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## Effects of interfascial injection of bicarbonated Ringer's solution, physiological saline and local anesthetic under ultrasonography for myofascial pain syndrome -Two prospective, randomized, double-blinded trials-

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### ABSTRACT

Myofascial pain syndrome (MPS) is a common clinical condition of muscle pain. Previous studies indicated that local injection of physiological saline (PS) into a muscle is equal to or more effective than a local anesthetic for MPS. We performed 2 randomized, double-blinded trials of interfascial injection under ultrasonography for outpatients with MPS over 3 months to assess the effects of PS (pH 6.0), 0.5% mepivacaine hydrochloride (MH) (pH 6.0), and bicarbonate Ringer's solution (BRS) (pH 7.4), and to elucidate their action mechanisms. Maximum pain related to motion, time of pain relief, and pain related to injection (intensity and duration) were measured up to 72 hrs. The first trial showed that PS decreased maximum pain related to motion compared to MH ( $p < 0.05$ ), although it increased pain related to injection compared to MH ( $p < 0.05$ ). The second trial showed that BRS exhibited as much efficacy in relieving maximum pain related to motion as PS ( $p = 0.33$ ), but decreased pain related to injection compared to PS ( $p < 0.05$ ). In conclusion, the interfascial injection of PS has a greater analgesic effect on MPS but produced stronger pain related to injection compared to MH. BRS is equivalent to PS in analgesic effect and produced less pain related to injection compared to PS. These results indicate that BRS is the appropriate solution for an interfascial injection to treat MPS, and that the action mechanisms are not related to the pain intensity associated with the injections or the pharmacological anesthetic effect.

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Key word: acupuncture, chronic pain, myofascia, trigger points, ultrasound

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### INTRODUCTION

Myofascial pain syndrome (MPS) is a common clinical condition of muscle pain. In the United States, MPS is estimated to affect approximately 3% of the general population<sup>1)</sup>. It was diagnosed in 30% of patients with pain complaints at a university general internal medicine department<sup>2)</sup>, and in 85%

of patients at a pain rehabilitation referral center<sup>3)</sup>. MPS is characterized by: 1) chronic muscle pain, 2) palpation of taut bands in painful muscles, and 3) exquisite tenderness spots in taut bands which evoke referred pain when physically pressed<sup>4)</sup>.

Various local therapies exist for MPS such as local anesthetic injection, dry needling, laser acupuncture, physiotherapy, and massage. In studies

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Abbreviations: BRS, bicarbonate Ringer's solution;ISM, infraspinatus muscle;LSM, levator scapulae muscle;MH, mepivacaine hydrochloride;MPS, myofascial pain syndrome;NRS, numeric rating scale;PS, physiological saline;ROM, range of motion;SM, middle scalene muscle;TM, upper parts of the trapezius muscle;TSM, cervical, thoracic and lumbar transversospinal muscle;VAS, visual analogue scale

using local anesthetic injection, physiological saline (PS) has traditionally been used for placebo control. However, a previous study showed that a local injection (into a muscle tissue) of PS for MPS patients was equally or more effective than an injection of 0.5% mepivacaine hydrochloride (MH) (local anesthetic)<sup>5</sup>. Pain related to injection of PS tends to be greater than that of a local anesthetic. Some studies indicated that the stronger the intensity of pain related to injection, the greater its analgesic effect, but these results are controversial<sup>6-8</sup>. The Systematic reviews in the Cochrane database showed that adjusting the pH of a solution to a level closer to the physiologic pH 7.4 reduces pain related to injection<sup>9</sup>. Accordingly, we expected that the local injection of bicarbonated Ringer's solution (BRS) (extracellular fluid similar to blood plasma, pH 7.4) would be far less painful than PS, but as effective as PS.

Interfascial injection with a local anesthetic has been used as a compartment block for nerve block anesthesia<sup>10-14</sup>. The interfascial block of a local anesthetic was suggested to be effective in treating MPS patients. The fluid injected into the interfascial space of cadavers under ultrasonography has been confirmed by anatomical dissection<sup>15</sup>. Dense innervation of sensory fibers, including presumably nociceptive fibers, on the outer layer of thoracolumbar fascia was reported<sup>16</sup>. Approaching the outside of the myofascia (epimysium) might be more effective than approaching the inside (muscle tissue). However, there are no prospective studies about the effect of interfascial injection in MPS patients.

Interfascial injection of PS or BRS is expected to reduce complications of local anesthetics. We performed interfascial injection under ultrasonography which enabled us to determine the injection site and the injected solution in the interfascial space. We compared the efficacy and safety of the interfascial injection of PS, MH and BRS for MPS patients, and attempted to elucidate the possible action mechanisms of interfascial injection.

