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Ⅳ. 研究成果の刊行物・別刷

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Health Survey of Numbness/Pain and Its Associated Factors in Kotohira, Japan

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Abstract

We conducted a survey of adults in Kotohira, a town of about 10,000 people located in the Nakatado District of Kagawa Prefecture, Japan. The survey was distributed to 8184 individuals, and effective responses were received from 3863 persons (response rate, 47.2%) during the survey period. Results regarding numbness and pain showed numbness alone in 7.7%, pain alone in 7.2%, both numbness and pain in 6.0%, and neither numbness nor pain in 79.6%. Spine and spinal cord damage was reported present by 5.4%, and absent by 94.6%. Analysis using the Short-Form Health Survey questionnaire, with comparison between subjects reporting both numbness and pain in the extremities and subjects with either numbness or pain alone, showed lower scores for in Short-Form Health Survey subscales (physical functioning, role [physical, emotional], bodily pain, vitality, and mental health). Subjects with numbness alone generally reported no disability in daily life. In a secondary survey, analysis of neurological findings by specialists identified 6 cases of "pain following spinal cord damage" in which spinal cord-related pain developed in the hands or feet. This represented 0.15% of the survey population starting from the primary survey.

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Introduction

Limb (arm and leg) numbness and pain can occur not only due to spine/spinal cord disorder, entrapment syndromes, diabetes, and neuropathy causing nerve dysfunction, but also due to muscle and vascular diseases. Because individuals with numbness or pain may experience great discomfort, elucidating the underlying mechanisms and developing effective treatments are very important.

Pain is an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1]. However, patients with neurological dysfunction due to spine/spinal cord disorder often first complain of "shibirekan" [2], or "numbness" in English. Numbness is listed in ICD10 section R20 "disturbances of skin sensation"; and anesthesia, paresthesia, and dysesthesia (which can clearly be defined), as well as hypesthesia and some symptoms that cannot be specified, are often referred to as "numbness." Moreover, even when pain is also present, this is sometimes expressed as "numbness." In particular, in refractory and difficult-to-treat diseases such as cervical myelopathy, ossification of the posterior longitudinal ligament (OPLL), and syringomyelia, as well as after spinal cord injury; limb numbness and pain (allodynia or pressure sensation in the body) is severe, pain may be resistant to treatment, and quality of life (QOL) and activities of daily living (ADLs) are markedly diminished [2,3,4,5]. Therefore, in pain following spinal cord damage, with symptoms of pain and numbness, elucidating the neuropathological and pharmacological mechanisms involved and developing effective treatments are of paramount importance.

According to recent nationwide surveys [6,7], the prevalence of chronic pain with neuropathic characteristics is reported to be 7 - 8%. However, numbness information and impacts of pain and numbness on health status are largely unknown. In addition, pain directly attributable to spinal cord damage may include allodynia, in which pain is triggered by tactile stimulation that ordinarily does not cause pain, and spontaneous pressure-like pain below the level of the damaged spinal cord. Some drugs, such as anticonvulsants, are effective in some patients, but the same treatment is often ineffective in other patients with similar symptoms. Many cases are treatment-resistant, and much remains unknown about this disease population [8].

In Kotohira where this survey was conducted, a high level of cooperation exists among the council of social welfare, welfare commissioners, women's groups, and local liaison councils; and the area is very small (8.46 km^2) with only a small degree of population shift. This provides conditions under which the current status of town residents can very easily be ascertained (http://www.town.kotohira.kagawa.jp/english/data/index.html). The aim of this study was to clarify the prevalence of numbness and pain and their impacts on health status in a rural community in

Japan, particularly spine-related symptoms were evaluated. The present study was undertaken as part of a survey on spinal-related pain (number of patients, percentage of population, symptom characteristics) (MHLW Research) in Kotohira, a town with a population of about 10,000 located in Kagawa Prefecture, Japan.

Results

Primary Survey Results (Fig. 1, Table 1)

Among the 119 neighborhood associations, surveys were collected from 108 neighborhood associations (2728 households, 8184 persons), and effective responses were received from 3863 persons (47.2%). This included 2141 women (55.4%) and 1722 men (44.6%). Age was <65 years in 2124 (54.5%), 65 to <75 years (young-old elderly) in 21.8%, and ≥75 years (old-old elderly) in 23.7%. Regarding limb numbness and pain, numbness alone was present in 297 (7.7%), pain alone in 280 (7.2%), both numbness and pain in 234 (6.1%), and neither numbness nor pain in 3052 (79.0%).

With regard to symptoms, 215 respondents (5.6%) had been diagnosed with spine/spinal cord disorder at a hospital, while 3648 persons (94.4%) had not. In addition, 372 individuals had a history of diabetes. Taken together, the number of persons with both spinal disorder and diabetes, spinal disorder only, diabetes only, and neither spinal disorder nor diabetes was 32, 183, 346, and 3308, respectively.

2691 individuals (32.8%) responded to SF-36 questionnaire. Analysis of SF-36 subscale scores showed that the group with both limb numbness and pain, as compared to the group with either pain alone or numbness alone, showed lower scores for all SF-36 subscale items except general health. Moreover, the group with either numbness or pain showed lower scores for each SF-36 item compared to the group with neither numbness nor pain. Scores for general health, physical functioning, and mental health were lower in the pain-alone group than in the numbness-alone group (Fig. 2). Among those individuals diagnosed with both diabetes and spine disease, the group with numbness or pain showed decreased health status as compared to the group without numbness or pain. This trend was stronger among individuals with a history of spine/spinal cord disorder (Fig. 3).

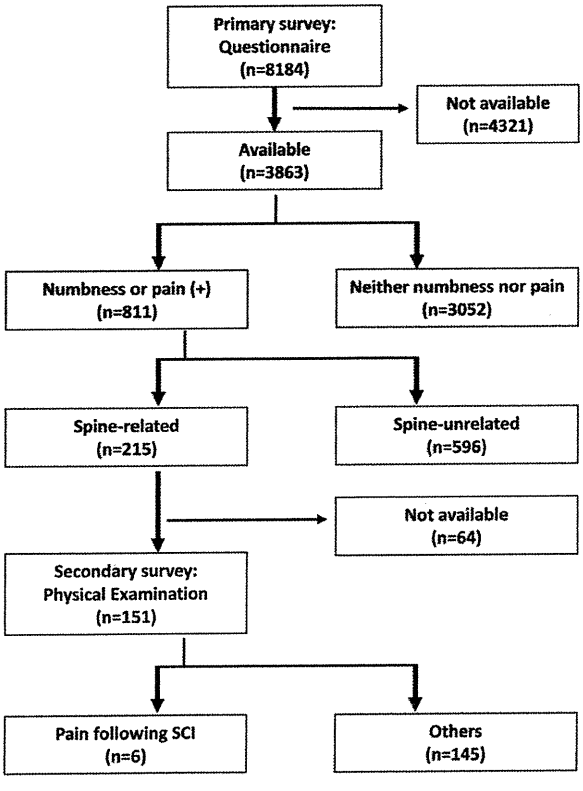


Figure 1. A flow diagram showing an outline of the study.
doi:10.1371/journal.pone.0060079.g001

Table 1. Limb numbness and pain according to sex and age.

