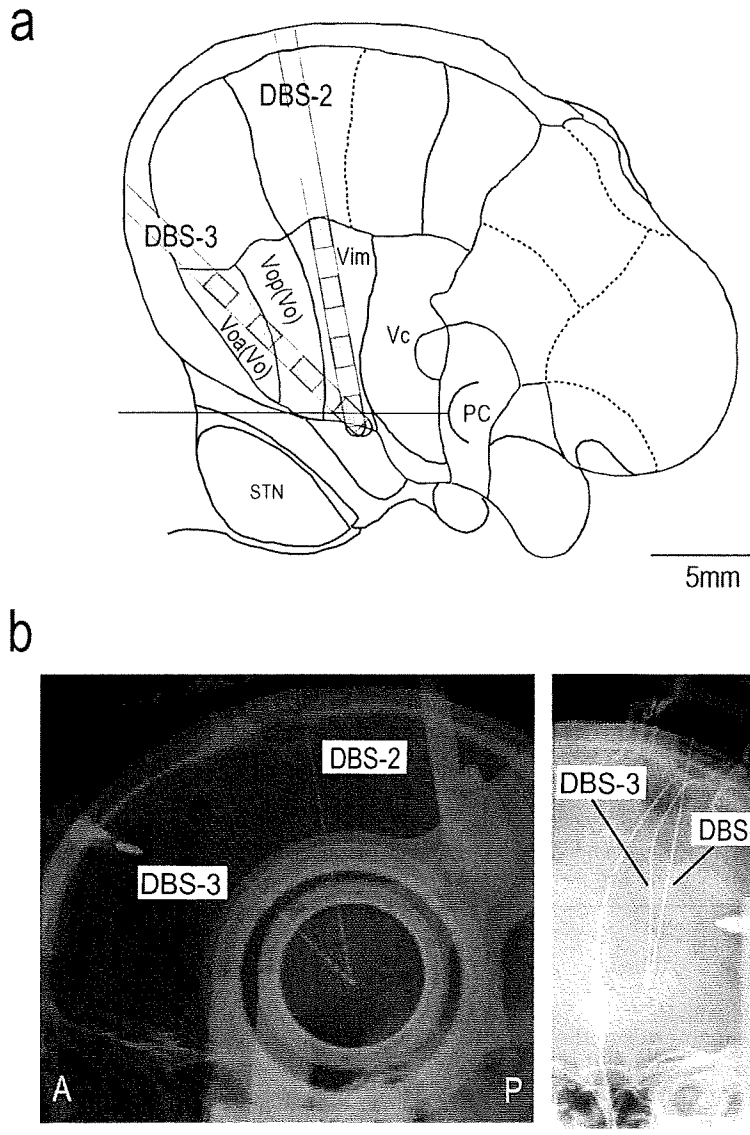

FIGURE 2. Intraoperative radiographs and anatomic relationship between thalamic nucleus and deep brain stimulation (DBS) electrode. (a) The 14.5-mm lateral section from the Schaltenbrand–Wahren human brain atlas with the anterior commissure–posterior commissure (AC–PC) length is stretched to fit the coordinates obtained from the patient's stereotactic magnetic resonance imaging. DBS-2, the second electrode of DBS, was temporarily implanted at a high angle to the AC–PC line. DBS-3, the third electrode of DBS, was placed at a low angle to the AC–PC line. PC, posterior commissure; STN, subthalamic nucleus; Vc, nucleus ventrocaudalis; Vim, nucleus ventralis intermedius; Vo, nucleus ventralis oralis; Voa, nucleus ventralis oralis anterior; Vop, nucleus ventralis oralis posterior. (b) Two radiographs are superimposed, each of which was obtained when the DBS electrode was inserted along a different trajectory. The labels DBS-2 and DBS-3 indicate DBS-2 and DBS-3 shown on the brain map in a, respectively. Left, lateral view; Right, anterior-posterior view.