## METHODS

Full ethical approval was granted for the study (Medical Ethics Committee of Kanazawa University). The study was registered in the University Hospital Medical Information Network in Japan (UMIN00009701). It was a prospective, randomized, active-controlled, double-blinded study performed at an outpatient pain clinic in Japan, divided into 2

parts; first, we compared PS (pH 6.0) and MH (pH 6.0)(as active controls) from January 26<sup>th</sup> to February 2<sup>nd</sup> 2013, and second, we compared BRS (pH 7.4) and PS (pH 6.0)(as active controls) from March 11<sup>th</sup> to 16<sup>th</sup> 2013. The protocols in the first and second trials were completely the same except for the solutions (MH or BRS) used.

## Patients

Recruitment ran from January to March 2013. Patients treated at the Kimura Pain Clinic (Maebashi, Japan) were invited to participate. Written informed consent was given by all patients before enrolment in the studies. A physician of the clinic preselected the patients and informed them about the eligibility and exclusion criteria. Patients who were eligible and willing to participate in the study were then assessed by an independent examiner including a detailed physical examination and collection of baseline data.

The eligibility criteria were MPS of specific muscles for at least 3 months. MPS criteria were the following: 1) regional muscle pain, 2) palpation of taut bands in painful muscles, 3) exquisite tenderness spots (myofascial trigger points) in the taut bands, 4) patient's recognition of pain evoked by physical pressing on a myofascial trigger point, and 5) limitation of the passive range of motion (ROM) due to muscle pain<sup>4</sup>. The specific muscles investigated in our study were the following: cervical, thoracic and lumbar transversospinal muscle (TSM), levator scapulae muscle (LSM), middle scalene muscle (SM), upper parts of the trapezius muscle (TM), and infraspinatus muscle (ISM). The exclusion criteria were the following: taking anti-thrombotic drugs or anti-coagulant drugs, history of bleeding disorders, presence of cancer, history of spinal or shoulder surgery, presence of a local or systemic infection, acute trauma (within a week), allergy to anesthetic agents, and extreme fear of needles<sup>1</sup>. In addition, we excluded the patients who disagreed to stop any other usual treatments (e.g., physical therapy, acupuncture, massage, or per-request medications) until their participating trial finished. Regular medications were allowed to take.

## Clinical trial endpoints

The endpoints were the same before and after the study was started. Here are our endpoints for the adapted final research protocol that was accepted by the Ethical Committee at Kanazawa University.

The primary endpoint was the change over time in the maximum pain related to motion which had been used in the previous study<sup>18</sup>. Patients were asked to move their MPS-affected muscle in the most pain-inducing direction and to score the pain intensity on a numeric rating scale (NRS) of 0 to 10 with 0 equaling “no pain” and 10 equaling “the worst pain possible.” The direction we measured was for the maximum extended positions of each muscle (TSM, LSM, SM, TM, and ISM). The respective change in pain intensity was recorded over time (before the intervention, 5, 15, and 30 min after, and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 48 and 72 hr after the injection). The pain intensities were recorded in the clinic until 2 hrs after the injection, and from 3 to 72 hr afterward were recorded by the patients at home. Patients did not need to record times when they forgot to keep track or during sleep.

We defined 4 secondary endpoints: 1) The time of pain relief was defined as the duration in which the patient felt efficacy from the intervention. Patients recorded if they felt efficacy or not at the same time that the maximum pain related to intensity was recorded. 2) The intensity and duration of pain associated with injection. Pain intensity was recorded by NRS. Pain duration was recorded as the time it lasted after the injection. 3) Changes in the passive ROM of the MPS muscle after the injection. Before the injection, an examiner examined the passive ROM of the MPS-affected muscle at maximum extension. Thirty minutes after the injection, the examiner examined again if the passive ROM improved or not (i.e. Yes or No). 4) Adverse events. We recorded any uncomfortable physiological symptoms and signs (e.g., paralysis, hypoesthesia, nausea, vasovagal reflex, hypotension, allergic reaction to the solutions, or major haemorrhage from the injection site).

### **Randomization and allocations**

After baseline assessment, patients were randomly assigned by a roll of the dice to either the PS group or MH group in the first trial, and to the PS group or BRS group in the second trial. The examiners were all blinded, as mentioned below.