		Male	
Age	−64	65–75	75–
n	1008	358	356
Numbness+	73 (7.2)	36 (10.1)	35 (9.8)
Pain+	26 (2.6)	24 (6.7)	23 (6.5)
Both+	37 (3.7)	23 (6.4)	39 (11.0)
		Female	
Age	−64	65–75	75–
n	1097	484	560
Numbness+	69 (6.3)	36 (7.4)	48 (8.6)
Pain+	70 (6.4)	54 (11.2)	83 (14.8)
Both+	39 (3.6)	29 (6.0)	67 (12.0)

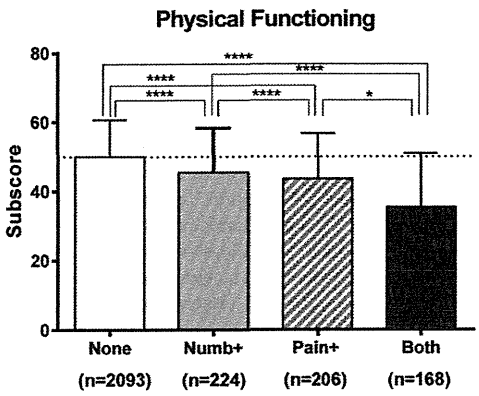
(Values in parentheses represent percentages).
doi:10.1371/journal.pone.0060079.t001

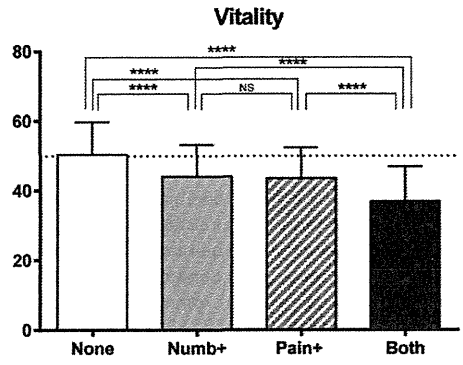
Secondary Survey Results (Fig. 1)

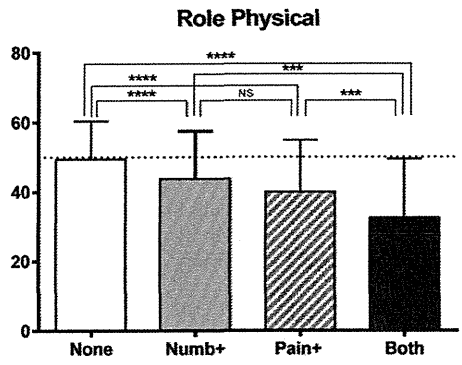
Among those individuals with limb numbness or pain at the primary survey who had been diagnosed with spine/spinal cord disorder at a hospital, the number from whom cooperation for the secondary survey was obtained. Among the 215 residents targeted for the secondary survey was 151 persons. Based on a medical examination and a detailed interview survey in these cases, 6 individuals who have intractable spinal cord-related numbness and pain in extremities were judged to have "pain following spinal cord damage" that was resistant to ordinal treatment such as non-steroidal anti-inflammatory drugs. This represented 0.15% of the survey population starting from the primary survey. However, there were 29 persons with lumbosacral-related numbness and pain such as spinal canal stenosis or a herniated lumbar disk. In addition, cases of another cause of numbness and tingling, even though spine/spinal cord disorder had been diagnosed at a hospital, included 5 persons with limb trauma and 16 persons with arthropathy (including rheumatoid arthritis and lateral epicondylitis of the humerus).

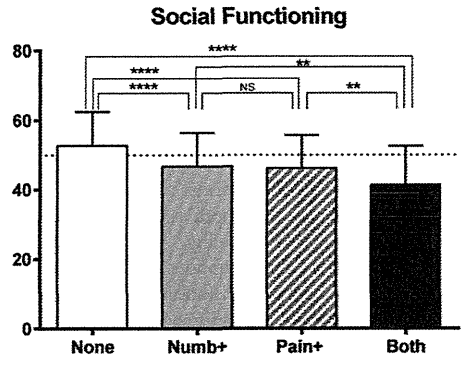
Discussion

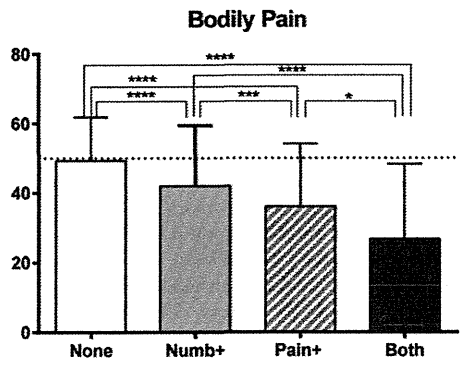
Numbness is a sensory abnormality and the word is often used to describe abnormal sensations such as paresthesia, dysesthesia, and hypesthesia. Numbness is seen not only in spine/spinal cord disorder, but also often in carpal tunnel syndrome. Tay et al. reported paresthesias in 70.1% of patients diagnosed with this syndrome [9]. However, because the etiology is multifaceted with regard to the population in whom symptoms of limb numbness and pain are frequently observed, the effects of these symptoms on

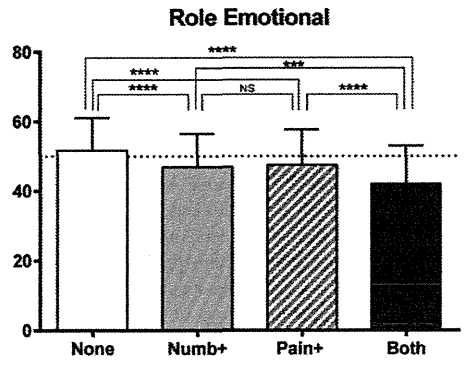

Physical Functioning
Subscore
80
60
40
20
0
None
Numb+
Pain+
Both
(n=2093)
(n=224)
(n=206)
(n=168)

