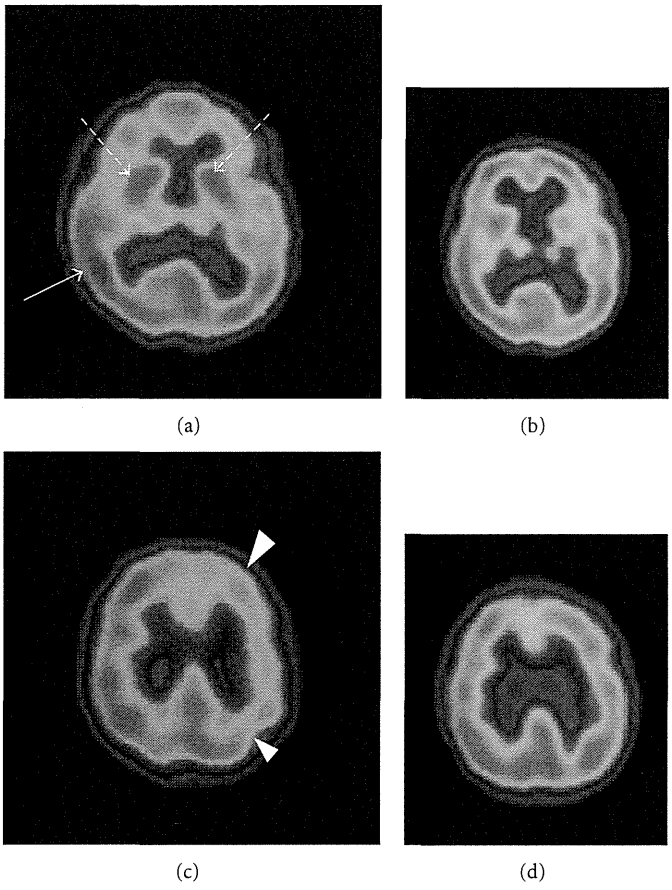

FIGURE 1: 99^{m}-HMPAO-SPECT images acquired during a seizure and 10 days later. (a) and (c) show relative hyperperfusion in the right parietal lobe (arrow) and both thalami (dotted arrows) and relative hypoperfusion in the left prefrontal and parietal lobes (arrow heads) during a seizure. (b) and (d) are the same axial slices as (a) and (c), respectively, obtained 10 days after the final seizure. In (b) and (d), relative hyperperfusion and hypoperfusion are not noted, as bilateral symmetrical cerebral perfusion has been normalized.

her left hand. The patient was treated with oral nonsteroidal anti-inflammatory drugs, but no favorable effects were observed. Her pain worsened, and she consulted our pain clinic 3 months after the second operation. She showed no signs and symptoms of neurological complications, except for pain and allodynia, before and after the cardiovascular surgeries.

During the first examination at our pain clinic, she complained of spontaneous burning pain and severe allodynia from her neck to her hand; her left hand was swollen, pale, and hot. We diagnosed her condition as complex regional pain syndrome (CRPS) [6] and began treatment, although the initiating injury was unknown. Because she was being administered anticoagulant therapy, many of the available neural blockades could not be used, except for a regional intravenous nerve blockade (Bier block, with 20 mL of 0.5% lidocaine). This neural blockade was performed 4 times per week concurrently with oral administration of a tricyclic antidepressant, nortriptyline (20 mg); this treatment resulted in the gradual reduction of pain and allodynia, which allowed the patient to receive physiotherapy. One month after treatment, pain and allodynia symptoms were nearly eliminated and swelling had also diminished. Additionally, her upper limb motor disturbance was significantly improved.

One hour after the 18th Bier block, the patient suddenly experienced a major epileptic seizure and lost consciousness during physiotherapy. This was the first time in the patient's life that a seizure episode had occurred. Intravenous administration of diazepam followed by thiamylal was used to control the seizure. An emergency CT scan of the brain showed no distinct lesions, which was confirmed by magnetic resonance imaging (MRI). The following day, the patient regained consciousness and complained of burning pain and severe allodynia localized in her left upper limb; subsequently, there was a recurrence of other CRPS symptoms (swelling, skin temperature escalation, and paleness). Despite regular intravenous administration of phenytoin, seizures occurred several times over the following 3 days, which occasionally required additional administrations of intravenous diazepam or thiamylal, and consciousness was again lost. When the patient was partially asleep due to intravenous anticonvulsants, she executed escaping movements for noxious stimulations on various healthy body parts but did not respond to noxious and tactile stimulations

on the left upper limb, suggesting an absence of hyperalgesia and allodynia. After 3 days, her consciousness was fully recovered and no seizure episodes occurred. The patient had no further complaints of burning pain or allodynia. SPECT examinations, using 99^{m}-Tc-hexamethyl-propylene amine oxime (HMPAO), were performed during the seizure period and 10 days later (Figure 1). The first image, obtained during a seizure, showed relative hyperperfusion in the right parietal lobe and both thalami and relative hypoperfusion in the left frontal and parietal lobes (Figures 1(a) and 1(c)), which improved after 10 days (Figures 1(b) and 1(d)). Electroencephalography (EEG) examinations were also carried out immediately following a seizure and 2 weeks later. EEG readings immediately following a seizure showed irregular and sporadic spiked waves in the left temporal lobe, followed by spikes in both the temporal lobes. Clinically, the patient showed an intermittent left upper limb spasm, although obvious epileptic discharges were not noted on EEG readings after the 3-day seizure episodes. Although postictal EEG readings occasionally displayed irregular spiked waves in the left posterior parietal and temporal lobes, the patient did not show epileptic symptoms. Clinical symptoms suggested that spiked waves were not related to the intermittent left upper limb spasm. On the basis of the SPECT and EEG findings, our neurologist diagnosed the patient as having temporal symptomatic epilepsy focused in the right parietal lobe. Her recovery was uneventful, and pain and allodynia nearly disappeared, although her skin color remained pale and her hand remained hot.

We obtained her consent to report her progress in accordance with the Declaration of Helsinki.

3. Discussion

The initiating injury causing CRPS symptoms in our patient was unknown. We speculated that an unconfirmed brachial plexus injury induced by a median sternotomy [7] and/or prolonged immobilization by sedative drug administration [8, 9] may have been a trigger. Furthermore, pain and allodynia may have been derived from disturbed cerebral function, possibly related to the use of heart-lung machines on 2 occasions and for many hours, and infectious endocarditis, which can induce epileptic seizures. Ictal pain related to an epileptic seizure has been noted in approximately 3% of reported epilepsy cases, typically involving an entire limb, a part of a limb, or hemibody [10–12]. Ictal allodynia-related epileptic seizures have been reported in only 2 cases, and both were in children [13, 14].

This is the first known case of successfully treated CRPS revived by an epileptic seizure. Following the first seizure, we suspected systemic toxicity of the local anesthetic (lidocaine, 100 mg) applied by Bier block. However, the anesthetic may not have been responsible for the seizures because the first seizure occurred one hour after Bier block, and the patient did not present symptoms of systemic toxicity to local anesthetics (e.g., change in speech pattern, lightheadedness, dizziness, or agitation) before the seizure, and seizures recurred several times for 3 days following Bier block cessation. The patient's SPECT and EEG abnormal findings were primarily concentrated to the temporal and parietal lobes, whereas epileptic discharges induced by systemic toxicity of local anesthetics are known to generally originate from nonspecific regions of the brain. The patient was therefore diagnosed with temporal symptomatic epilepsy.

A previous report of a brain tumor case suggested that epileptic discharges involved in the main pain pathways (i.e., primary and secondary somatosensory cortices (SI, SII), insula, and amygdale) can cause ictal pain and allodynia [13]. A congenital epilepsy case report suggested that deregulation of pain control established by relative hypoperfusion in the thalamus may play an important role in causing ictal pain and allodynia [14]. Furthermore, acute CRPS is reported to be related to hyperperfusion in the thalamus [15]. On the basis of these findings, we considered that the epileptic discharges noted on the EEG readings and subsequent hyper- and hypoperfusion in the specific brain regions, as revealed by 99^{m}-HMPAO SPECT, originated from the right parietal lobe, which includes the two main pain pathway regions (i.e., SI and SII); hyperfusion and hypofusion then spread over the entire brain, including other regions in the pain pathways (i.e., thalamus, anterior cingulate cortex, insula, and amygdala), during the seizure. This abnormal brain condition likely resulted in pain and allodynia. Further, recent advancements in functional brain imaging revealed that the anterior insula, which is strongly associated with autonomic nervous function, is reorganized in CRPS patients [16]. For our patient, abnormal autonomic-like symptoms (i.e., edema, skin discoloration, and skin temperature asymmetry) were revived by epileptic seizures. This may be related to reorganization of autonomic cerebral regions. In the present case, the second episode of CRPS symptoms occurred immediately after the first epileptic seizure episode and then rapidly disappeared with the control of epileptic discharges, although we administered antiepileptic medications, which has little potential to improve neuropathic pain. We therefore concluded that epileptic discharges relapsed into CRPS. Alternatively, we speculate that repeated seizures contributed to improvement of the second bout of CRPS symptoms. For epileptic seizure and pain relief, it has been reported that electroconvulsive therapy (ECT) can be used as an alternative treatment for chronic neuropathic pain [17]. In ECT, epileptic seizures are necessary for pain relief, as fewer seizures are related to a reduced analgesic effect. A possible mechanism of ECT for pain relief may involve alteration of neurotransmitter levels in cerebrospinal fluid, resulting in pain perception modulation. Therefore, we cannot completely rule out the possibility that repeated seizure episodes may have improved the second occurrence of CRPS symptoms.

In conclusion, the present case suggests that a pathophysiological condition(s), such as epileptic discharge and/or abnormal brain perfusion, can repeatedly trigger ictal pain, allodynia, and other signs and symptoms of CRPS when brain regions participating in pain perception have been sensitized. However, why abnormal autonomic-like symptoms of CRPS remain after controlling epileptic discharges and improvement of pain and allodynia is unclear.

4. Conclusion

We present a case of CRPS in which the symptoms of burning pain and severe allodynia were once resolved but returned following an epileptic seizure. These symptoms disappeared following the control of epileptic discharges. This suggests that CRPS symptoms may be sustained by abnormall brain conditions, and our results contribute to the understanding of how the CNS participates in maintaining pain and allodynia associated with CRPS.

Acknowledgments

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References

[1] W. Jänig and R. Baron, "Complex regional pain syndrome: mystery explained?" *Lancet Neurology*, vol. 2, no. 11, pp. 687–697, 2003.