Because the Vim forms an oblong structure on the lateral view, the DBS electrode must be inserted at a high angle to the horizontal plane of the AC–PC line, thereby allowing the contacts of the electrode to be arranged in the Vim as much as possible. However, in our patient, despite arranging the four contacts of the first and second DBS electrodes in the Vim, his tremor was not affected. The target for the third DBS electrode was approached at an angle of 45° to

the horizontal plane of the AC–PC line. This trajectory produced a microthalamotomy effect even though the target was nearly the same as that for the second DBS electrode. The main difference in the placement of the second and third DBS electrodes was the trajectory through the thalamus (Fig. 2). However, it is possible that the second DBS electrode was located in the somatotopic area of the Vim corresponding to the lower extremity instead of in the area corresponding to the upper extremity because the second DBS electrode was slightly lateral to the third DBS electrode. That is, contact 0 of the second DBS electrode was approximately 0.5 mm lateral to contact 0 of the third DBS electrode and contact 3 of the second DBS electrode was approximately 1.5 mm lateral to contact 3 of the third DBS electrode (A–P view shown in Fig. 2b). There are few reports on thalamic stimulation therapy for tremor in which the optimal angle of the DBS electrode to the AC–PC line or optimal trajectory through the thalamic regions is reported. However, it was demonstrated that stimulation of both Vim and Vo is necessary in many cases. One study implied that the optimal angle of the DBS electrode to the AC–PC line should be approximately 45° (9). In the large series of cases presented by Benabid et al., (2) the optimal tremor control site was located 4 to 8 mm anterior to the PC, and 0 to 2 mm superior to the AC–PC line. Therefore, with these coordinates, it is possible that the areas affected by the spread of the current stimulation included not only the Vim but also the Vo (23).

Thalamic neurons firing at the same frequency as that of tremor have been recorded during surgery and such neurons are widely distributed over an area extending from the Vim to the Vo (24–28). Some of these neurons are involved in the generation of tremor (24,29). That is, the wide area of the ventral thalamic nuclei may be involved in the generation of tremor. It would therefore be difficult to ablate the extensive area implicated in the generation of tremor without any side-effects. In contrast, DBS electrodes can be implanted to affect an area wider than that affected by thalamotomy, and still allow a surgeon to select a location to place the contacts and modify the stimulation intensity as required, thereby achieving the best clinical benefits (1–3,9,10).

Because of the large angle of the trajectory of the third DBS electrode, there is a possibility of inadvertently making a burr hole in the forehead. In our patient, specific management was not required to maintain an esthetic appearance of the forehead. If we had considered that an accidental of burr hole in the forehead was likely, we would have made a transverse skin incision on the hair line.

Conclusion

We report on a patient who had different effects on tremor depending on the trajectory angle of the DBS electrode to the AC–PC line. The trajectory of the DBS electrode may be a considerable factor for the implantation of a DBS electrode for tremor therapy.

Conflict of Interest

The authors reported no conflict of interest.

References

1. Benabid AL, Pollak P, Gervason C et al. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 1991;337:403–406.

2. Benabid AL, Pollak P, Gao D et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *J Neurosurg* 1996;84:203–214.

3. Blond S, Caparros-Lefebvre D, Parker F et al. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. *J Neurosurg* 1992;77:62–68.

4. Caparros-Lefebvre D, Blond S, Vermersch P, Pecheux N, Guieu JD, Petit H. Chronic thalamic stimulation improves tremor and levodopa induced dyskinesias in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1993;56:268–273.

5. Katayama Y, Fukaya C, Yamamoto T. Control of post-stroke involuntary and voluntary movement disorders with deep brain or epidural cortical stimulation. *Stereotact Funct Neurosurg* 1997;69:73–79.

6. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor. *Mov Disord* 2001;16:464–468.

7. Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry* 1999;66:289–296.

8. Nguyen JP, Degos JD. Thalamic stimulation and proximal tremor. A specific target in the nucleus ventrointermedius thalami. *Arch Neurol* 1993;50:498–500.

9. Yamamoto T, Katayama Y, Kano T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity. *J Neurosurg* 2004;101:201–209.

10. Yamamoto T, Katayama Y, Fukaya C, Oshima H, Kasai M, Kobayashi K. New method of deep brain stimulation therapy with two electrodes implanted in parallel and side by side. *J Neurosurg* 2001;95:1075–1078.

11. Nagaseki Y, Shibazaki T, Hirai T et al. Long-term follow-up results of selective VIM-thalamotomy. *J Neurosurg* 1986; 65:296–302.

12. Ohye C, Narabayashi H. Physiological study of presumed ventralis intermedius neurons in the human thalamus. *J Neurosurg* 1979;50:290–297.

13. Lenz FA, Normand SL, Kwan HC et al. Statistical prediction of the optimal site for thalamotomy in parkinsonian tremor. *Mov Disord* 1995;10:318–328.

14. Gabriel EM, Nashold BS Jr. Evolution of neuroablative surgery for involuntary movement disorders: an historical review. *Neurosurgery* 1998;42:575–590; discussion 590–591.

15. Schuurman PR, Bosch DA, Bossuyt PM et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000;342:461–468.