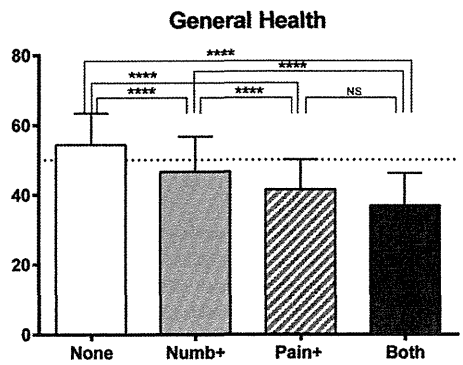

Vitality
80
60
40
20
0
None
Numb+
Pain+
Both


Role Physical
80
60
40
20
0
None
Numb+
Pain+
Both


Social Functioning
80
60
40
20
0
None
Numb+
Pain+
Both


Bodily Pain
80
60
40
20
0
None
Numb+
Pain+
Both


Role Emotional
80
60
40
20
0
None
Numb+
Pain+
Both


General Health
80
60
40
20
0
None
Numb+
Pain+
Both

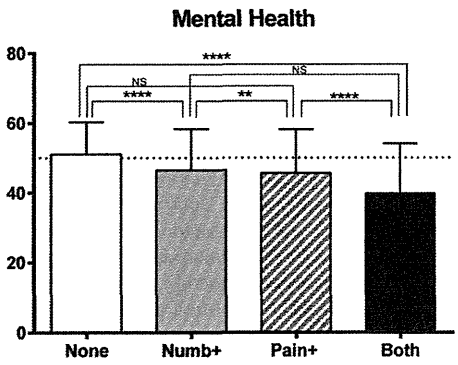

Mental Health
80
60
40
20
0
None
Numb+
Pain+
Both

Figure 2. SF-36 subscale scores with presence or absence of numbness or pain. In the group with both numbness and pain, scores were significantly decreased as compared to the group with neither. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.
doi:10.1371/journal.pone.0060079.g002

health status remain unclear, and thorough surveys have not been conducted to date.

In the present survey used in Kotohira, 7.7% of the population had limb numbness alone, 7.3% had pain alone, and 6.0% had both. Many individuals show symptoms, and prevalence increases with aging. One reason for an increase in numbness (a sensory abnormality caused by multiple etiologies, as described above) in older persons is that the population with spine/spinal cord disorders such as lumbar spinal canal stenosis [10,11] and cervical spondylotic myelopathy [12], which can cause these symptoms, increases with older age. Regarding decreased sensory function, a decrease in the number of peripheral mechanoreceptors has been reported with aging, even in the absence of disease, and hypofunction [13] and myelin degeneration might be due to the involvement of such mechanisms [14]. This is thought to be linked to the mechanism by which numbness is increased in older persons. The percentage of the population of Kotohira aged 65 or older is relatively high (32%) compared with that of Japan as a whole (23%). Therefore, it is possible that the prevalence of symptoms in this study is higher than the national average.

Our survey showed that in persons with both limb numbness and pain, SF-36 subscores (physical functioning, role physical, bodily pain, vitality, social functioning, role emotional, and mental health) were lower than in participants with numbness alone or pain alone. Individuals with numbness alone generally reported no disability in daily life. However, the characteristics of numbness were not available because the questionnaire simply asked for the presence or absence of numbness in this study. It is possible that "numbness" in this study included abnormal sensation such as paresthesia and dysesthesia. A more detailed survey that can be linked to development of treatment for numbness may thus be necessary.

In a previously conducted cohort survey overseas, in all SF-36 domains except mental health, health status was impaired in the diabetes group compared to healthy persons [15]. In our survey, SF-36 subscale scores were markedly decreased in participants who had been diagnosed with spine/spinal cord disorder. In diabetes as well, when there was limb pain, each of the subscale scores tended to be decreased. This demonstrates the importance of maintaining locomotor function to control medical diseases such as diabetes and prevent chronic pain. Future development of intervention strategies to promote health status is needed [16].

Spinal cord-related pain, as pain caused by direct damage to the spinal cord, and the effects on ADL associated with this pain represent conditions caused by many diseases. Because of difficult-to-treat symptoms, treatment strategy is challenging even at facilities specializing in spine/spinal cord disorder. Causative disorders include not only spinal cord injury, but also a wide range of a smaller number of cases such as compressive myelopathy due to OPLL, syringomyelia, and spinal cord tumors. Ascertaining the whole clinical picture may thus be difficult. In our survey conducted in about half of the population of Kotohira, the data showed 6 such cases (0.15%) among about 4000 adults. The population shift in Kotohira is small, and cooperation between the town, council of social welfare and neighborhood associations is high. In this area, neighborhood associations function with support centering on the council of social welfare. Because patients with spinal cord injury usually need social support, it is unlikely that we missed a certain number of patients with severe pain related to spinal cord injury.

Mechanisms of numbness and pain in spinal cord-related pain syndromes include: 1) damage at the dorsal root level [17]; 2) damage to the dorsal horn (synapse region) (including effects of inhibition and facilitation of propagation, sprouting, and glial activation) [18]; 3) damage to spinothalamic tract [19]; 4) damage to descending inhibition pathways [20]; 5) muscle pain due to nerve damage [21]; and 6) psychosocial factors together with brain memory mechanisms [22]. To further analyze these neuropathological mechanisms and develop new treatments, a network must first be established to collect these types of patients.

Methods

The study was conducted in cooperation among the Kotohira Council of Social Welfare, the Federation of Neighborhood Associations comprised of neighborhood association presidents, Kotohira Women's Association, welfare commissioners, and Kotohira Town Office. All participants gave their informed written consent to the study. The requirements of data protection and medical professional secrecy were respected by all study investigators. All consent and protocols for both primary and secondary surveys had been specifically approved by the ethical committee of the Aichi Medical University.

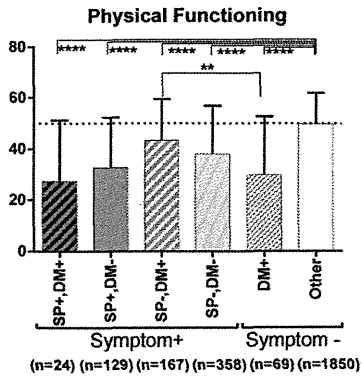
Primary Survey

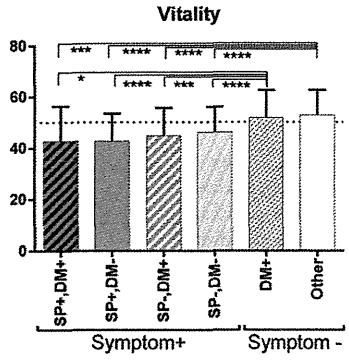
The survey questionnaire, through the Kotohira Council of Social Welfare and Federation of Neighborhood Associations, was distributed and collected by neighborhood association presidents to 119 neighborhood associations in Kotohira Town using the placement survey method. For areas where distribution was difficult, the council of social welfare officers, welfare commissioners, and the women's club provided assistance. Because the study would be hindered if persons in charge of distributing and collecting the surveys were unable to explain the survey, opinions of the Federation of Neighborhood Associations were sought during the stage of questionnaire creation to enable the survey to also be conducted among elderly persons. The questionnaire included items about limb numbness and pain, history of spine/spinal cord disorder, a history of diabetes, and the Short-Form Health Survey (SF-36). Because it simply asked for the presence or absence of symptoms and disease history, details of symptom and disease severity were not obtained from the primary survey. The surveys were distributed beginning on January 21, 2010 and collected by March 3, 2010.