[2] T. J. Coderre, D. N. Xanthos, L. Francis, and G. J. Bennett, "Chronic post-ischemia pain (CPIP): a novel animal model of complex regional pain syndrome-Type I (CRPS-I; reflex sympathetic dystrophy) produced by prolonged hindpaw ischemia and reperfusion in the rat," *Pain*, vol. 112, no. 1-2, pp. 94–105, 2004.

[3] R. Baron and C. Maier, "Reflex sympathetic dystrophy: skin blood flow, sympathetic vasoconstrictor reflexes and pain before and after surgical sympathectomy," *Pain*, vol. 67, no. 2-3, pp. 317–326, 1996.

[4] R. N. Harden, T. A. Duc, T. R. Williams, D. Coley, J. C. Cate, and R. H. Gracely, "Norepinephrine and epinephrine levels in affected versus unaffected limbs in sympathetically maintained pain," *Clinical Journal of Pain*, vol. 10, no. 4, pp. 324–330, 1994.

[5] R. H. Gracely, S. A. Lynch, and G. J. Bennett, "Painful neuropathy: altered central processing maintained dynamically by peripheral input," *Pain*, vol. 51, no. 2, pp. 175–194, 1992.

[6] M. Sumitani, M. Shibata, G. Sakaue, and T. Mashimo, "Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population," *Pain*, vol. 150, no. 2, pp. 243–249, 2010.

[7] B. Ben-David and S. Stahl, "Prognosis of intraoperative brachial plexus injury: a review of 22 cases," *British Journal of Anaesthesia*, vol. 79, no. 4, pp. 440–445, 1997.

[8] A. J. Terkelsen, F. W. Bach, and T. S. Jensen, "Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia," *Anesthesiology*, vol. 109, no. 2, pp. 297–307, 2008.

[9] H. P. Singh and T. R. C. Davis, "The effect of short-term dependency and immobility on skin temperature and colour in the hand," *Journal of Hand Surgery*, vol. 31, no. 6, pp. 611–615, 2006.

[10] W. T. Blume, D. C. Jones, G. B. Young, J. P. Girvin, and R. S. McLachlan, "Seizures involving secondary sensory and related areas," *Brain*, vol. 115, no. 5, pp. 1509–1520, 1992.

[11] G. B. Young and W. T. Blume, "Painful epileptic seizures," *Brain*, vol. 106, no. 3, pp. 537–554, 1983.

[12] F. Mauguiere and J. Courjon, "Somatosensory epilepsy," *Brain*, vol. 101, no. 2, pp. 307–332, 1978.

[13] L. Kocher, L. Rambaud, C. Rousselle, C. Mottolese, P. Ryvlin, and P. M. Gonnaud, "Painful seizures with allodynia in an 11-year-old boy," *Developmental Medicine and Child Neurology*, vol. 41, no. 10, pp. 704–707, 1999.

[14] S. Tanaka, S. I. Osari, M. Ozawa et al., "Recurrent pain attacks in a 3-year-old patient with myoclonus epilepsy associated with ragged-red fibers (MERRF): a single-photon emission computed tomographic (SPECT) and electrophysiological study," *Brain and Development*, vol. 19, no. 3, pp. 205–208, 1997.

[15] M. Fukumoto, T. Ushida, V. S. Zinchuk, H. Yamamoto, and S. Yoshida, "Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome," *Lancet*, vol. 354, no. 9192, pp. 1790–1791, 1999.

[16] P. Y. Geha, M. N. Baliki, R. N. Harden, W. R. Bauer, T. B. Parrish, and A. V. Apkarian, "The brain in chronic CRPS pain: abnormal gray-white matter interactions in emotional and autonomic regions," *Neuron*, vol. 60, no. 4, pp. 570–581, 2008.

[17] J. R. Bloomstein, T. A. Rummans, T. Maruta, S. C. Lin, and T. S. Pileggi, "The use of electroconvulsive therapy in pain patients," *Psychosomatics*, vol. 37, no. 4, pp. 374–379, 1996.

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ORIGINAL ARTICLE

Human brain activity associated with painful mechanical stimulation to muscle and bone

Lynn Maeda · Mayu Ono · Tetsuo Koyama · Yoshitetsu Oshiro · Masahiko Sumitani · Takashi Mashimo · Masahiko Shibata

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Abstract
Purpose The purpose of this study was to elucidate the central processing of painful mechanical stimulation to muscle and bone by measuring blood oxygen level-dependent signal changes using functional magnetic resonance imaging (fMRI).
Methods Twelve healthy volunteers were enrolled. Mechanical pressure on muscle and bone were applied at the right lower leg by an algometer. Intensities were adjusted to cause weak and strong pain sensation at either target site in preliminary testing. Brain activation in response to mechanical nociceptive stimulation targeting muscle and bone were measured by fMRI and analyzed.
Results Painful mechanical stimulation targeting muscle and bone activated the common areas including bilateral insula, anterior cingulate cortex, posterior cingulate cortex, secondary somatosensory cortex (S2), inferior parietal lobe, and basal ganglia. The contralateral S2 was more activated by strong stimulation than by weak stimulation. Some areas in the basal ganglia (bilateral putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.
Conclusions The putamen and caudate nucleus may have a more significant role in brain processing of muscle pain compared with bone pain.

Keywords Pain · Muscle · Bone · Neuroimaging · fMRI

L. Maeda
Department of Anesthesia and Pain Medicine, Nishinomiya Municipal Central Hospital, Nishinomiya, Japan

L. Maeda · T. Mashimo
Department of Anesthesiology and Intensive Care Medicine, Osaka University Graduate School of Medicine, Suita, Japan

M. Ono
Department of Anesthesia, Ikeda City Hospital, Ikeda, Japan

T. Koyama
Department of Rehabilitation, Kyoritsu Neurosurgery Hospital, Nishinomiya, Japan

Y. Oshiro
Himeji Ishikawa Functional Brain Imaging Laboratory, Himeji, Japan

M. Sumitani
Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, Tokyo, Japan

M. Shibata (✉)
Department of Pain Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: mshibata@pain.med.osaka-u.ac.jp

Introduction

Physical pain originating from deep tissues—including sprains, fibromyalgia, rheumatic polymyalgia, and other muscle-derived pain, and bone-derived pain such as fractures, spondylosis, and bone tumors—is very commonly encountered. Consequently, understanding how these conditions come to be painful through brain processing is clinically important. Recent imaging research using the blood oxygen level-dependent-based (BOLD) functional magnetic resonance imaging (fMRI) method successfully revealed cognitive mechanisms in response to painful stimulation.

In the field of anesthesiology, fMRI has been on trial as a tool for investigating cerebral pain processing [1–5]. Previous reports, however, have mainly been studies of

heat stimulation to skin [6, 7]. More recently, studies targeting brain activation when muscle pain is caused using electric stimulation or hypertonic saline have successfully demonstrated that some areas are differently activated, including the contralateral primary somatosensory cortex (S1), the ipsilateral anterior insula, the contralateral motor cortex, the cingulate motor area, and the perigenual cingulate [8–10]. However, there are few studies of the brain processing activated by mechanical stimulation to deep tissues [11]. To elucidate the central processing of painful mechanical stimulation to deep tissues (muscle and bone), we compared the brain activation induced by two different intensities of stimulation (strong and weak) at two different targets (muscle and bone), using fMRI.

Materials and methods

Subjects

All the procedures were approved by the Osaka University Hospital Institutional Review Board. Twelve healthy volunteers (7 men, 5 women; aged 24–56 years) agreed to receive painful stimulation while their brain activation was evaluated. They had no neurological disorders or detectable MRI abnormalities in the brain and were free from any medication within 24 h before the study. In written informed consent, each acknowledged that they were willing to receive experimental painful stimulation. Before the protocols were carried out, each volunteer was familiarized with the experimental protocol, the types of stimulation, and the tasks performed.

Painful stimulation

To determine suitable stimulation intensities for each subject, a preliminary testing was performed immediately before the fMRI study. Perpendicularly applying a round 10-mm solid tip of an algometer probe (Pressure Algometer NPA-1, Shinko, Japan) on the surface (skin) at the medial point of the right tibia (Fig. 1), the experimenter gradually increased the pressure until the subject verbally indicated that the stimulation was painful. At that point, the pain intensity was taken to be '3' on a subjective 10-point numerical rating scale (NRS). The three median values of five trials were averaged to determine the weak stimulation to be applied to the tibia of particular volunteers. Similarly, the subject was asked to verbally indicate when the pain was such that it would probably be intolerable for more than 20 s without withdrawal movement. At this point, pain intensity was scored as '8' on the volunteer's subjective 10-point NRS. Similar grading of muscle pain was also carried out [12]. Here the tip of the probe was applied to the skin on the gastrocnemius muscle at a medial point 3–5 cm from the stimulation point of the tibia (Fig. 1). For each volunteer, as in the bone protocol, subjective NRS pain scores of '3' and '8' were obtained. These procedures were conducted by one experimenter (M.S.) who, in each instance and so far as possible, endeavored to consistently apply the required level of pressure perpendicularly.

Protocol

Each subject participated in a trial comprising 12 fMRI task sessions. At each right-leg site that was evaluated in the preliminary testing, three trials of 20 s of strong or weak stimulation were applied in each session. The site and strength of stimulation were pseudo random for each series. After each series of three stimulations (in a session lasting 3 min; Fig. 2), there was a pause of 1 min before the next session. MRI scans were acquired throughout the 36-min period. The subjects were asked to rate, using NRS, the overall pain at the end of each series of three stimulations (mean of three periods of 20-s stimulation). Before the

Fig. 1 Photograph showing how a digital algometer was used to apply stimulation to muscle (*left*) and bone (*right*). Bone stimulation was applied to the surface (skin) at the midpoint of tibia. Muscle stimulation was applied to the surface of gastrocnemius 3–5 cm posterior from bone stimulation point. Intensities of stimulation (muscle vs. bone, strong vs. weak) were decided for each subject by averaging the values of the median of three of five trials

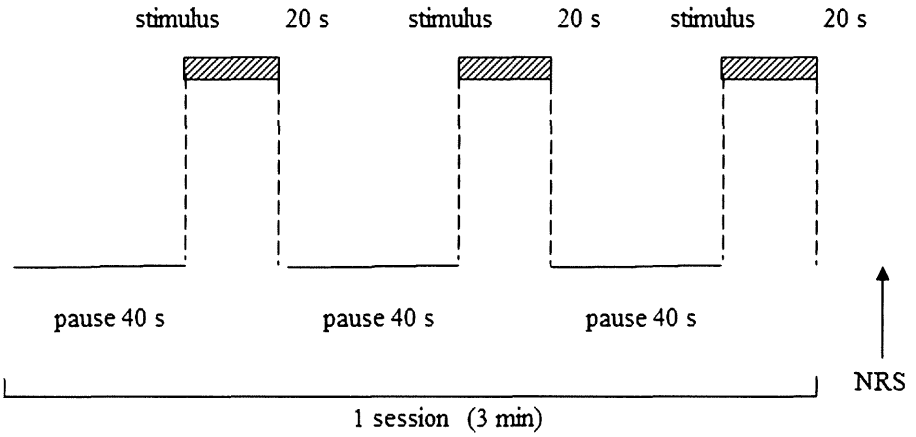

Fig. 2 Schematic representation of the experiment. Each subject underwent one trial comprising 12 sessions with a 1-min interval between sessions. Each session, lasting a total of 3 min, started with 40-s pause, and then a 20-s strong or weak stimulation to either muscle or bone. Weak and strong stimulations for each volunteer were decided in the preliminary testing. The order of stimulation was pseudo randomized. After each session, volunteers were asked to score the perceived pain. *NRS* numerical rating scale

commencement of the protocol, each volunteer was informed that the site (muscle or bone) and intensity (weak or strong) of the forthcoming series of stimulation would be random.