The specific steps of randomization and allocation were as follows: 1) Physician A preselected the patients and informed them about the eligibility and exclusion criteria. 2) Physician B assessed the participants who were eligible and willing to participate in the trial. This

assessment included a detailed physical examination and collection of baseline data. 3) Nurse A rolled the dice for the randomization to the first patient every day, assigning one group even numbers and the other group odd numbers on the cast of the dice. The first patient was assigned to the one group, the second patient was assigned to the other group, the third to the one group, and so on. 4) Nurse B prepared the medicinal solutions (PS, MH, or BRS), and tools (syringes and boxes were of the same shape, and every solution was transparent, colorless and odorless). 5) Nurse A handed over a randomized syringe to physician B. 6) Physician B performed the interfascial injection under ultrasonography. 7) Nurse C (estimator of the outcomes) recorded the outcome measurements.

### **Injection points and injected volume**

The injected points were either the most painful point on the margins of the MPS-affected muscle (inter-muscles) or the point between the muscle and the bone. We selected the 4 following spaces and injection volumes: between TSM and the vertebra when the affected muscle was TSM (injected volume: 10 ml); between LSM and SM when the affected muscle was LSM and SM (5 ml); the space between LSM and TM when the MPS-affected muscle was LSM and TM (5 ml); between ISM and the scapula when the affected muscle was ISM (7 ml).

### **Protocol of interfascial injection under ultrasonography**

We defined “interfascial space” as the space outside of a muscle or a tendon (i.e., subcutaneous space, the space between epimysiums, the space between the periosteum and epimysium, and the space around tendons). Each patient was given a single injection of a randomized solution. The patients’ positions during the injection were supine, lateral or prone, for comfort. We performed the injections with 23-gauge needle (outer diameter: 0.60 mm, length: 60 mm) for the space between TSM and the vertebra, and with 27-gauge needles (outer diameter: 0.40 mm, length: 19 mm or 38 mm) for the others.

We performed interfascial injection under ultrasonography. The representative injected solutions between the LSM and TM were shown in Fig. 1a. To identify the interfascial space between TSM and the vertebra, we also applied the so-called “loss-of-resistance technique,”<sup>17</sup> which were

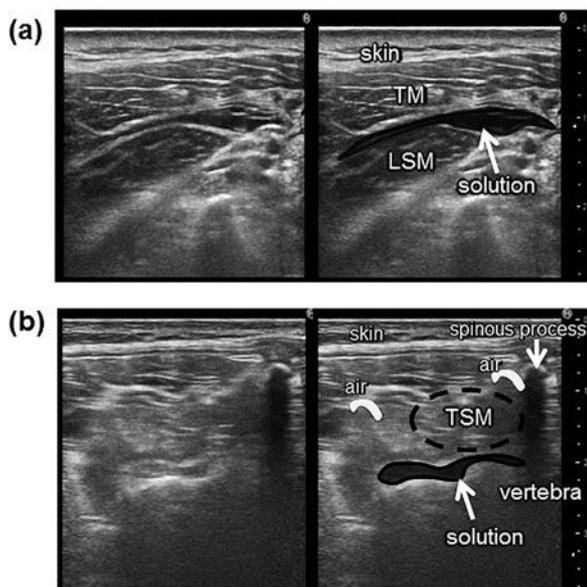


Fig. 1. Injected solutions between interfascial spaces under ultrasonography.

(a) Injected solution between the levator scapulae muscle (LSM) and the trapezius muscle (TM). (b) Injected solution between the transversospinal muscle (TSM) and the vertebra after the "Loss of resistance method."

generally performed to identify the epidural space during epidural puncture under ultrasonography (Noblus by Hitachi Aloka Medical, Co., Ltd., Tokyo, Japan. Authorization number: 224ABBZX-00092000); 1) A needle with air in the syringe was inserted into the skin. 2) By slowly introducing the needle into the interfascial space with intermittent or continuous pressure on plunger of the syringe, we confirmed the interfascial space by checking air spreading into the space under ultrasonography and/or the feeling of sudden loss of the pressure on plunger of the syringe. 3) We injected the randomized solution at the designated site under ultrasonography. The injected solutions between the TSM and the vertebra were shown in Fig. 1b.

#### Protocol after interfascial injection

We used no other treatment (e.g., no physiological therapy, acupuncture, massage, hot pack, nor additional medications). We kept the patients at rest in bed until 30 minutes after the injection, and then checked their blood pressure and looked for any adverse events. We asked patients for their cooperation in not using any other treatments until their recordings were finished, but they were allowed to receive any other treatment they wished. If they received any other treatments,

however, we would exclude them from the study. We allowed the patients to ask us about the present study and their conditions by snail mail, e-mail and telephone. The patients were asked to turn in their finished records to the clinic by hand or mail after the protocol.

#### Statistics

For analyses of change in maximum pain related to motion (NRS) of primary endpoint, we tested the 2-way repeated measure ANOVA, followed by Holm-Sidak multiple comparison tests, if warranted. The data were expressed as mean  $\pm$  SEM. We tested our hypotheses on quantitative data about the time of pain relief, pain related to interfascial injection, adverse events, and passive ROM with Mann-Whitney's *U* test. A *P* value of  $< 0.05$  was considered significant. All calculations were carried out with the SigmaPlot 12.5 statistical software (Systat Software, Inc. USA).