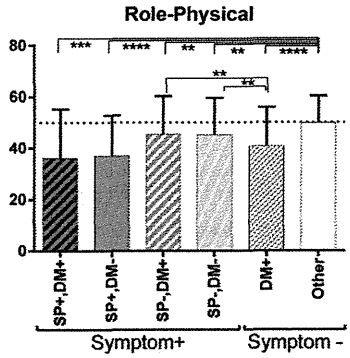
For survey results, national standard norm-based scoring (NBS) was used for the data obtained from the SF-36. The results, including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health, were analyzed using the Kruskal-Wallis test. Items with significant differences were examined with Dunn's multiple comparison test.

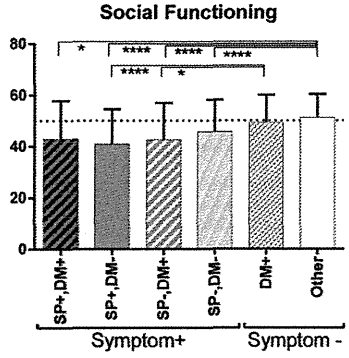
Secondary Survey

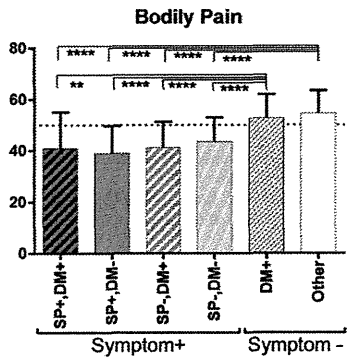
Among respondents to the primary survey with limb numbness or pain and who reported previous diagnosis of with spine/spinal cord disorder in a hospital, in those from whom cooperation was obtained, a secondary survey was conducted by specialists in spine/spinal cord disorder or neurological diagnosis. This survey was conducted as a secondary screening, or for non-participants in screening, by a telephone interview, to obtain detailed neurolog-

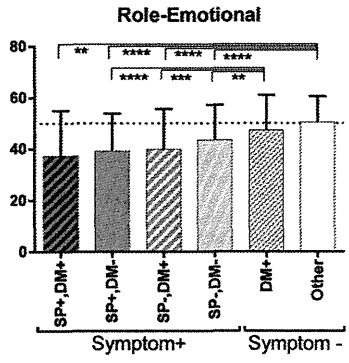

Physical Functioning
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -
(n=24) (n=129) (n=167) (n=358) (n=69) (n=1850)


Vitality
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -


Role-Physical
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -


Social Functioning
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -


Bodily Pain
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -


Role-Emotional
80
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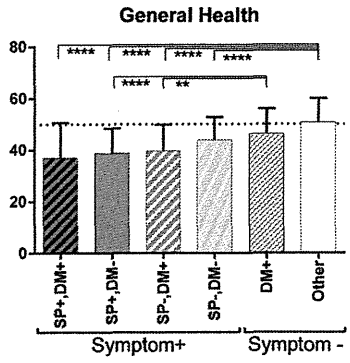
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -


General Health
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -

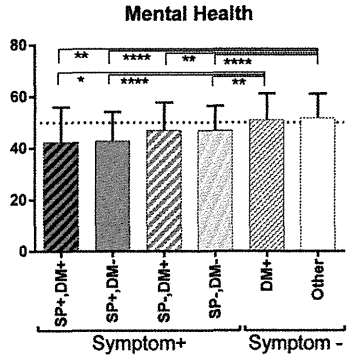

Mental Health
80
60
40
20
0
SP+,DM+
SP+,DM-
SP-,DM+
SP-,DM-
DM+
Other
Symptom+
Symptom -

Figure 3. SF-36 subscale scores for presence or absence of spine/spinal cord-related disorder and diabetes. Diagnosed with spine/spinal cord-disorder (SP+), with diabetes (DM+), positive for numbness or pain (symptom +). Among individuals diagnosed with diabetes and spinal disease, health status was lower in the group with numbness or pain as compared to the group with neither. This trend was strong in those diagnosed with spine/spinal cord disorder. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.
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ical findings. These patients were narrowed down to cases of refractory spinal-related pain following spinal cord damage based, when necessary, on the results of specialist examinations and imaging studies. The secondary survey was conducted from August 2010 to December 2010.

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Author Contributions

Conceived and designed the experiments: TU SI MN CK. Performed the experiments: KO TI MK MI TT. Analyzed the data: TU MN CK. Contributed reagents/materials/analysis tools: TU SI MN CK. Wrote the paper: SI MI TU.

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Randomized Trial

Combinations of Low-Dose Antidepressants and Low-Dose Pregabalin as Useful Adjuvants to Opioids for Intractable, Painful Bone Metastases

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Background: Systemic analgesics would not provide good enough pain relief for some kinds of cancer pain. Metastatic bone pain is characteristic of one of the refractory cancer pains, since the pain is not only nociceptive but also neuropathic. A low-dose antiepileptic-antidepressant combination with opioids is effective in the management of neuropathic cancer pain.

Objective: The aim was to see whether a low-dose antiepileptic-antidepressant combination is effective in the treatment of bone metastases.

Study Design: Randomized, controlled trial

Setting: Pain Clinic in Japan.

Methods: Thirty-seven cancer patients, confirmed to have bone metastases, were allocated into 3 groups: P group took pregabalin 50 mg every 8 hours orally; P-I group took pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally; P-M group took pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally. Pain assessments were performed for 2 weeks.

Results: The total pain score significantly decreased in all 3 groups even one day after the start of the medication. The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups at Day 1. The decreases in the P-M groups were significantly greater than those in the P group from Day 1. The decreases in the P-I group were significantly greater than those in the P group from Day 3.

Conclusion: Low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases.

Key words: Cancer pain, painful bone metastases, antidepressant and anticonvulsants, *pregabalin, mirtazapin*

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In the treatment of cancer pain, adequate pain relief has been obtained in a lot of cases by the recommended approach using systemic medications according to the World Health Organization analgesic ladder (1). However, systemic analgesics would not provide good enough pain relief for some kind of cancer pains. Metastatic bone pain is characteristic of cancer pain and one of the refractory cancer pains (2,3). Although the complete mechanism is not yet fully characterized, metastatic bone pain exhibits components of both inflammatory and neuropathic pain (4-6). Standard treatment includes radiotherapy

and a pharmacologic approach using nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and bisphosphonates. However, the current standard treatment is inadequate for a sizeable number of patients (7).

Neuropathic pain results from a dysfunction of peripheral and central nerves (8,9). Neuropathic cancer pain often shows little response to non-opioid and opioid analgesics, but may be relieved by adjuvants such as antidepressants and antiepileptics (10,11). Also, we previously reported that a low-dose gabapentin-imipramine combination with opioids was effective in the management of neuropathic cancer pain (12). Since mirtazapine is one of the noradrenergic and specific serotonergic antidepressants, it is believed to have potential as an adjuvant analgesic (13,14). However, mirtazapine alone does not provide an improvement in cancer pain. For this reason, we hypothesized that mirtazapine would lead to an improvement in pain when combined with antiepileptics. We thus performed an evaluation of the analgesic effect of a low-dose antiepileptic-antidepressant combination on metastatic bone pain.