MRI

Imaging was performed with a 1.5-T MRI scanner (Signa EXCITE XI 11.0; GE Healthcare, Milwaukee, WI, USA). Functional MR images were obtained using a multislice echo planar imaging technique (EPI) based on 30 oblique slices (repetition time, 3,000 ms; time to echo, 60 ms; flip angle, 90°; slice thickness, 5 mm; gap, 0 mm; field of view, 300 mm × 300 mm; in-plane resolution, 4.69 mm × 4.69 mm). All the subjects were positioned in the scanner with a foam rubber pad to minimize head movement and instructed simply to lie with their eyes closed without moving or speaking. Their heads were placed so that the uppermost superior aspect of brain was within the field of view. High-resolution T_1-weighted anatomic images with the same orientation as the EPI slices were collected from each subject. In the subsequent analysis, these images were used for coregistration of functional and anatomic data.

Data analysis

Psychophysics

Using paired *t* testing, we compared the stimulation intensity and the average subjective NRS scores for muscle (weak and strong) and bone (weak and strong), respectively. Effects of order of stimulus application on NRS were evaluated with two-way analysis of variance (ANOVA); $P < 0.05$ was regarded as significant. Values are given as mean ± SD.

fMRI data analysis

The fMRI data were analyzed with Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.1 (Mathworks, Sherborn, MA, USA). The functional images were realigned to correct for head movements, coregistered with each subject's anatomic MRI, and transformed to the format of the standard brain according to Talairach coordinates [13]. The functional images were spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel. We fitted a linear regression model (fixed effects within subjects). Each condition was modeled with a boxcar function and convolved with a hemodynamic response function. Temporally, the voxel time series were high-pass filtered (124-s cutoff periods) to remove slow trends in the data, and low-pass filtered with a hemodynamic response filter.

We compared image data for each group—weak muscle stimulation, strong muscle stimulation; weak bone stimulation, strong bone stimulation—against the data from each resting condition, respectively. All the data were pooled for group statistical comparisons. Across the subjects, random effect analysis was performed to determine the significant activation associated with different sites and intensities of stimulation ($P < 0.001$ uncorrected; minimum cluster size, 20 voxels). To investigate the brain network related to painful stimulation intensity, we calculated the difference in the areas activated by strong stimulation minus weak stimulation (paired *t* test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels). To identify the brain areas that are differently activated by muscle and bone stimulation, we also analyzed the data separately (strong muscle minus strong bone; weak muscle minus weak bone; and all

together) (paired t test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels).

Results

Stimulation and pain intensity

The mean intensity of muscle stimulation was 21.1 ± 8.4 N for weak stimulation and 40.7 ± 7.8 N for strong stimulation; the mean intensity of bone stimulation was 14.2 ± 5.7 N for weak stimulation and 30.1 ± 7.9 N for strong stimulation. The NRS scores with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation, respectively ($P < 0.05$ for both) (Table 1). All the volunteers clearly distinguished the two intensities of stimulation because the weaker stimulation was always scored lower. Although the volunteers found weak muscle stimulation trials more painful ($P < 0.05$) than weak bone stimulation, no similar difference was found for strong stimulations. Comparing the data among the three trials of the same intensity at the same site, no differences in NRS scores were found; this indicates that repeated mechanical stimulation did not sensitize or desensitize the volunteers ($P > 0.05$).

fMRI

In response to painful muscle stimulation, brain activation was apparent within the bilateral anterior cingulate cortex (ACC), insula cortex, the secondary somatosensory cortex (S2), the inferior parietal lobule (IPL), the posterior cingulate cortex (PCC), putamen, the ipsilateral dorsolateral prefrontal cortex (DLPFC), thalamus, caudate, and the contralateral claustrum (Fig. 3a,b; Table 2). In response to painful bone stimulation, brain activation was also apparent within the bilateral ACC, the IPL, the S2, the PCC, the ipsilateral DLPFC, and the contralateral claustrum (Fig. 4a,b; Table 2). Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space and Z-scores (>6.00) for the activated brain regions by muscle and bone pain are shown in Table 2. Differences in the areas activated by strong versus weak muscle stimulation were mainly found in the contralateral S2 and the bilateral thalamus (Fig. 3c). For strong versus weak bone stimulation, the difference was found in the contralateral S2 (Fig. 4c). With weak stimulations, the activation differences between muscle and bone stimulation were apparent in the bilateral caudate nucleus and contralateral Brodmann areas 22 and 45 (Fig. 5a). With strong stimulations, the activation differences were apparent in the bilateral putamen, the ipsilateral ACC, and the contralateral claustrum (Fig. 5b). Analyzing the sum of the differences between muscle- and bone-related pain revealed that activation was different in the bilateral caudate and contralateral putamen (Fig. 5c; Table 3).

Discussion

In this study, as an initial step toward elucidating the brain activation associated with mechanically induced deep tissue pain, we found that the contralateral S2 was more activated by stronger stimulations to muscle or bone. We also found that parts of the basal ganglia (putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.

Psychophysics

The NRS scores measured during fMRI were higher than those determined in the preliminary testing. Although the reason is not clear, the difference of the rate of pressure increase between preliminary testing and the fMRI session may be a cause.

On the other hand, the NRS scores for the two sets of three stimulations at each site did not change during the protocol (see Table 1), suggesting that no further change in sensitivity occurred. Nie et al. [14] have reported that after

Table 1 Numerical rating scale (0–10 NRS) by mechanical stimulation

	1st stimulation	2nd stimulation	3rd stimulation	mean
weak muscle stimulation	4.83±1.99	4.67±1.88	4.5±1.98	4.67±1.90
strong muscle stimulation	8.17±1.34	8.5±1.17	8.25±1.42	8.31±1.28
weak bone stimulation	4.25 ±2.14	3.25 ±1.14	3.92 ±1.78	3.81±1.74
strong bone stimulation	8.83 ±1.03	8.25 ±1.36	8.17 ±1.70	8.42 ±1.38

NRS with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation (*$P < 0.05$). In weak stimulations, NRS with muscle stimulation was higher than with bone stimulation (**$P < 0.05$). There were no differences between strong muscle and bone stimulations among NRS with 1st, 2nd, and 3rd stimulation in the same study groups

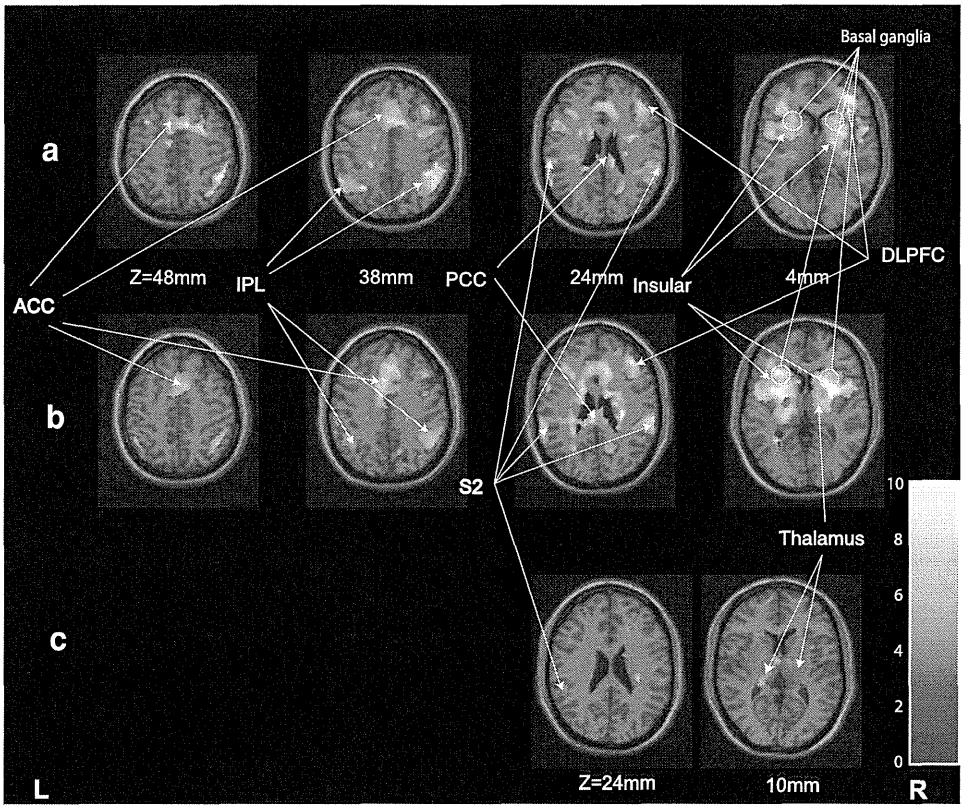

Fig. 3 Brain activation induced by muscle stimulation: weak stimulation (**a**), strong stimulation (**b**), and contrast of strong and weak stimulation (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.001$ (**a**, **b**, uncorrected), and $P < 0.005$ (**c**, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *ACC* anterior cingulate cortex; *IPL* inferior parietal lobule; *S2* secondary sensory cortex; *DLPFC* dorsolateral prefrontal cortex; *PCC* posterior cingulate cortex

ten stimulations with 30-s intervals between stimulations, subjects gave higher VAS scores, increasing to 192% ± 71% for stimulation of the tibia and to 117% ± 42% for stimulation of the tibia anterior muscle. In the present study, the protocol specified a 60-s interval during all the sessions. This interval was apparently long enough to prevent temporal sensitization. To evoke equivalent pain in muscle and bone, greater stimulation had to be applied largely to the muscle; this may be because nociceptive nerve density is greater in the periosteum than in muscle [15].