Sample size calculation was performed to primary endpoint before the studies started. Our intention was to analyze at least 18 patients per group, which if given a standard deviation of 1.8<sup>18)</sup>, would have provided 90% power at the 5% significance level to detect a 2-point difference in change in maximum pain related to motion. We estimated a dropout rate of 10% and therefore aimed to recruit 40 patients for each trial. Forty-one patients participated in the first trial as well as the second. The size was decided upon considering the minimum number of participants needed to detect a clinically-worthwhile difference from an ethical point of view<sup>19)20)</sup>.

## RESULTS

#### Baseline characteristics

In the first trial (Fig. 2a), we included 41 patients; 20 patients were randomly assigned to the PS group and 21 patients to the MH group. In the second trial (Fig. 2b), we also included 41 patients; 21 patients were randomly assigned to the BRS group and 20 to the PS group. No patients were lost to follow-up in either trial. Six patients were overlapped between the first trial and the second. The groups of patients in both trials had no statistically significant difference in demographic (e.g., mean age, woman sex, mean disease duration, drugs taken) and disease characteristics (e.g., mean pain intensity of MPS affected muscle before the injection) (Table 1).

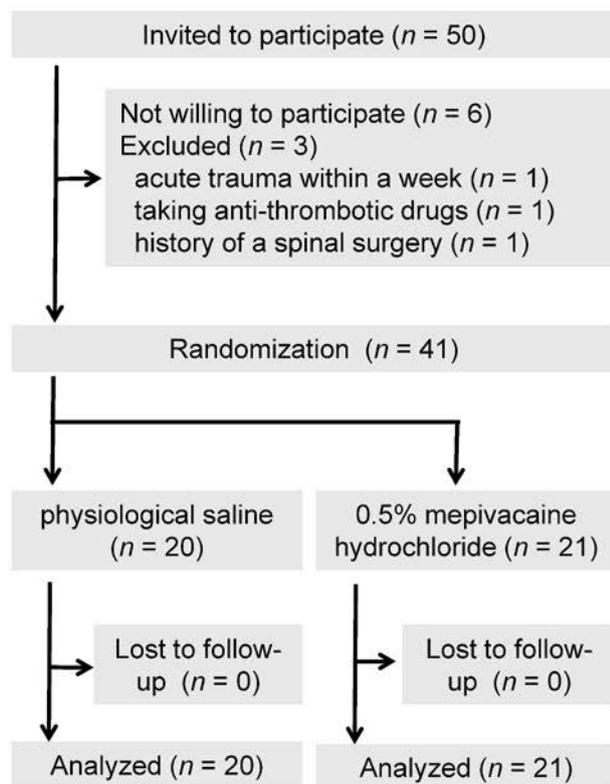
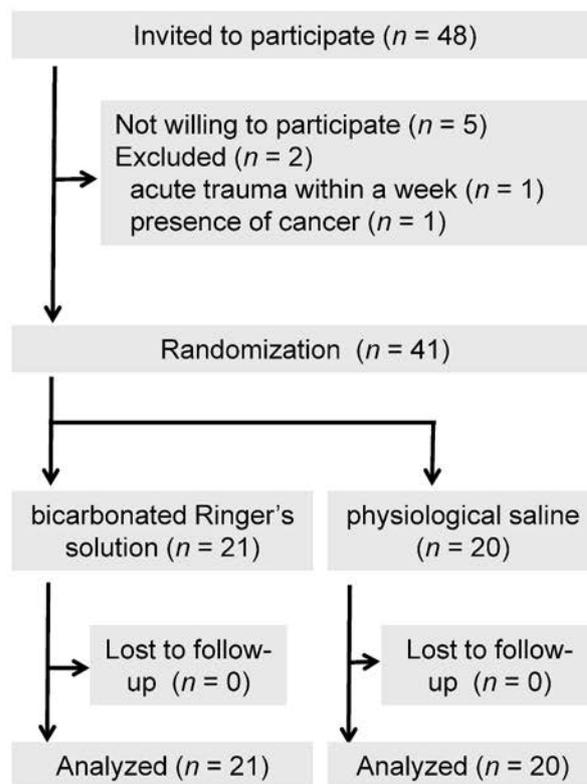
**(a) In the first trial****(b) In the second trial**

Fig. 2. Flowchart diagram according to CONSORT statement for the report of randomized controlled trials. (a) Participant flow chart in the first trial. (b) Participant flow chart in the second trial.