Methods

Patients with intractable pain due to bone metastases were enrolled in this study from January 2010 to September 2011. Cancer metastases in bones were confirmed by bone scintigraphy and computed tomography (CT) in all patients. Approval from the local ethics committee and oral informed consent from the patients was obtained, and if the pain was not adequately relieved by opioids and NSAIDs, or the opioid dose was restricted by side effects, pregabalin and imipramine or mirtazapine were started after the first referral visit to our clinic.

In this randomized, controlled trial, the cancer patients were randomized to one of 3 groups using computer-generated random numbers:

1. P group: pregabalin 50 mg every 8 hours orally.
2. P-I group: pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally.
3. P-M group: pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally.

Previous 24-hour average intensity of total pain was assessed on 0 – 10 numerical scales and previous 24-hour paroxysmal pain (shooting or lancinating pain) episodes were recorded (12,15). Pain assessments were performed at the first visit (Day 0) and one to 7 days and 10 and 14 days after the start of the medication. Opioid "rescue" doses were available as needed. NSAIDs that were already administered were kept unchanged. No new drug was started during this period. An electrocardiogram (ECG) was performed before and at the end of the study and estimated glomerular filtration rate (eGFR) was measured before the study in all patients.

Our previous study showed the mean (SD) of the total pain score at 7 days after the start of the combination medication to be 2.3 (1.5). Thus, the sample size of 12 was needed to show intergroup differences of 2.0 (1.5) with a significant level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Data are presented as the median (range), number or the median with the twenty-fifth and seventy-fifth percentiles. Since the Kolmogorov-Smirnov test failed, the patients' characteristics, daily opioid dose (oral morphine equivalent (16), pain score, and paroxysmal pain episodes were analyzed using the Kruskal-Wallis test for intergroup comparison or the Friedman test for intragroup comparison followed by Dunn's method for multiple comparisons. Gender was analyzed by the chi-squared test. A P-value less than 0.05 was regarded as significant.

Results

There were no significant differences in patient characteristics and daily opioid dose (oral morphine equivalents) among the 3 groups (Table 1). Loxoprofen sodium (180mg/day) and bisphosphonates were used in all patients. Acetaminophen up to 2400 mg was used in 2 patients in the P group, 3 in the P-I, and 3 in the P-M. There were no patients with advanced chronic kidney disease who required a dose reduction of drugs.

The 3 groups were comparable with respect to the total pain score and daily paroxysmal pain episodes at base (Figs. 1 and 2). The total pain score significantly decreased in all 3 groups even one day after the start of the medication (Fig. 1). The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups even one day after the start of the medication (Fig. 2). The decreases in the P-M groups were significantly greater than those in the P group from Day one. The decreases in the P-I group were significantly greater than those in the P group from Day 3. Since pain control was not sufficient in the P group, mirtazapine was prescribed at Day 7 and the patients were withdrawn from the present study. Then, the P-I and P-M groups were followed.

Table 1. *Demographics and baseline characteristics of patients. Values are median (range) or number.*

	P (n = 12)	P-I (n = 12)	P-M (n = 13)	*P*
Age (year)	64 (47-71)	54 (40-77)	64 (37-72)	0.4709
Sex (M/F)	8/4	8/4	8/5	0.9538
Weight (kg)	54 (40-64)	53.5 (36-70)	50 (43-68)	0.7877
Daily opioid dose[a] (mg/day)	60 (20-180)	55 (20-200)	60 (20-120)	0.9342
Oxycodone SR	6	7	7	
Fentanyl Patch	6	5	6	

[a]Oral morphine equivalent.

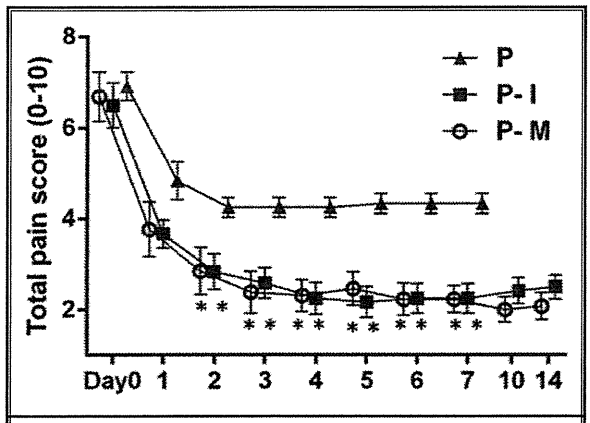

Fig. 1. *Changes of the total pain score. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin- mirtazapine. Error bar represents standard error of the mean (SEM). * P < 0.05 vs pregablin.*

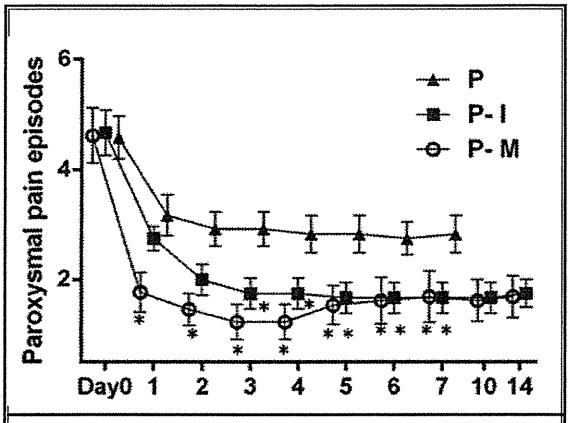

Fig. 2. *Changes of the daily paroxysmal pain episodes. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin-mirtazapine. Error bar represents standard error of the mean (SEM). * P < 0.05 vs pregablin.*

The pain relieving effects in the P-I and P-M groups were maintained for one more week (Figs. 1 and 2). A few patients developed adverse symptoms such as mild dizziness and mild drowsiness in the 3 groups. Significant ECG abnormalities including QT interval prolongation did not develop during the study in any of the patients.

Discussion

Some cancer pain syndromes are intractable even with the use of opioid analgesics. There are multiple mechanisms in the pathophysiology. Metastatic bone pain includes neuropathic as well as nociceptive factors (4-6). A neuropathic pathophysiology leads to a refractory outcome to opioid use. This fact indicates the need for the use of non-opioid analgesics in combination with opioids. Antiepileptics and antidepressants are the most commonly used adjuvant analgesics in pain syndromes of cancer patients when a neuropathic factor is implied from clinical observations (10,11). Thus, we intended to prescribe pregabalin, imipramine, and mirtazapine instead of increasing the opioid dose at the first visit in the present study.