Imaging

A previous positron emission tomography (PET) study and event-related fMRI study using noxious electronic stimulation of muscle showed activation in the ACC, S2, and anterior insula [8, 10]. Also, PET and fMRI study using injection of hypertonic saline into muscle evoked the activation in contralateral insula and putamen [9, 16]. In our study, the results for mechanical stimulation are consistent with the previous muscle pain studies, which have shown that the different types of stimulation (hypertonic saline, electrical stimulation, and mechanical stimulation) applied to muscle induce equivalent activation patterns [8, 10, 16]. We found that stronger muscle stimulation resulted in greater activation in the contralateral S2, the bilateral thalamus (contralateral > ipsilateral), and that stronger bone stimulation caused greater activation in the contralateral S2. In each case, the contralateral S2 was more activated by strong stimulation. However, caution is needed in interpreting these results because greater application of the force to skin is also involved during strong stimulation. The activation of the contralateral S2 may also come from greater cutaneous stimulation. In a PET study investigating thermal stimulation to skin, Coghill et al. [17] have shown that the ipsilateral cerebellum, the contralateral S1, the supplementary motor area, the bilateral S2, the lentiform nucleus, the insular cortex, and the thalamus and ACC are more activated depending on perceived pain intensity. In an fMRI study, using mechanical phasic stimulation on the skin, Ringler et al. [18] have shown that the contralateral S2 is more activated by stronger stimulation. The contralateral S2 may take part in processing pain intensity derived from both skin and deep tissues.

Comparison of the activation associated with muscle and bone stimulation revealed that caudate nucleus and putamen were more activated by muscle than by bone stimulation. No activation existed that was evoked by (bone > muscle) stimulation (data not shown). The activation in these areas is supposed to be related to stimulated sites (muscle or bone), not to stimulation or pain intensity, because these areas were not included as a contrast when we stimulated the single target (muscle or bone) with the

Table 2 Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space and Z-scores (>6.00) for the activated brain regions by muscle and bone pain

Region	BA	Muscle pain				BA	Bone pain			
		Peak voxel coordinate			Z-score		Peak voxel coordinate			Z-score
		x	y	z			x	y	z	
ACC	32	−8	12	44	7.07					
	32	−6	18	32	6.42					
	32	−12	26	30	6.42					
Insula right	13	28	26	2	6.33					
		34	4	8	6.09					
Insula left		−34	6	8	6.25	44	−48	10	6	6.27
	47	−28	24	−8	6.05					
S2 right	40	62	−32	30	6.32					
S2 left	40	−60	−32	28	6.39					
IPL left						40	−48	−52	40	6.57
	40	−48	−58	42	6.33	40	−48	−40	28	6.48
	40	−44	−48	42	6.13	40	−62	−36	32	6.27
Thalamus right		20	−18	10	6.04					
Putamen right		26	2	6	6.16					
		20	−4	8	6.10					
Putamen left		−32	6	6	6.54					
Claustrum left		−26	12	10	6.39		−30	10	6	6.18
Caudate right		16	12	8	6.13					

Brodmann areas are given where available

BA Broadmann area, *ACC* anterior cingulate cortex, *S2* secondary sensory cortex, *IPL* inferior parietal lobule

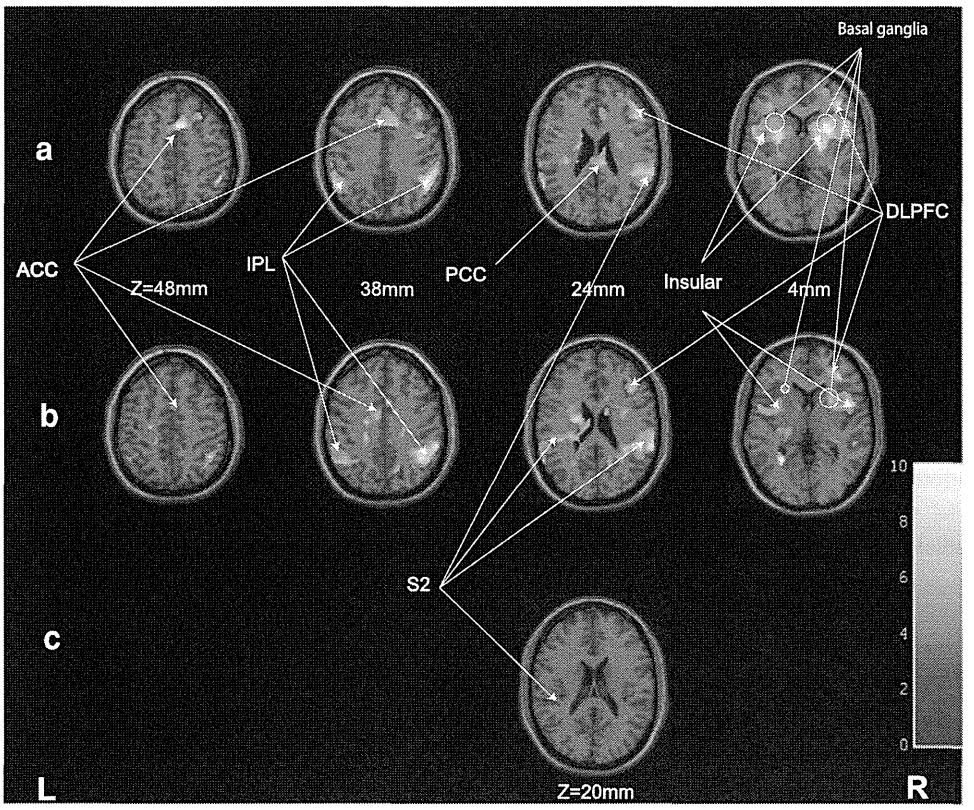

Fig. 4 Brain activation induced by bone stimulation: weak stimulation (**a**), strong stimulation (**b**), and contrast of strong and weak stimulation (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.001$ (**a**, **b**, uncorrected), and $P < 0.005$ (**c**, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *ACC* anterior cingulate cortex; *IPL* inferior parietal lobule; *S2* secondary sensory cortex; *DLPFC* dorsolateral prefrontal cortex; *PCC* posterior cingulate cortex

different intensities. Additionally, pain intensities were identical between strong muscle and strong bone pain. Reports of the previous pain imaging studies have suggested that the putamen is activated by nociceptive stimulation [17, 19], including muscle pain with hypertonic saline [16]. Basal ganglia are reported to have a role in

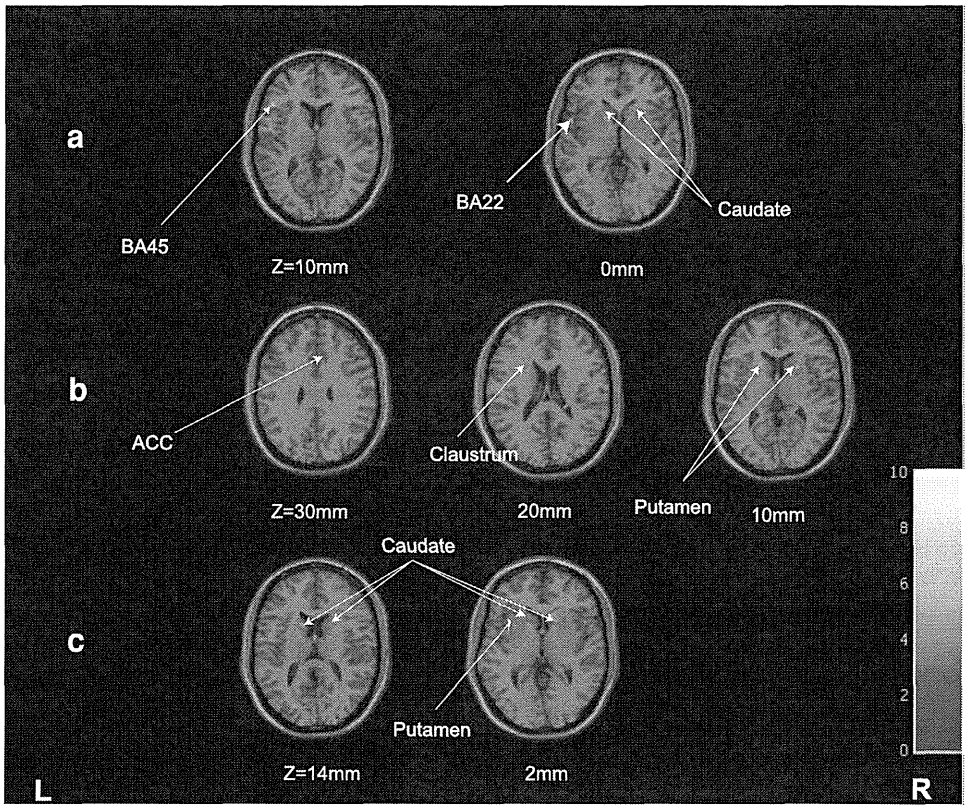

Fig. 5 Contrast of brain activation induced by muscle and bone stimulation: contrast of weak stimulation to muscle and bone (**a**), contrast of strong stimulation to muscle and bone (**b**), and contrast of all the stimulations to muscle and bone (**c**). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (*left*) to ventral (*right*). Statistical map thresholds are $P < 0.005$ (uncorrected, paired test). Minimum cluster size is 20 voxels. Right (*R*) and left (*L*) sides are indicated. *BA* Brodmann area; *ACC* anterior cingulate cortex

Table 3 Peak coordinates (*x*, *y*, *z*) in Montreal Neurological Institute (MNI) space and *Z*-scores for activated brain regions by muscle–bone pain

Region	(Muscle–bone) pain			
	Peak voxel coordinate			*Z*-score
	x	*y*	*z*	
Putamen left	−24	12	24	4.12
Caudate left	−18	16	8	4.01
Caudate right	16	22	0	3.95

motor preparation, movement control, and emotional, motivational, and cognitive function [20–22]. Processing in the putamen and caudate nucleus is also reported to be related to pain-avoidance behavior [23]. Our results suggest that the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared with bone pain.

Conclusion

In conclusion, the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared to bone pain.