Table 1. Baseline characteristics of the first and second trial

Characteristics	First trial		Second trial	
	PS (n = 20)	MH (n = 21)	BRS (n = 21)	PS (n = 20)
Mean (SD) age (years)	44.5 (13.9)	53.0 (14.8)	43.0 (13.0)	47.0 (14.9)
Woman sex (No (%))	13 (65.0)	12 (57.1)	10 (47.6)	13 (65.0)
Mean (SD) disease duration (years)	3.4 (3.8)	3.6 (2.8)	3.9 (4.3)	4.2 (2.6)
Mean (SEM) pain intensity before injection (NRS)	7.2 (0.3)	6.9 (0.3)	7.7 (0.2)	7.4 (0.4)
Injection points (No (%)):				
between TSM and vertebra	5 (25.0)	9 (42.9)	9 (42.9)	6 (30.0)
between LSM and SM	9 (45.0)	6 (28.6)	5 (23.8)	8 (40.0)
between LSM and TM	6 (30.0)	6 (28.6)	6 (28.6)	5 (25.0)
between ISM and scapula	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.7)
Fibromyalgia (No (%)) <sup>a)</sup>	1 (5.0)	1 (4.7)	0 (0.0)	1 (4.7)
Drugs taken (total) (No (%)) <sup>b)</sup>				
non-steroidal anti-inflammatory drugs (No (%))	0 (0.0)	1 (4.7)	2 (9.5)	2 (10.0)
psychotropic drugs (No (%))	2 (10.0)	2 (9.5)	3 (14.3)	2 (10.0)
herbal medicine (No (%))	2 (10.0)	3 (14.3)	3 (14.3)	4 (20.0)

PS: physiological saline. MH: 0.5% mepivacaine hydrochloride. BRS: bicarbonate Ringer's solution. TSM: transversospinal muscle. LSM: levator scapulae muscle. SM: middle scalene muscle. TM: upper parts of the trapezius muscle. ISM: infraspinatus muscle.

<sup>a)</sup>Diagnostic criteria of fibromyalgia (American College of Rheumatology. "FAST FACTSa") are as follows. There are 18 designated possible tender points. The patient must feel pain at 11 or more of these points for fibromyalgia to be considered. <sup>b)</sup>The detail includes overlap.

**Confirmation of interfascial injection under ultrasonography**

We checked the injected fluid in the interfascial space by ultrasonography. Ultrasonography examination revealed that we could successfully perform the “interfascial” injection in all patients involved in our trials.

**Endpoints in the first trial (MH vs. PS)**

Regarding the primary endpoint, the mean NRS score in maximum pain related to motion decreased significantly “after the treatment” compared to “before the treatment” during the entire observation in both the PS and MH groups ( $p < 0.01$ ). The PS group showed significantly lower NRS scores compared to the MH group (adjusted whole group difference;  $p < 0.05$ ). Although there was no

statistical difference between the groups until 9 hrs after injection, decreases in the NRS score in the PS group were significantly greater than in the MH group from 10 through 72 hrs after injection; from 10 to 12 hrs after injection ( $p < 0.05$ ), and from 24 to 72 hrs after injection ( $p < 0.01$ )(Fig. 3a).

Concerning 4 secondary endpoints, the PS group showed a significantly longer lasting time of pain relief ( $p < 0.01$ )(Fig. 3b) compared to MH. The PS group showed greater intensity ( $p < 0.05$ )(Fig. 3c) and duration ( $p < 0.01$ )(Fig. 3d) of pain related to injection compared to the MH group. The passive ROM of the MPS affected muscle after the injection improved in both groups (20/20 in the PS group, 21/21 in the MH group). No serious adverse reactions were observed. Mild reactions after the injection (heavy feeling around the injection area) were reported by 2 patients