Presently, antiepileptics, such as gabapentin and pregabalin, are widely used to relieve pain. They bind to the $\alpha 2\delta$ calcium channel subunits which are expressed in the central terminals of peripheral sensory nerves in the dorsal horn and inhibit the influx of calcium (17). Consequently, they inhibit signal transduction of pain by reducing the release of neurotransmitters (18). Several studies have confirmed that they are effective in the treatment of neuropathic pain caused by not only non-malignant but also malignant aetiology (19-25). Also, antiepileptics in combination with morphine or antidepressants provide better analgesia at lower doses of each drug than each drug alone (12,15,26-30). Morphine acts on opioid receptors located on neuronal

cell membranes and inhibits neurotransmitter release, which is considered to be the major mechanism of action responsible for its analgesic effects (31). The main proposed mechanism of action of antidepressants is reuptake inhibition of both serotonin and norepinephrine in the central nervous system, which increases the activity of these neurotransmitters and subsequently reduces the perception of pain by modulating the pain signals (19). Although these drugs are used in treating neuropathic pain (19), as monotherapy they are associated with limited efficacy and dose-related side effects. The combination of mechanically distinct analgesic agents is expected to result in additivity or synergism at lower doses and with fewer side effects than with the use of one drug alone.

Mirtazapine, which is a potent antagonist at central presynaptic α2-autoreceptors, postsynaptic 5HT2 and 5HT3 receptors, and H1 receptor, is an effective antidepressant drug (32,33). It differs in structure and mechanism action from other compounds of its class (32,33). Although mirtazapine alone is not used as an analgesic drug, its analgesic effects through opioid receptors and both serotonergic and noradrenergic receptors have been reported (34,35). Based on our results, low-dose pregabalin and mirtazapine were effective in the management of painful bone metastasis compared with twofold pregabalin. We thus believe that the present results showed the additive/synergistic effects of antiepileptic -antidepressant combination pharmacotherapy in the treatment of cancer-related neuropathic pain. Furthermore, mirtazapine has antiemetic effects as a 5HT antagonist (13,14), and as an H1 antagonist, it could stimulate appetite and increase body weight as well as regulate sleep disturbances (36). Although these beneficial secondary effects of mirtazapine were not evaluated in this study, the combination pharmacotherapy including mirtazapine might be an appropriate choice to treat cancer-induced bone pain in patients with many distressing somatic symptoms.

It is widely believed that the onset of beneficial antidepressant effects in depression is delayed for 2 or 3 weeks and maximal antidepressant-induced improvement of depression takes several weeks to occur (37). Also, the pain-relieving effects of antidepressants are generally believed to occur about 2 weeks after the initiation of treatment (38). Referring to our previous results (12), however, the pain-reducing effects of antidepressants combined with antiepileptics occur in a week. Moreover, an interesting finding in the present study was that the pain-relieving effects of antidepressants in combination with antiepileptics appeared within a few days after the initiation of the treatment and remained for 2 weeks, compared with those of 2 antiepileptics. We thus postulate that the pain-reducing effects of antidepressants could appear faster under combination pharmacotherapy.

Although the combination pharmacotherapy is promising in treating cancer-induced bone pain, drug-drug interactions should be taken into consideration. Many drug-drug interactions are the result of an alteration of cytochrome P450 (CYP450) metabolism (39,40). Physicians should be cautious when prescribing a drug known to be metabolized by CYP450. The target drug may need to be substituted or the dose adjusted to account for a potential decrease or increase in metabolism. Among drugs used in this study, oxycodone, imipramine, and mirtazapine are predominantly metabolized by CYP2D6 (41). We think that the absence of significant drug-drug interactions in this study was possibly due to the low dose of each drug. Compared with tricyclic antidepressants including imipramine, mirtazapine as a newer antidepressant rarely inhibits CYP isoforms and is not expected to affect the disposition of concomitantly administered drugs (41). Therefore, in terms of the drug-drug interaction, the combination of mirtazapine and pregabalin in addition to opioids would be theoretically more favorable than the combination of imipramine and pregabalin. Further clinical studies are needed to prove this.

Conclusion

In conclusion, low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases without severe adverse effects.

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MR-guided focused ultrasound for the novel and innovative management of osteoarthritic knee pain

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Abstract

Background: Severe knee pain associated with osteoarthritis (OA) is one of the most common and troublesome symptoms in the elderly. Recently, local bone denervation by MR-guided focused ultrasound (MRgFUS) has been demonstrated as a promising tool for pain palliation of bone metastases. The purpose of this study was to develop a novel treatment for knee OA using MRgFUS, and to validate its safety and efficacy.

Methods: Eight patients with medial knee pain and eligible for total knee arthroplasty were included. MR-guided focused sonication treatments were applied to bone surface just below the rim osteophyte of medial tibia plateau with real-time monitoring of the temperature in the target sites. The pain intensity during walking was assessed on a 100 mm visual analog scale (VAS) before and after treatment. Pressure pain thresholds (PPTs) were also evaluated over several test sites adjacent to the sonication area and control sites one month after treatment.

Results: Six patients (75%) showed immediate pain alleviation after treatment, and four of them demonstrated long-lasting effect at 6-month follow up (mean VAS reduction; 72.6%). In responders, PPTs in medial knee were significantly increased after treatment (Median; pre- 358 kpa vs post- 534 kpa, $p < 0.0001$). There were no adverse side effects or complications during and after treatment.

Conclusions: These initial results illustrate the safety and efficacy of the newly developing MRgFUS treatment. Significant increase of PPTs on treated area showed successful denervation effect on the nociceptive nerve terminals. MRgFUS is a promising and innovative procedure for noninvasive pain management of knee OA.

Trial registration: Trial Registration: UMIN000010193

Keywords: MR-guided Focused Ultrasound (MRgFUS), Knee, Osteoarthritis, Pain

Background

Knee Osteoarthritis (OA) ranks among the most common disabling arthritic conditions in the elderly [1]. A major symptom of knee OA is chronic knee pain which has a significant effect on patients' quality of life [2]. There are several conservative options for pain management, including physical therapy, use of non-steroidal anti-inflammatory drugs, intraarticular injection with steroids or hyaluronic acids [3]. However, these treatments are not sufficient to control severe knee OA pain [4]. Although total knee arthroplasty (TKA) is a validated and reliable intervention for alleviating severe knee pain [5], there are some patients who are at high risk during surgery and other patients who are not willing to undergo surgery. The number of these patients is expected to increase because of population aging, therefore, it is necessary to explore additional nonsurgical treatments for knee OA to achieve better pain relief.