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Conflict of interest None.

References

1. Hoffman HG, Richards TL, Van Oostrom T, Coda BA, Jensen MP, Blough DK, Sharar SR. The analgesic effects of opioids and immersive virtual reality distraction: evidence from subjective and functional brain imaging assessments. Anesth Analg. 2007;105:1776–83.
2. Buvanendran A, Ali A, Stoub TR, Berger RA, Kroin JS. The use of brain positron emission tomography to identify sites of postoperative pain processing with and without epidural analgesia. Anesth Analg. 2007;105:1784–6.
3. Liu SS, Brown EN. Will seeing become believing? Anesth Analg. 2007;105:1526–7.
4. Lorenz IH, Egger K, Schubert H, Schnurer C, Tiefenthaler W, Hohlrieder M, Schocke MF, Kremser C, Esterhammer R, Ischebeck A, Moser PL, Kolbitsch C. Lornoxicam characteristically modulates cerebral pain-processing in human volunteers: a functional magnetic resonance imaging study. Br J Anaesth. 2008;100:827–33.

5. Kurata J. A potential role of functional magnetic resonance imaging in the diagnosis of pain. Jpn J Anesthesiol. 2009;58: 1350–9. (in Japanese with English abstract).
6. Seifert F, Jungfer I, Schmelz M, Maihofner C. Representation of UV-B-induced thermal and mechanical hyperalgesia in the human brain: a functional MRI study. Hum Brain Mapp. 2008; 29:1327–42.
7. Borsook D, Moulton EA, Tully S, Schmahmann JD, Becerra L. Human cerebellar responses to brush and heat stimuli in healthy and neuropathic pain subjects. Cerebellum. 2007;22:1–21.
8. Niddam DM, Yeh TC, Wu YT, Lee PL, Ho LT, Arendt-Nielsen L, Chen AC, Hsieh JC. Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. Neuroimage. 2002;17:1437–50.
9. Henderson LA, Bandler R, Gandevia SC, Macefield VG. Distinct forebrain activity patterns during deep versus superficial pain. Pain. 2006;120:286–96.
10. Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL. Cerebral processing of acute skin and muscle pain in humans. J Neurophysiol. 1997;78:450–60.
11. Kobayashi Y, Kurata J, Sekiguchi M, Kokubun M, Akaishizawa T, Chiba Y, Konno S, Kikuchi S. Augmented cerebral activation by lumbar mechanical stimulus in chronic low back pain patients: an FMRI study. Spine. 2009;34:2431–6.
12. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46:1333–43.
13. Talairach J, Tournoux P. Co-planar stereotactic atlas of the human brain: 3-dimensional proportional system—an approach to cerebral imaging. New York: Thieme; 2002.
14. Nie H, Arendt Nielsen L, Andersen H, Graven Nielsen T. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. J Pain. 2005;6:348–55.
15. Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, Keyser CP, Clohisy DR, Adams DJ, O'Leary P, Mantyh PW. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. Neuroscience. 2002;113:155–66.
16. Korotkov A, Radovanovic S, Ljubisavljevic M, Lyskov E, Kataeva G, Roudas M, Pakhomov S, Thunberg J, Medvedev S, Johansson H. Comparison of brain activation after sustained non-fatiguing and fatiguing muscle contraction: a positron emission tomography study. Exp Brain Res. 2005;163:65–74.
17. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol. 1999;82:1934–43.
18. Ringler R, Greiner M, Kohlloeffel L, Handwerker HO, Forster C. BOLD effects in different areas of the cerebral cortex during painful mechanical stimulation. Pain. 2003;105:445–53.
19. Bingel U, Glascher J, Weiller C, Buchel C. Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study. Cereb Cortex. 2004;14:1340–5.
20. Doyon J, Bellec P, Amsel R, Penhune V, Monchi O, Carrier J, Lehericy S, Benali H. Contributions of the basal ganglia and functionally related brain structures to motor learning. Behav Brain Res. 2009;199:61–75.
21. Marchand WR. Cortico-basal ganglia circuitry: a review of key research and implications for functional connectivity studies of mood and anxiety disorders. Brain Struct Funct. 2010;215:73–96.
22. Grahn JA, Parkinson JA, Owen AM. The role of the basal ganglia in learning and memory: neuropsychological studies. Behav Brain Res. 2009;199:53–60.
23. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain. 1995;60:3–38.

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Case Report

Oral Local Anesthesia Successfully Ameliorated Neuropathic Pain in an Upper Limb Suggesting Pain Alleviation through Neural Plasticity within the Central Nervous System: A Case Report

Jun Hozumi,[1] Masahiko Sumitani,[1] Arito Yozu,[2] Toshiya Tomioka,[1] Hiroshi Sekiyama,[1] Satoru Miyauchi,[3] and Yoshitsugu Yamada[1]

[1] *Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[2] *Department of Rehabilitation Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[3] *Kobe Advanced ICT Research Center, National Institute of Information and Communications Technology, Kobe 651-2492, Japan*

Correspondence should be addressed to Masahiko Sumitani, sumitanim-ane@h.u-tokyo.ac.jp

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Neural blockades are considered an alternative to pharmacotherapy for neuropathic pain although these blockades elicit limited effects. We encountered a patient with postbrachial plexus avulsion injury pain, which was refractory to conventional treatments but disappeared temporarily with the administration of the local anesthetic lidocaine around the left mandibular molar tooth during dental treatments. This analgesic effect on neuropathic pain by oral local anesthesia was reproducible. Under conditions of neuropathic pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain has been observed. Either expansion or shrinkage of the somatotopic representation of a deafferentated body part correlates with the degree of neuropathic pain. In our case, administration of an oral local anesthetic shrank the somatotopic representation of the mouth, which is next to the upper limb representation and thereby expanded the upper limb representation in a normal manner. Consequently, oral local anesthesia improved the pain in the upper limb. This case suggests that pain alleviation through neural plasticity within the brain is related to neural blockade.

1. Introduction

Neuropathic pain typically appears following peripheral nerve injury due to neuropathies, plexopathies, and trauma to selected sites within the central nervous system (CNS). Recently, evidence-based recommendations of pharmacological treatments for neuropathic pain have been proposed based on both positive and negative results from multiple randomized controlled trials. However, approximately 10–15% of all neuropathic pain patients are refractory to pharmacotherapy. For these cases, more invasive pain-management interventions, such as intrathecal drug delivery, neurostimulation, or neural blockade, may be used. Ideally, blocking neural transmission, either temporarily by using local anesthetics or permanently by surgical nerve ablation, can reduce neuropathic pain; however, no neural blockades have been found to be consistently successful [1]. Here, we report on a case of a patient with postbrachial plexus avulsion injury pain whose neuropathic pain had been refractory to several evidence-based pharmacotherapies and interventions, such as spinal cord stimulation, cervical epidural blockade, and brachial plexus blockade. His pain could be well controlled by oral local anesthesia, suggesting pain alleviation through neural plasticity within the CNS.

2. Case Report

A 49-year-old man, who had a left brachial plexus avulsion injury 10 years before, experienced severe neuropathic pain in his left upper limb immediately after the trauma. The patient complained of continuous burning, pressing, and

tingling pain in the upper limb. From the beginning of the perception of the pain in his upper limb, he felt illusory perceptions of fingers touching his face although he did not perceive pain or any other sensory deficits in the face. He had been treated several times for the pain through left brachial plexus blockades and cervical epidural blockades, with no success. His neuropathic pain decreased slightly when taking pregabalin and with the application of cervical spinal cord stimulation (SCS), but it remained severe. He did not have any pain or trigger areas in the face getting caries of the teeth. He once underwent a dental treatment for his left mandibular molar tooth. When local anesthesia was applied around the left mandibular molar tooth (3 mL, 0.5% lidocaine), he felt the enlargement of that region, which was followed by an immediate disappearance of his neuropathic pain. At that time, the illusory finger sensations in the face disappeared. Approximately 2 hours after the dental treatment, the neuropathic pain returned and gradually increased to predental treatment levels. A nonsteroidal anti-inflammatory drug, loxoprofen, completely ameliorated the dental pain but was not effective against the neuropathic pain. Since then, the patient had 3 dental treatments, and local anesthesia around the left molar tooth consistently ameliorated his neuropathic pain. Analgesic effects consistently lasted for several hours following the administration of the local anesthesia. His neuropathic pain was able to be mildly controlled by a combination of pregabalin, SCS, and local anesthesia around the left molar tooth although the molar tooth had completely improved. The use of oral local anesthesia for breakthrough neuropathic pain had been especially effective.

We obtained the patient's consent to report his progress, in accordance with the Declaration of Helsinki.

3. Discussion

Under conditions of neuropathic pain, particularly for deafferentation pain following massive nerve injury, such as postamputation phantom limb pain, postbrachial plexus injury pain, or postspinal cord injury pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain is observed. Following deafferentation of an upper limb by nerve injury, the somatotopic region corresponding to the upper limb in the sensorimotor cortices shrinks, and the somatotopic region responding to the facial region, which is located next to the upper limb, expands (Figure 1(a)) [2, 3]. The degree of shrinkage of the upper limb representation correlated linearly with the severity of the neuropathic pain [4]. Further, expansion of the somatotopic representation of the affected body part correlated with pain alleviation through neurorehabilitation techniques [5–7]. Therefore, somatotopic reorganization in the sensorimotor cortices closely relates to pathophysiological mechanisms underlying neuropathic pain and its alleviation.