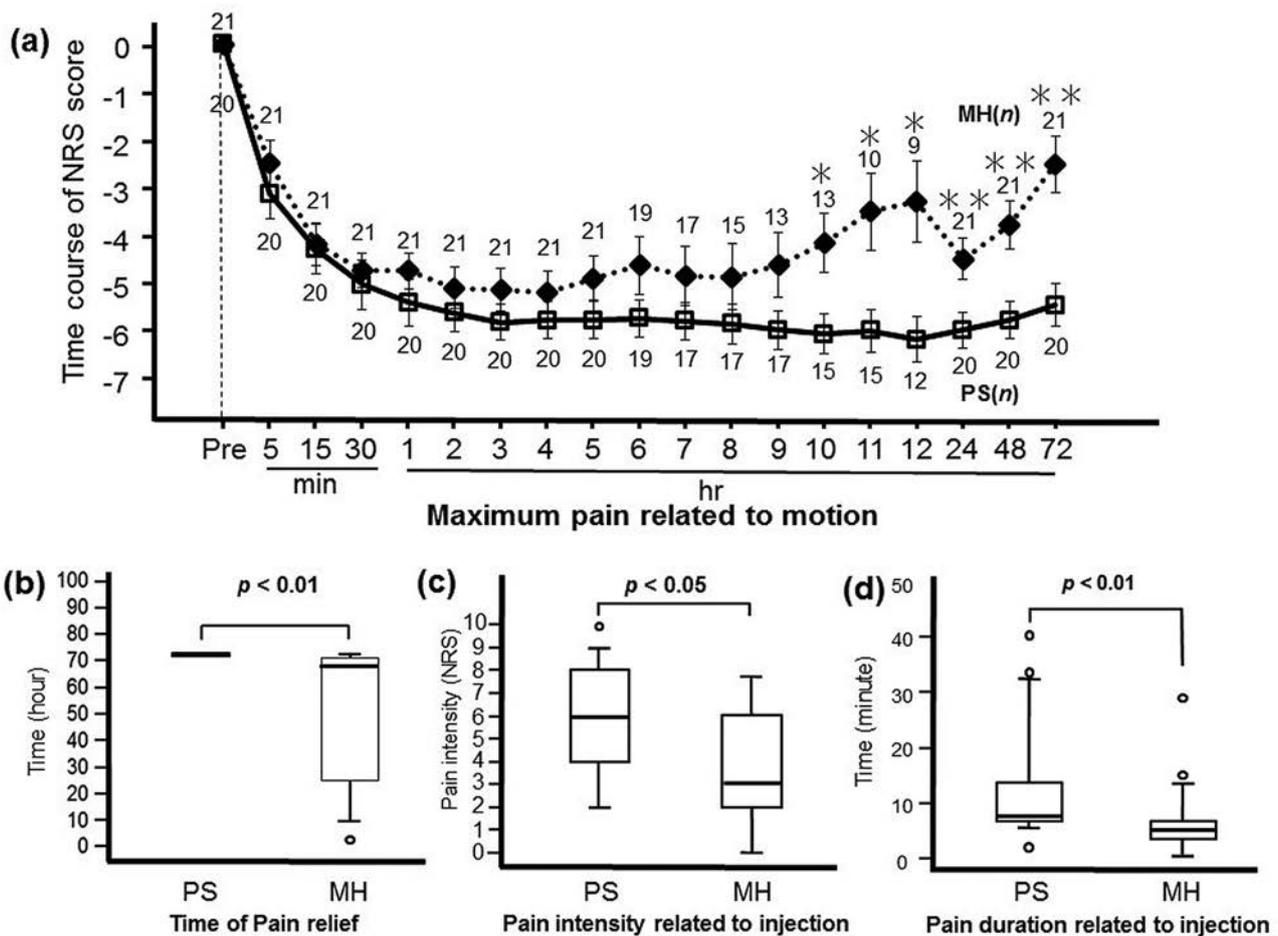


Fig. 3. Results of the first trial. (a) The time course of the NRS score in the maximum pain related to motion (the primary endpoint) in the first trial. MH: (·◆·). PS (◻). Data are presented as mean ± SEM. \* $p < 0.05$ , \*\* $p < 0.01$ . (b) Time of pain relief (hr). (c) Pain related to injection (pain intensity (NRS)). (d) Pain related to injection (pain duration (minute)). Data are presented as box (median ± interquartile (IQR) and whiskers (10 and 90 percentile values). o: outliers. PS: physiological saline. MH: 0.5% mepivacaine hydrochloride.

in the PS group, and by 3 patients in the MH group.

To confirm that participants were kept blind until the study had finished, they were asked whether they knew the group to which they were assigned after turning in the records of the first trial. The answers of PS-injected patients ( $n = 20$ ) were as follows. Four patients answered “PS”, 2 patients answered “MH”, and 14 patients answered “unknown”. The answers of MH-injected patients ( $n = 21$ ) were as follows. Eight patients answered “PS”, 5 patients answered “MH”, and 8 patients answered “unknown”. The percentage of correct answer was 22% (9/41, 95% confidence interval 13-35%). The percentage of “unknown” was 54% (22/41, 38-69%). The results suggested that participants of the first trial were indicated to be blinded throughout the trial.

**Endpoints in the second trial (BRS vs. PS)**

Regarding primary endpoints, the mean NRS score of maximum pain related to motion decreased significantly “after the treatment” compared to “before the treatment” in both the BRS and PS groups ( $p < 0.01$ ). However, the time courses of the NRS scores were not statistically different between the BRS group and the PS group ( $p = 0.33$ )(Fig. 4a).