MR-guided focused ultrasound (MRgFUS) treatment is a noninvasive technique that enables to perform localized thermal ablation by focusing the acoustic energy precisely to the targeted sites [6]. Three-dimensional treatment planning and continuous real-time monitoring of the temperature in the target sites by MR imaging are

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the two crucial advantages of this system [7]. Clinically, the feasibility and effectiveness of MRgFUS have been evaluated in several benign and malignant tumors such as uterine fibroids [8,9], breast cancer [10,11], and brain tumors [12]. In recent years, palliative therapy of bone pain due to metastasis has been recognized as a promising alternative treatment with the mechanism of local bone denervation [13-15]. As for a treatment of chronic musculoskeletal pain, however, there was only one case-series of MRgFUS application to osteoarthritic lumbar facet joints, which targeted periosteum around facet joint to achieve local bone denervation and reported safe and effective outcomes against low back pain [16]. In knee OA, tenderness of the bony margins of the joint is a quite common symptom involved in American College of Rheumatology criteria for clinical diagnosis [17], which might be caused by rich nociceptive nerve terminals in this area. Therefore, it is reasonable to assume that the same mechanism as facet joint treatment is certainly available to alleviate joint pain caused by knee OA. The purpose of this study was to develop a novel treatment for knee OA using MRgFUS, and to validate its safety and efficacy in an initial case series.

Methods

Patients

This case series study was carried out with the approval of the Institutional Review Board and in a prospective, non-controlled manner. All patients were informed about the intervention prior to treatment, and written consent for participation and publication of individual clinical details were obtained. Participation was voluntary and did not preclude other treatment options. The study and all interventions were carried out in the Department of Orthopaedic Surgery in Kochi university hospital between December 2010 and April 2012. Patients complaining severe medial knee pain associated with radiological OA were recruited for this study. Inclusion criteria were age older than 60 years, previous conservative treatments longer than 3 months, and pain scores on an visual analog scale (VAS, 100 mm) greater than 40 mm during walking. Radiological inclusion was restricted to grade 4 medial knee OA according to Kellgren-Lawrence classification [18], because the patients could be salvaged by TKA conversion. Exclusion criteria were contraindications for MRI, psychiatric conditions, and allergies of local anesthetics.

In this series, eight patients (6 female, 2 male) with the mean age of 78 (± 6.4; standard deviation) years were treated. The mean clinical score (Japanese Orthopedic Association score for knee OA) was 48 (± 5.3) points (maximum 100 points: domains are pain on walking or stair stepping, range of motion, and joint effusion). All patients were eligible for TKA, and half of them were scheduled surgery and underwent MRgFUS treatment during waiting period. The others were scheduled only for MRgFUS treatment because they were not willing to undergo surgery.

MR-guided focused ultrasound procedures

The treatment was conducted as an outpatient setting, using the MRgFUS system (ExAblate® 2100, InSightec Ltd, Haifa, Israel) integrated with an MRI scanner (GE Signa EXCITE 3.0 T MRI, Milwaukee, WI, USA). In this series, the criteria of sonication area was determined as the bone surface just below the rim osteophyte of medial tibia plateau, which is the insertion site of deep medial collateral ligament. Patients underwent local anesthesia with 15 ml of 0.75% ropivacaine around the periosteum in treatment sites and lay supine on the MRI table. A conformal sonication device was strapped onto the medial knee (Figure 1). This is a newly developed transducer and chilled water is circulated within a semi-permeable membrane to provide acoustic coupling and cool the skin during treatment. Coronal, sagittal, and axial unenhanced T2-weighted MR images were obtained and loaded into MRgFUS workstation to allow accurate three-dimensional planning and targeting of the lesion. The outline of bone surface as well as skin and the area to be treated were carefully drawn on the planning images of coronal and axial view. The system automatically generated the optimal treatment plan including energy levels and number of sonications (Figure 2). The ultrasound beam was angled to avoid popliteal neurovascular bundles. Initially, a low energy test sonication was performed to ensure safety and accuracy of the procedure. Then, therapeutic sonications began with higher energy to achieve ablation. Throughout the treatment, the location of each sonication and the temperature elevation in the tissue adjacent to the target area were monitored in real time (Figure 3). The temperature elevation was aimed at 60°C, and treatment parameters such as energy, sonication duration or spot size were modified in response to the monitoring. The patients held a stop switch and were able to interrupt anytime during the treatment.

Outcome measures

The primary outcome measure was VAS scores during walking on a scale graduated from 0 (no pain) to 100 mm (maximal pain). A response to treatment was defined as a 50% or greater decrease in the pain VAS according to a proposal of Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International [19]. The VAS was collected before, 3 days, 10 days, and 1 month after the MRgFUS in all patients and in some patients additional VAS scores were obtained at 3, 6, 12, and 18 months.

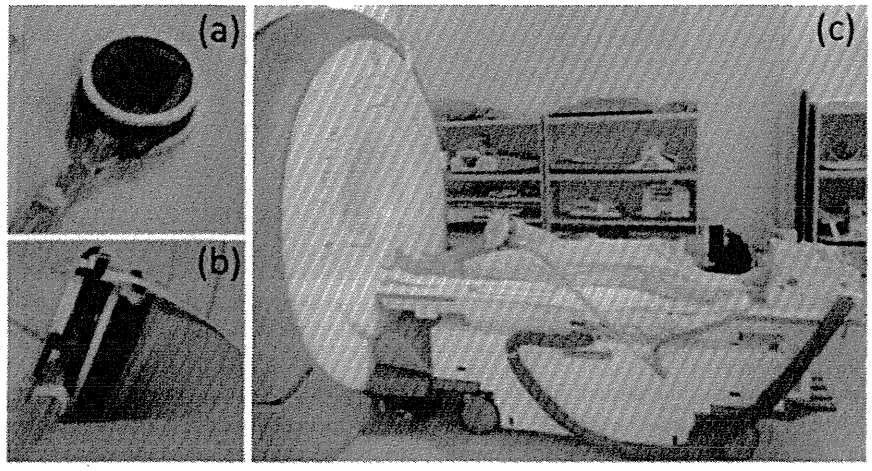

Figure 1 System set up. (a) Conformal sonication devise **(b)** Strapped onto the medial knee. Chilled water is circulated within a semi-permeable membrane. **(c)** Full view of the patient.

In addition, pressure pain thresholds (PPTs) were measured over 6 test sites adjacent to the sonication area and at 2 control sites. The test sites in medial knee were; A: anterior joint space; B: middle joint space; C: posterior joint space; D: anterior tibia plateau; E: middle tibia plateau; F: posterior tibia plateau. All sites were easily identified based on the location of joint space, medial collateral ligament and tibial osteophyte. As control sites, lateral joint space and ipsilateral upper arm (3 cm proximal to the humerus insertion of deltoid muscle) were examined. A handheld algometer (Commander, J Tech Medical Industries, Heber city, UT, USA) with a 1 cm^2 probe was used to record PPTs. The PPT was defined as the first point at which patients perceived the pressure as slight pain. PPTs were measured by single examiner (MI) at pre- and one month post-treatment. Prior to the pre-treatment assessment, high intra-rater reliability was confirmed in each patient. PPTs were recorded two times on each site and the mean threshold was used for statistical analysis.