Concerning the somatotopic reorganization of the face and hand regions, the overlapping of these regions can sometimes induce the following illusion in patients with a deafferentation of a hand: touching the face creates obvious referred sensation of fingers in the face as if the fingers

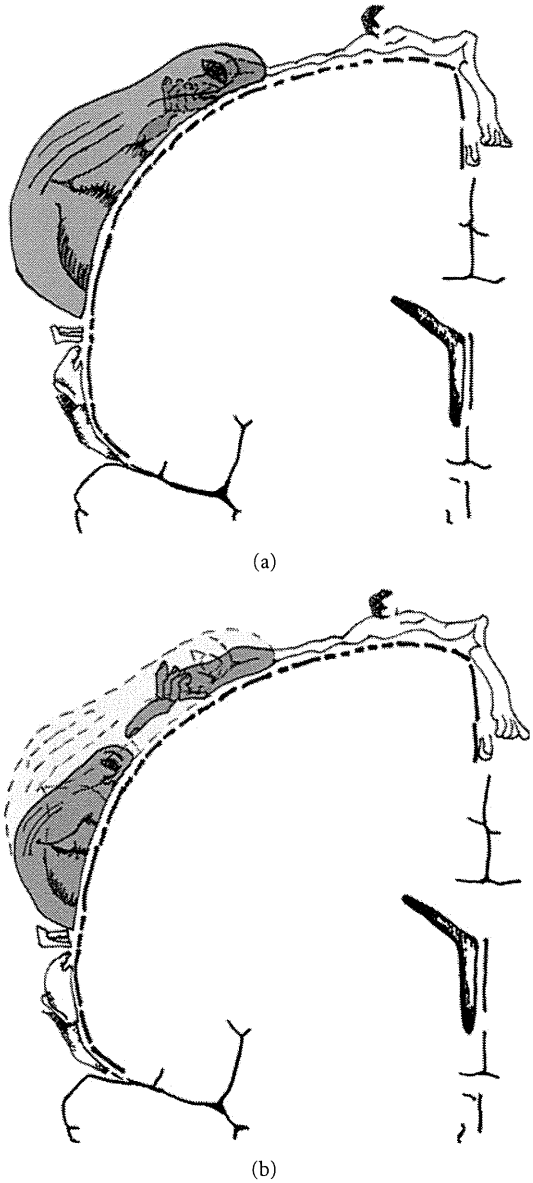

Figure 1: Topographical somatotopic reorganization in the sensorimotor cortices following deafferentation by a brachial plexus avulsion injury (a) and normalization of the reorganization by application of local anesthesia in the mouth (b).

are embedded in the face [8]. We consider one possibility that the analgesic effects of the oral local anesthesia in our case were derived from the neural plasticity in the sensorimotor cortices because our patient perceived a similar illusory sensation of fingers in the face. Deafferentation by local anesthesia, as well as that by nerve injury, shrinks the somatotopic representation of the exposed body part and simultaneously expands the nearby somatotopic representation in the sensorimotor cortices, and these are not associated with subcortical changes [9, 10]. On the basis of this notion, we speculated that, in our case, local anesthesia in the mouth shrank the mouth/face representation and subsequently expanded the somatotopic representation of the hand/upper

limb within the sensorimotor cortices (Figure 1(b)), resulting in amelioration of the neuropathic pain in the upper limb. The disappearance of the illusory finger sensations in the face soon after the oral local anesthesia supported the intimate relationship between analgesic effects of the upper limb pain and cerebral reorganization of hand/upper limb and face/mouth representations.

In general, neural blockades are applied to painful body parts in order to block neural transmission; however, the clinical significance of neural transmission blockades remains unclear for nerve-injured neuropathic pain because of deafferentation. Local anesthesia at an intact limb contralateral to the painful limb has been reported to display clear analgesic effects on postamputation phantom limb pain, suggesting pain alleviation through neural plasticity within the CNS [11]. Thus, several types of local anesthesia or neural blockades on unaffected body parts have distinct clinical significance compared to neural transmission blockades, whereas peripheral nerve blockades shrink the somatotopic area of the exposed body part and seem to have no analgesic effect on neuropathic pain in general. Specific analgesic effects on neuropathic pain from local anesthesia and neural blockade could be derived from CNS plasticity. In the future, functional brain imaging studies examining the relationship between neural blockade application for neuropathic pain and CNS plasticity need to be performed in order to better understand somatotopic reorganization in the sensorimotor cortices induced by neural blockades.

4. Conclusion

For neural blockades, oral local anesthesia is a novel candidate for treating neuropathic pain in the upper limb, and the analgesic effect might be derived from its effects on neural plasticity within the CNS.

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References

[1] M. S. Chong and Z. H. Bajwa, "Diagnosis and treatment of neuropathic pain," *Journal of Pain and Symptom Management*, vol. 25, no. 5, pp. S4–S11, 2003.

[2] H. Flor, L. Nikolajsen, and T. S. Jensen, "Phantom limb pain: a case of maladaptive CNS plasticity?" *Nature Reviews Neuroscience*, vol. 7, no. 11, pp. 873–881, 2006.

[3] M. Sumitani, S. Miyauchi, A. Yozu, Y. Otake, Y. Saitoh, and Y. Yamada, "Phantom limb pain in the primary motor cortex: topical review," *Journal of Anesthesia*, vol. 24, no. 2, pp. 337–341, 2010.

[4] H. Flor, T. Elbert, S. Knecht et al., "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, no. 6531, pp. 482–484, 1995.

[5] H. Flor, C. Denke, M. Schaefer, and S. Grüsser, "Effect of sensory discrimination training on cortical reorganisation and phantom limb pain," *The Lancet*, vol. 357, no. 9270, pp. 1763–1764, 2001.

[6] M. Sumitani, S. Miyauchi, C. S. Mccabe et al., "Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report," *Rheumatology*, vol. 47, no. 7, pp. 1038–1043, 2008.

[7] K. MacIver, D. M. Lloyd, S. Kelly, N. Roberts, and T. Nurmikko, "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery," *Brain*, vol. 131, no. 8, pp. 2181–2191, 2008.

[8] V. S. Ramachandran, "Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 22, pp. 10413–10420, 1993.

[9] P. M. Rossini, G. Martino, L. Narici et al., "Short-term brain 'plasticity' in humans: transient finger representation changes in sensory cortex somatotopy following ischemic anesthesia," *Brain Research*, vol. 642, no. 1-2, pp. 169–177, 1994.

[10] M. Tinazzi, G. Zanette, A. Polo et al., "Transient deafferentation in humans induces rapid modulation of primary sensory cortex not associated with subcortical changes: a somatosensory evoked potential study," *Neuroscience Letters*, vol. 223, no. 1, pp. 21–24, 1997.

[11] D. Gross, "Contralateral local anesthesia in stump, phantom and post-traumatic pain," *Anaesthesist*, vol. 7, no. 2, pp. 65–73, 1984.

[12] D. B. Bayer and T. G. Stenger, "Trigeminal neuralgia: an overview," *Oral Surgery Oral Medicine and Oral Pathology*, vol. 48, no. 5, pp. 393–399, 1979.

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ORIGINAL ARTICLE

Impact of remifentanil introduction on practice patterns in general anesthesia

Kanji Uchida · Hideo Yasunaga · Hiroaki Miyata · Masahiko Sumitani · Hiromasa Horiguchi · Ken Kuwajima · Shinya Matsuda · Yoshitsugu Yamada

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Abstract
Purpose The introduction of new medicine can change clinical practice patterns and may affect patient outcomes. In the present study, we investigated whether introduction of remifentanil in Japan affected the practice patterns of anesthesia.
Methods Using the Japanese Diagnosis Procedure Combination database, we extracted records of 423,491 patients who underwent surgery with general anesthesia in 243 hospitals before (2006) and after (2007) the introduction of remifentanil, and identified anesthetic agents used for each patient. A hierarchical mixed-effects logistic regression analysis was performed to analyze the factors that affected selection of remifentanil. Further, we compared postoperative length of stay (LOS), in-hospital mortality, and total costs between 2006 and 2007.
Results In 2007, remifentanil was used for up to 41.4% of all general anesthesia, accompanied by a reduction in nitrous oxide use and an increase in total intravenous anesthesia. Female gender, increasing age, and preoperative comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with the use of remifentanil, whereas accompanying cardiac disease and co-application of epidural anesthesia were negatively associated. In 2007, a similar in-hospital death rate, similar or decreased total costs, slightly reduced duration of anesthesia, and substantially reduced postoperative LOS were seen compared to those in 2006.
Conclusions Our data revealed rapid changes in practice patterns in anesthesia after the introduction of remifentanil in Japan. Remifentanil was used more often in patients with comorbidities and without epidural anesthesia, and its introduction did not affect increase in total medical costs.

Keywords Remifentanil · Anesthetic practice · Postoperative outcome · In-patient medical cost

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K. Uchida (✉) · M. Sumitani · K. Kuwajima · Y. Yamada
Department of Anesthesiology, Tokyo University Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: UCHIDAK-ANE@h.u-tokyo.ac.jp

H. Yasunaga · H. Horiguchi
Department of Health Management and Policy, Tokyo University Graduate School of Medicine, Tokyo, Japan

H. Miyata
Department of Health Quality Assessment, Tokyo University Graduate School of Medicine, Tokyo, Japan

S. Matsuda
Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kitakyushu, Japan

Introduction

The introduction of new medical devices such as the drug-eluting stent for angina pectoris [1] or new drugs such as anti-tumor necrosis factor-α antibody for rheumatoid arthritis [2] had a major impact on medical practice patterns over a short time period, affecting not only patient outcomes but also total medical costs, although published reports gave variable results [3].

In anesthesiology, only a limited number of reports show changes in practice patterns in anesthesia [4]. It is

also not clear to what extent such changes affect medical costs and patient outcome [5].

Remifentanil, a mu-opioid receptor agonist, has a unique pharmacokinetic profile, characterized by rapid equilibration with the central compartment, and a short half-life, independent of infusion duration [6, 7]. Although its use is common in Western countries [8], it was finally approved in Japan in December 2006, and its use in clinical practice commenced in January 2007. The unique pharmacological properties of this novel drug facilitated its rapid assimilation into Japanese clinical procedures, making a considerable impact on anesthetic practice. However, accurate data have not been reported on the expansion of remifentanil use and the subsequent changes in practice patterns in general anesthesia. In addition, the effects of remifentanil introduction on patient outcomes remain unclear.

In the present study, we investigated the proportion of remifentanil use in the first year of its introduction and changes in the patterns of anesthetic drug use. Then, we analyzed factors affecting selection of remifentanil. We also compared duration of anesthesia and total costs as well as postoperative length of stay (LOS) and in-hospital mortality before and after introduction of remifentanil, using the nationwide Japanese administrative claims database, the Diagnosis Procedure Combination (DPC) database.

Materials and methods

DPC database and participants

The DPC is a mixed-case system, similar to the diagnosis-related groups (DRG) in the U.S. Medicare program. It was launched in 2002 by the Ministry of Health, Labor and Welfare of Japan and is linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance [9, 10]. All 82 university teaching hospitals must adopt the DPC system, and community hospitals can voluntarily adopt this system. Data are mainly used for profiling practice patterns, refining case-mix classification, and planning health policies such as resource allocation.