Concerning 4 secondary endpoints, there was no difference in the time of pain relief between the groups ( $p = 0.84$ )(Fig. 4b). The BRS group showed less intensity ( $p = 0.05$ )(Fig. 4c) and duration ( $p < 0.01$ ) (Fig. 4d) of pain related to injection than the PS group. The passive ROM of the MPS affected muscle after the injection improved in both groups (20/20 in the PS group, 21/21 in the BRS group). No serious adverse reactions were observed. Mild reactions after the

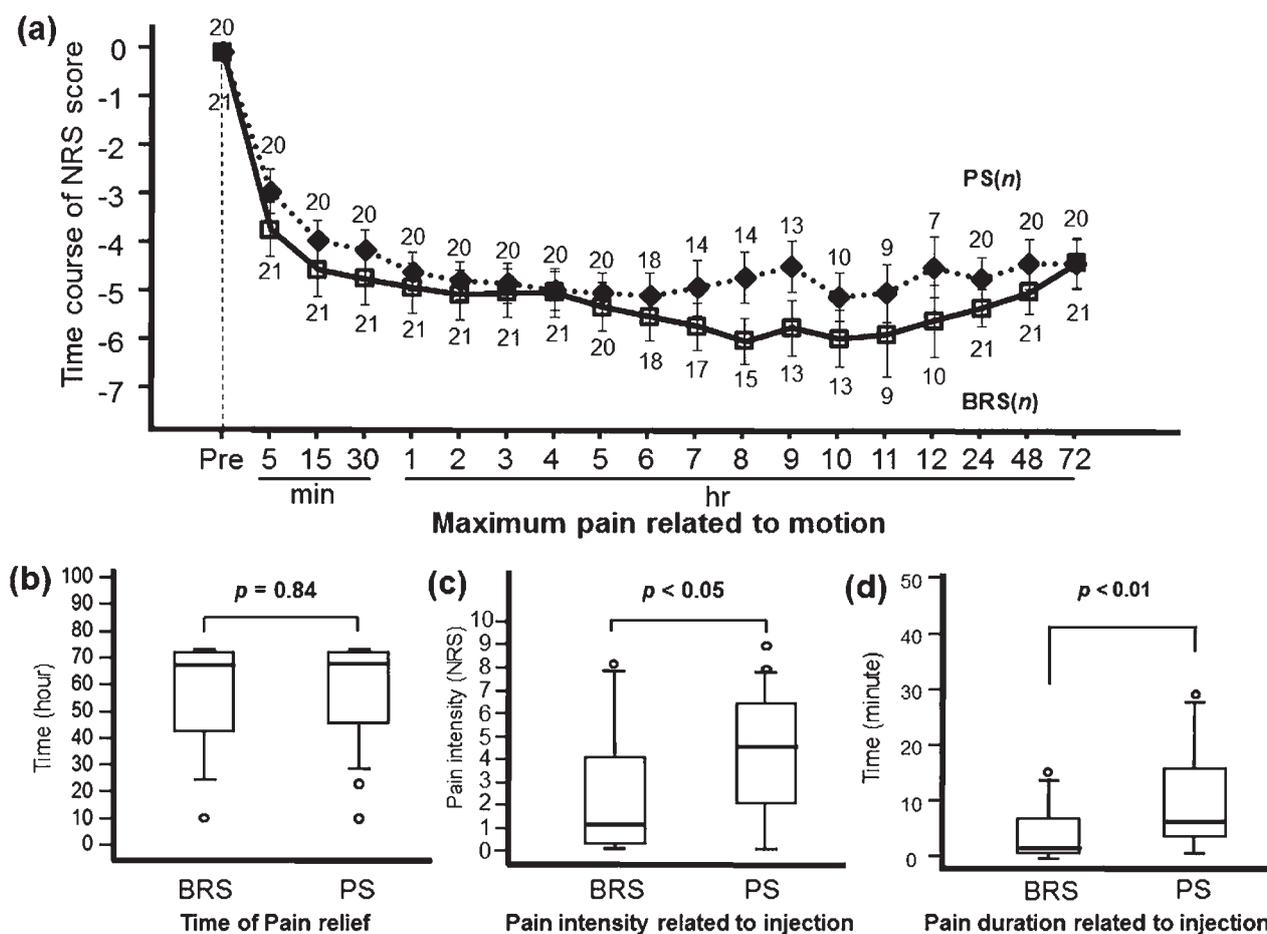


Fig. 4. Results of the second trial. (a) The time course of the NRS score in the maximum pain related to motion (the primary endpoint) in the second trial. PS (·◆·). BRS (◻). Data are presented as mean ± SEM. (b) Time of pain relief (hr). (c) Pain related to injection (pain intensity (NRS)). (d) Pain related to injection (pain duration (minute)). Data are presented as box (median ± interquartile (IQR)) and whiskers (10 and 90 percentile values). o: outliers. BRS: bicarbonate Ringer’s solution. PS: physiological saline.

injection (heavy feeling around the injection area) were reported by a patient in the PS group, but not in the BRS group.