Radiological assessments were performed at 3 days, 1 month, 6 months and 12 months by X-ray, at 3 months

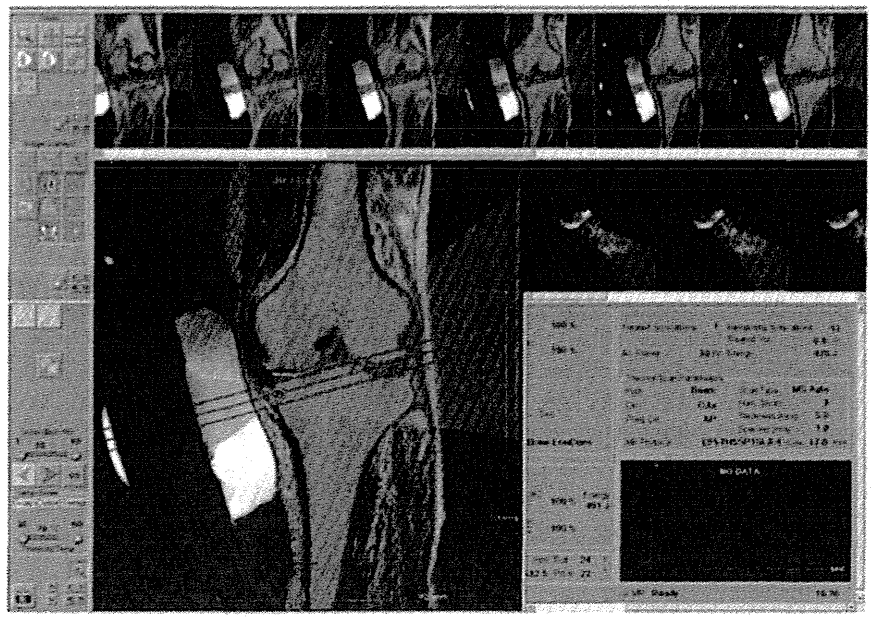

Figure 2 Three-dimensional treatment planning. Sonication site and ultrasound beam pathway are indicated by the examiner. The system automatically generated the optimal treatment plan including energy levels and number of sonications.

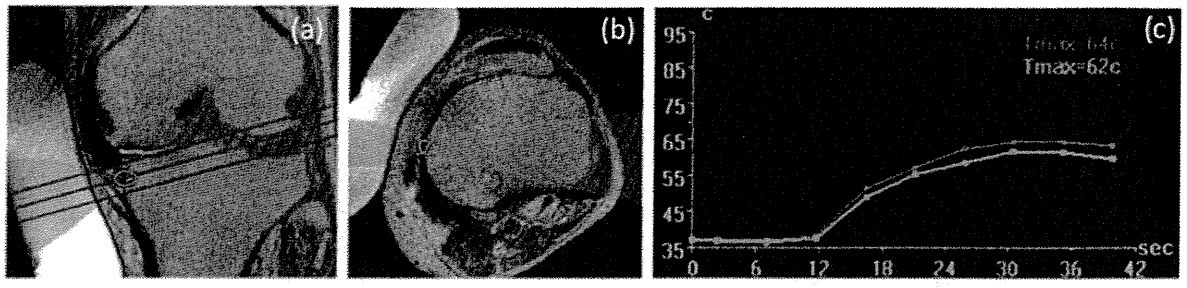

Figure 3 Real-time monitoring. Current sonication spot (green circle) and ultrasound beam pathway are shown in Coronal view **(a)** and axial view **(b)**. Temperature elevation is monitored by two curves indicated mean (green) and maximum (red) temperature in the spot **(c)**.

by routine plain MRI of the knee. The treated bone sample was taken from patients who underwent TKA after MRgFUS treatment and histopathological evaluation was performed using hematoxylin and eosin staining.

Statistical analysis

The PPT data are presented as median and interquartile range in text and figures. Kruskal-Wallis test followed by Dunn's test was used to compare PPTs among eight sites at pre-treatment. Wilcoxon signed rank test was used for comparison of difference between pre- and post-treatment PPTs in medial knee (including 6 sites; A-F) and on each site. Significant difference was set at $p < 0.05$.

Results

The mean time used for preparing the system was 86 minutes (50–120 min) while the mean treatment time was 74 minutes (50–120 min). The mean therapeutic energy level was 735 Joules (491–952) and the mean number of sonication was 12.4 (10–20) per patient. The mean follow-up period was 9 (6–18) months after treatment. There were no adverse side effects or complications reported during and after treatment.

Pain intensity effects

The VAS scores were reduced 3 days, 10 days, and one month compared with pre-treatment in the 6 responders (Figure 4). In particular, four patients (Case 1, 4, 5, and 6) had long-lasting pain alleviation (mean VAS reduction at 6 months: 72.6%). One patient (Case 7) showed recurrence of pain at 6-month follow up. Two patients (Case 2 and 3) underwent total knee arthroplasty one month after MRgFUS treatment. One of the non-responders (Case 8) dropped out and switched to opioid therapy one month after MRgFUS treatment.

Pressure pain sensitivity

At pre-treatment and compared with the arm, the middle and posterior tibia plateau as well as posterior joint space showed significant lower PPTs ($P < 0.05$; Figure 5). In the 6 responders, the PPTs in medial knee were 358 kpa [290 - 431]at pre-treatment and 534 kpa [461 - 605]at post-treatment, which showed significant difference ($p < 0.0001$). In site-specific evaluation, the PPTs on middle, posterior joint space and tibia plateau were significantly increased after treatment ($P < 0.05$; Figure 5), suggesting that the nociceptive nerve terminals in the medial knee were successfully treated. In the two non-responders, the PPT values post-treatment were comparable with the pre-treatment values.

Histopahological evaluation

The cortical bone sample of the treated area was taken from 2 patients during TKA. Light microscopic assessment showed maintained bone morphology (Figure 6a) and normal osteocytes (Figure 6b), which demonstrated no significant focal bone necrosis due to MRgFUS treatment.

Case

A-82 year-old woman (Case 1) underwent MRgFUS treatment for her left knee. She had successfully

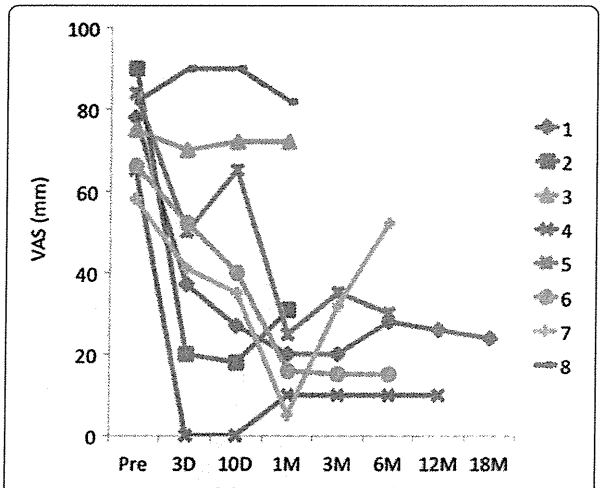

Figure 4 VAS scores of the pain intensity during walking at each follow-up time point. Six patients (Case 1, 2, 4, 5, 6 and 7) showed good pain relief after treatment.