The DPC database comprises discharge abstracts and administrative claims, with data compiled between July 1 and December 31 each year by the DPC Research Group [10–13]. The database initially included 82 hospitals in 2003. The numbers of inpatients and participant hospitals are increasing each year, with around 3 million patients from 926 hospitals in 2007, which represented approximately 45% of all acute care inpatient hospitalizations in Japan [11]. The database includes the following data: unique identification number of each hospital; patient age and sex; diagnoses recorded in the Japanese language together with the *International Classification of Diseases, 10th Revision*; surgical procedures coded with original Japanese codes; drugs and devices used; LOS; in-hospital mortality; and total costs (including costs for hospitalization, surgery, anesthesia, drugs and devices used).

The DPC database corresponds to the Nationwide Inpatient Sample in the United States [14] to some extent but has several advantages [10]. To optimize the validity of the recorded diagnoses, physicians in charge record the diagnoses in reference to the medical charts. Detailed data are available for the treatments administered on a daily basis (e.g., types of drugs administered, duration of anesthesia, volume of blood transfusion). Medical clerks and licensed medical information managers accurately record the dates of each surgery and other procedures and the dates of use of each drug and device. Physicians and hospitals consistently comply with data submission because it is mandatory to obtain DPC-based reimbursement of medical fees.

All patient identifiers have been removed from this database. Because of the anonymous nature of the data, obtaining informed consent from patients was unnecessary. The Institutional Review Board of the University of Occupational and Environmental Health approved this study design.

Data extraction

To compare the pre-remifentanil period (July–December 2006) with the remifentanil treatment period (July–December 2007), we included data from all 243 hospitals that participated in the DPC survey in both years. We extracted data on all surgical patients who underwent general anesthesia in these hospitals, including type of hospital, type of admission, patient age, sex, surgical procedures, duration of anesthesia (min), volume of blood transfusion, postoperative LOS (days), in-hospital mortality, and total costs. General anesthesia was defined as anesthesia for surgery for at least 20 min with volatile anesthetics and/or intravenous anesthetics supplemented with oxygen via a mask including laryngeal mask or endotracheal tube.

We also extracted data regarding medications used for general anesthesia, including barbiturates, nitrous oxide, volatile anesthetic agents, muscle relaxants, hypnotics, and narcotics.

Patients who underwent the following eight classes of surgery in 2007 were subdivided to evaluate differences in distribution of remifentanil among surgical subcategories: cardiac surgery, neurosurgery, thoracic surgery, vascular surgery, general surgery, gynecology, orthopedic surgery, and otolaryngology. When a patient underwent two or more surgeries during the hospitalization, the patient was

classified into one group according to the most recent surgery. If a patient underwent multiple surgeries at the same time, we selected the one surgery that required the most medical resources. Postoperative LOS was determined as the days between the day of the surgery and that of discharge.

Descriptive statistics

The proportions of patients who received each drug were compared between 2006 and 2007. Combinations of remifentanil and fentanyl, and of nitrous oxide and volatile agents, were also compared between the 2 years. Further, postoperative in-hospital mortality, duration of anesthesia, postoperative LOS, and total costs were compared between the 2 years for all populations and eight surgical subcategories.

Logistic regression to determine factors for selecting remifentanil

To determine possible contributing factors for selection of remifentanil, we extracted the data of patients who had general anesthesia with either fentanyl alone or remifentanil and fentanyl in 2007. In the logistic regression model, the dependent variable was set as "remifentanil use" (fentanyl alone = 0; both remifentanil and fentanyl = 1). A hierarchical mixed-effects logistic regression analysis was performed in which age, sex, intraoperative use of epidural anesthesia, comorbidities, and surgical subcategories were set as fixed effects, and sites (described by unique identifiers for all 243 hospitals) were used as random intercepts.

Statistical analysis

We performed univariate comparisons of variables for the two groups, using the Mann–Whitney *U* test for nonparametric data and the chi-square test for categorical data as appropriate. All statistical analyses were conducted using the SAS 9.1 (SAS Institute, Cary, NC, USA), and *P* values <0.05 were considered to be significant. The exchange rate was assumed to be 100 yen to 1 U.S. dollar (USD).

Results

Patient demographics

All 243 acute care hospitals that participated in DPC in both 2006 and 2007 were enrolled in this study. A total of 423,491 patients (206,102 in 2006 and 217,389 in 2007) were identified. Overall, 59.6% of patients were admitted to 53 teaching hospitals, while the remaining 40.4% were treated at 190 non-teaching hospitals (Supplemental Tables 1, 2).

Anesthetic drug used

Table 1 shows the use of each anesthetic drug in 2006 and 2007. Remifentanil accounted for 41.4% of all general anesthesia usage in 2007. The proportion of cases in which either fentanyl or remifentanil was used increased from 76.5% in 2006 to 83.3% in 2007. The proportion including remifentanil in 2007 was higher in teaching hospitals than

Table 1 Anesthetic drugs used

Drug	2006 (n = 206,102) (%)	2007 (n = 217,389) (%)	P*
Narcotics			
Remifentanil	0.0	41.4	<0.001
Fentanyl	76.5	71.2	<0.001
Morphine	13.7	13.4	<0.001
Hypnotics			
Barbiturates	18.4	14.9	<0.001
Propofol	72.8	76.9	<0.001
Midazolam	9.4	12.6	<0.001
Nitrous oxide	25.8	14.0	<0.001
Volatile anesthetic agents			
Sevoflurane	79.5	74.2	<0.001
Isoflurane	4.6	3.3	<0.001
Halothane	0.1	0.1	0.732
Muscle relaxants			
Suxamethonium	0.5	1.3	<0.001
Vecuronium	84.2	81.9	<0.001
Rocuronium	0.0	2.6	<0.001
Pancuronium	1.0	0.9	0.158
Others			
Droperidol	12.2	13.9	<0.001
Ketamine	5.1	3.8	<0.001
Diazepam	1.3	1.2	0.023
Combination of fentanyl and remifentanil			
Neither	23.5	16.7	<0.001
Fentanyl alone	76.5	41.9	<0.001
Remifentanil alone	0.0	12.1	<0.001
Both	0.0	29.3	<0.001
Combination of nitrous oxide and volatile agents			
Neither	14.0	21.0	<0.001
Nitrous oxide alone	2.1	1.6	<0.001
Volatile agents alone	60.1	65.0	<0.001
Both	23.8	12.4	<0.001

* P value for the comparison between 2006 and 2007 evaluated with the chi-square test

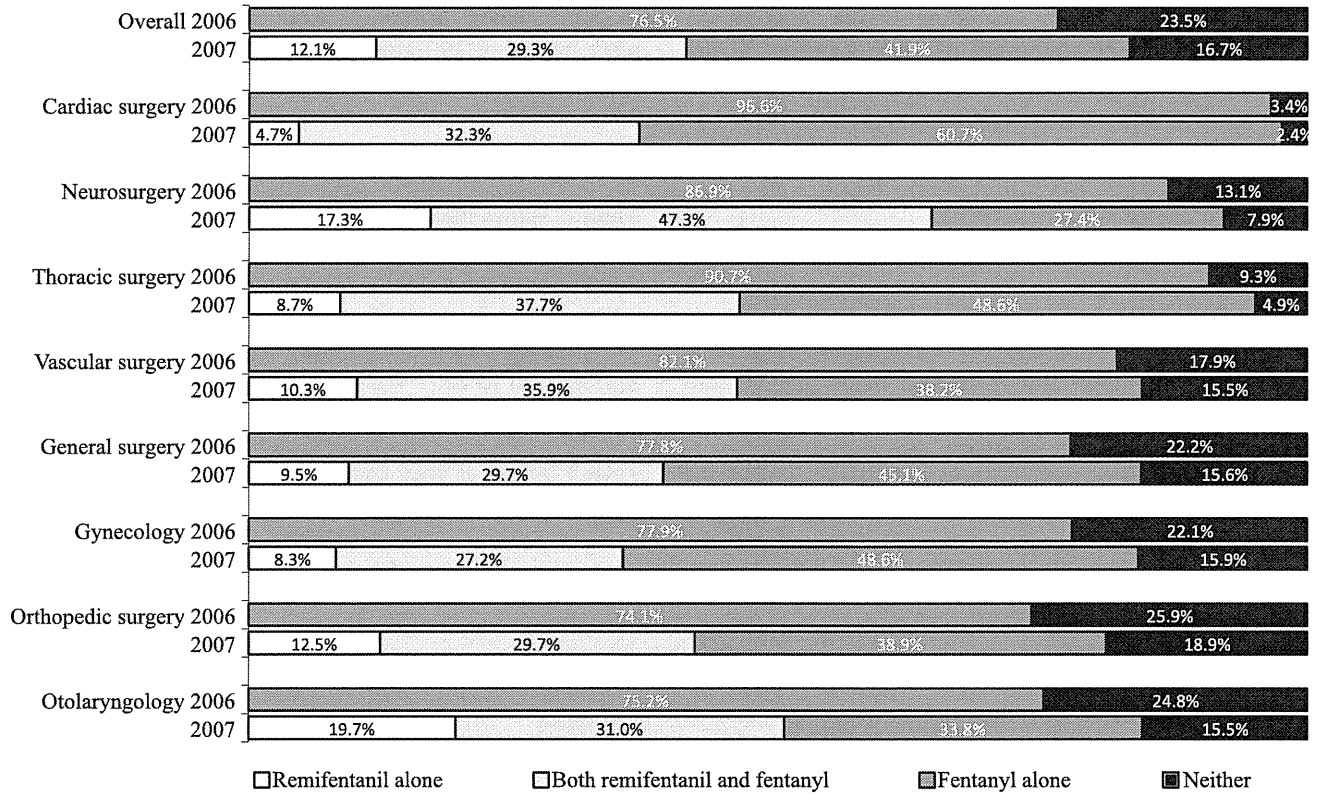

Fig. 1 Combination of remifentanil and fentanyl in each surgical field: percentage of surgeries using fentanyl and/or remifentanil in 2006 and 2007. *Open bars* cases in which remifentanil alone was used; *light gray bars* both remifentanil and fentanyl; *dark gray bars* fentanyl alone; *closed bars* neither remifentanil nor fentanyl

in non-teaching hospitals (48.1% vs. 36.9%, $P < 0.01$). The use of remifentanil in 2007 was exceptionally high in neurosurgery (64.6%) and otolaryngology (50.7%) (Fig. 1). The use of nitrous oxide decreased from 25.9% in 2006 to 14.0% in 2007. The proportion of patients who received neither nitrous oxide nor volatile agents, i.e., those undergoing total intravenous anesthesia (TIVA), increased from 14.0% in 2006 to 21.0% in 2007.

Barbiturate use was lower in 2007 (14.9%) than in 2006 (18.4%), whereas use of propofol was higher in 2007 (76.9%) than in 2006 (72.8%). Vecuronium was used in more than 80% of general anesthesias in both years, whereas rocuronium, which was introduced in September 2007, was utilized in 2.6% of surgeries in that year.

Factors associated with selection of remifentanil

Among 217,389 patients in 2007, 91,097 received fentanyl alone, and 63,739 received both remifentanil and fentanyl. Both patient factors and surgical factors affecting use of remifentanil were analyzed with adjustment for site effects by incorporating hospital identification numbers into the hierarchical mixed-effects logistic regression model. Female sex, increasing age, and comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with selection of remifentanil. In contrast, cardiac diseases and intraoperative epidural anesthesia were negatively associated with selection of remifentanil. Neurosurgical patients were more than fivefold more likely to receive remifentanil compared with cardiac surgery patients (Table 2).

Postoperative outcomes

Table 3 shows in-hospital mortality, mean duration of anesthesia, mean postoperative LOS, and mean total cost in each surgical field. All outcomes were compared between 2006 and 2007. No significant difference in in-hospital mortality was seen in any surgical subcategory showed between the 2 years. The mean duration of anesthesia was slightly shorter in 2007 than in 2006, and the differences were statistically significant in general surgery, gynecology, and orthopedic surgery. Mean postoperative LOS was shorter in 2007 in all surgical subcategories, and most of these findings were statistically significant, except for otolaryngology cases. Total cost was comparable between the 2 years, except for general surgery and gynecology, which were significantly less in 2007 compared with 2006.

Table 2 A hierarchical mixed-effects logistic regression analysis for selecting remifentanil (fentanyl alone = 0; both remifentanil and fentanyl = 1)

	Odds ratio	95% confidence interval	*P* value
Sex (female)	1.09	1.06–1.12	<0.001
Age	1.02	1.02–1.02	<0.001
Epidural anesthesia	0.36	0.35–0.37	<0.001
Diabetes mellitus	1.07	1.02–1.11	0.006
Hypertension	1.08	1.04–1.13	<0.001
Cardiac diseases	0.91	0.86–0.95	<0.001
Cerebrovascular diseases	1.07	1.00–1.15	0.068
Chronic lung diseases	1.01	0.93–1.08	0.888
Liver cirrhosis	1.19	1.00–1.41	0.049
Chronic renal failure	1.17	1.08–1.27	<0.001
Surgical category			
Cardiac surgery	Reference		<0.001
Neurosurgery	5.49	5.05–5.98	
Thoracic surgery	3.20	2.94–3.47	
Vascular surgery	2.36	2.17–2.58	
General surgery	2.00	1.87–2.13	
Gynecology	2.01	1.86–2.17	
Orthopedic surgery	1.89	1.76–2.02	
Otolaryngology	2.48	2.31–2.76	

Discussion

Population representation

According to the Survey of Medical Institutions 2008 in Japan, the average number of surgeries under general anesthesia throughout the country was 187,097 per month. [Survey of Medical Institutions 2008 (in Japanese). Vital and Health Statistics Division, Ministry of Health, Labour and Welfare, Japan. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/index.html. Accessed June 14, 2011.] Our data included 423,491 cases in 12 months, representing about 19% of all patients who underwent general anesthesia during the data extraction period in Japan. The age distribution was similar to that in another large database of anesthesia maintained by the Japanese Society of Anesthesiologists [15, 16].

Spread of remifentanil use and factors associated with its selection

Remifentanil was administered in more than 40% of all general anesthesias in the first year of its introduction, an extremely rapid increase in the proportion of its use [17].

Remifentanil was more frequently selected for patients with comorbidities, including hypertension, diabetes mellitus, and liver and kidney disease, presumably because it has advantages over other opioids such as a controllable, strong antinociceptive effect and rapid extrahepatic metabolism and elimination.

Epidural anesthesia was negatively associated with selection of remifentanil. Multiple publications suggest better patient intra- and postoperative condition with epidural anesthesia [18, 19]. It is anticipated that anesthesiologists did not believe it necessary to use remifentanil when they applied epidural anesthesia intraoperatively. The proportion of remifentanil use was higher in the nonepidural group than in the epidural group (45.2% vs. 30.6%). It was also higher in neurosurgery (64.6%) and otolaryngology (50.7%) cases. These results suggest that the pharmacological properties of remifentanil are highly

Table 3 Comparison of in-hospital mortality, average duration of anesthesia, postoperative length of stay, and total cost between 2006 and 2007 in each surgical subcategory

	In-hospital mortality (%)			Duration of anesthesia (min)			Postoperative length of stay (days)			Total costs (USD)		
	2006	2007	*P**	2006	2007	*P*†	2006	2007	*P*†	2006	2007	*P*†
Overall	1.41	1.36	0.242	211	208	<0.001	16.4	15.7	<0.001	12,733	12,648	0.051
Cardiac surgery	4.78	4.53	0.403	407	403	0.111	24.7	24.1	0.039	43,797	43,427	0.327
Neurosurgery	5.46	5.47	0.985	316	314	0.352	28.7	27.6	0.004	23,255	23,193	0.784
Thoracic surgery	1.73	1.69	0.862	259	255	0.296	14.5	14.0	0.046	15,926	15,820	0.669
Vascular surgery	3.59	3.50	0.761	267	262	0.074	24.0	22.6	0.002	18,489	18,458	0.927
General surgery	2.02	2.02	0.952	220	216	<0.001	16.9	16.1	<0.001	12,096	11,935	0.019
Gynecology	0.15	0.12	0.381	163	161	0.043	10.1	9.2	<0.001	7,046	6,951	0.042
Orthopedic surgery	0.66	0.56	0.092	191	188	<0.001	23.0	22.3	<0.001	14,108	14,112	0.957
Otolaryngology	1.33	1.43	0.314	177	174	0.429	12.3	12.1	0.222	8,448	8,555	0.330

LOS length of stay

* *P* value for the comparison between 2006 and 2007 evaluated with the chi-square test. Continuous variables, indicated with †, were evaluated using the Mann–Whitney *U* test

appreciated in those surgeries in which a neuraxial blockade cannot be applied.

Cardiac surgery had the smallest impact on the choice of remifentanil, presumably because of the greater surgical insult to patients, who frequently require postoperative mechanical ventilation; therefore, anesthetists can apply a large dose of fentanyl intraoperatively without considering early postoperative emergence and extubation in the operating theater. Coexisting cardiac disease was negatively associated with selection of remifentanil (Table 2). The well-known circulatory suppressive effect of remifentanil [20] may be another reason for the anesthetists to refrain from applying it in cardiac surgery.

Bramhall pointed out three prerequisites for an anesthetic drug to obtain a major share in the market. (Bramhall J. Remifentanil: Clinical use of an evanescent opioid. Available at: http://faculty.washington.edu/bramhall/lectures/opioids/remife~1.htm. Accessed June 14, 2011.) First, the drug must fit a "niche," allowing techniques to be used that were previously impractical; second, the drug must be cost effective; and third, it must have a safer profile than currently available agents. The safety of novel agents is generally extensively evaluated before clinical application, but it is usually difficult to show that the drug is "safer" than other drugs before substantial use. Similarly, the cost-effectiveness of anesthetic drugs cannot be clearly determined before substantial use, because various parameters can affect postoperative medical costs [21]. In contrast, intraoperative clinical advantages of remifentanil are evident even before substantial use. Its unique property as an ultra-short-acting opioid allowed application of new techniques that were previously impractical. For example, it enabled extensive opioid use as primary treatment for intraoperative pain that did not affect early postoperative emergence [22]. Bramhall also stated that the superiority of a drug over others should be assessed quite accurately, even if subjectively, by individual anesthetists in their daily practice. Because other short-acting opioids, i.e., sufentanil and alfentanil, had not been introduced into clinical use in Japan, the effect of remifentanil was likely to have a greater impression on Japanese anesthesiologists, and this may have boosted its penetration into the market.

The Japanese health insurance system does not offer economic incentives to anesthesiologists, and the reimbursement of costs for surgery and anesthesia is based on a fee-for-service system [23]. Therefore, anesthesiologists in Japan choose drugs according to their clinical applicability and convenience, with little economic consideration. Indeed, the present study revealed that sevoflurane was used in an exceptionally large population of general anesthesia cases despite its relatively high costs compared with other volatile agents (Table 1) [24]. Because there was more than a 10-year delay in the clinical application of remifentanil in Japan from Western countries, anesthesiologists should already have been familiar with its pharmacological properties and practical clinical application, thus making it easy for them to bring it into their clinical practice.

Change in patterns of drugs used for general anesthesia

Along with the rapid escalation of remifentanil use, an increase in TIVA and a reciprocal decrease in nitrous oxide use were obvious. Increase in propofol users by 4.1% in contrast to the reduction in barbiturates users by 3.5% may be the consequence of the increase in TIVA population, because propofol, which is the most popular hypnotic for maintenance of TIVA, can also substitute for barbiturates as an induction agent. Remifentanil may be superior to nitrous oxide for pain control with less environmental effect (i.e., contamination of the atmosphere in the operating room) and fewer adverse effects on patients, such as postoperative nausea and vomiting [25]. Other volatile anesthetic agents, specifically sevoflurane and isoflurane, were significantly reduced in use in 2007, but the magnitudes are less than that of nitrous oxide (Table 1). These observations may possibly be the result of their known organ-protective effects [26], recognized by most of the anesthesiologists in Japan, as well as their easy and titratable properties in regular clinical practice.

Impact on patient postoperative outcome and cost

Postoperative LOS was significantly reduced in all the surgeries except for otolaryngology, although the magnitude of surgical insult indicated by duration of anesthesia were relatively similar in both years. However, whether application of remifentanil led to better postoperative recovery is not clear. Currently few publications have reported association between use of remifentanil and better postoperative recovery [27]. Other factors, such as less-invasive surgical techniques and improved perioperative care, which affects enhanced recovery after surgery [28], may have contributed to the reduction in postoperative LOS in surgical patients.

Remifentanil is relatively expensive, a 2-mg vial costing 25.34 USD, about 10 times that of fentanyl (0.1 mg ampule for 2.45 USD) in Japan. Rapid increase in the proportion of remifentanil use was anticipated to cause increase in total costs. However, all surgical subcategories showed similar or less total cost in 2007 compared with 2006. Although multiple factors affect patient postoperative outcome and total costs, we can at least say from the present results that application of remifentanil did not affect increase in total costs. To disclose the possible contribution of remifentanil to better postoperative recovery, further evaluation using a wider dataset or a randomized controlled trial is necessary.