## DISCUSSION

The present studies indicated that interfascial injection of PS provided MPS patients with a longer analgesic effect and more pain related to injection than MH. In addition, BRS was equivalent to PS in analgesic effect and less problematic than PS in pain related to injection. The interfascial injection of BRS can thus be recommended as a more effective, and less painful local treatment for MPS patients.

### Study design and limitations

Our study had 4 limitations. First, we chose to conduct 2 rounds of two-armed studies instead of one round of a three-armed trial. A three-armed trial would have required 75 patients. We sized up the situation that the maximum number of MPS patients was approximately 40 in a week when we could conduct one trial. We were concerned that symptoms and responses to our injections of the patients would be influenced by various factors including weather if more than one trial was conducted in different seasons. Symptoms of patients with chronic pain were influenced by bad weather and oncoming bad weather<sup>21)22)</sup>. Second, we examined the short-term outcomes of a one-time approach to chronic pain (MPS) in our trials. Seventy-two hrs was considered to be the longest observation period possible that would not ethically interfere with the patients' usual treatments, since we treat MPS patients twice a week when needed. Systematic reviews have shown that a one-time treatment of chronic pain does not result in long-term effects<sup>23)24)</sup>. Irinich indicated the possible longer-lasting benefit of acupuncture, which might have action mechanisms similar to interfascial injection of BRS<sup>18)</sup>. In the future, we should evaluate the long-term effects (beyond 72 hrs) and the effects of repeated interfascial injections of BRS. Third, although 6 patients were overlapped between the first trial (from January 26<sup>th</sup> to February 2<sup>nd</sup> 2013) and the second (from March 11<sup>th</sup> to 16<sup>th</sup> 2013), we did not consider it a problem because we performed the second trial more than a month after the first trial. Finally, the difference in the maximum pain related to motion between "before" and "after the injection" might have been affected by the placebo effects (e.g., the use of ultrasonography as a high-tech device, the

expectation for the therapeutic procedure in the clinical study), and confounding factor (e.g. repeat measurement of maximum pain related to motion is associated with stretching, one of the therapies for MPS.). We used NRS as pain intensity scale instead of visual analogue scale (VAS) for the assessment of the maximum pain related to motion, although the assessment of pain in motion by NRS was rarely reported. Because, NRS has been shown to be as much sensitive as the VAS, and is preferred over VAS by patients for its relative simplicity and ease of administration and scaling<sup>25)</sup>.

### Choice of solutions

The Cochrane Database showed that adjusting the pH of a solution to a level closer to the physiologic pH 7.4 reduces pain related to injection<sup>9)</sup>. Commercially available PS usually has a pH around 5.5 but can be as low as 4.6<sup>26)</sup>. Commercially available MH can have a variable pH (between 4.5 and 6.8). In the first trial, we chose the MH (pH 6.0, osmotic pressure 1.1 to PS; AstraZeneca plc, London, United Kingdom) as the local anesthetic, and the PS (pH 6.0; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), because both have a pH and osmotic pressure very similar to each other and have been widely used for local injection in Japan. In the second trial, we chose BICANATE® (pH 7.4, osmotic pressure 0.9 to PS, Mg<sup>2+</sup> 2 mEq/L; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) as BRS, because BICANATE® has the pH most similar to blood plasma (pH 7.4) available in Japan.

### Choice of injection points

Although the interfascial space with thick nerves (e.g., brachial plexus, axillary nerve, dorsal scapular nerve) running was presumed to be an effective space for performing the interfascial injections of a non-anesthetic agent, this space was not selected for our trials because the injection of a local anesthetic may cause hypoesthesia or paralysis. Therefore, we chose the 4 interfascial spaces so as not to let the participants know to which group they were assigned.

### Pathophysiology of MPS

The pathophysiology of MPS has not been fully understood. Some hypotheses have been proposed<sup>27-29)</sup>. More recently, myofascial trigger points have been considered as sites where nociceptors, such as

polymodal-type receptors, are sensitized by various factors (e.g., chemical, thermal, and mechanical stimulations)<sup>30-32</sup>. In the myofascial trigger points compared to a normal muscle tissue, pH was low and the concentration of algescic substances (e.g., substance P and bradykinin) was high<sup>33</sup>. Low pH might contribute to the pathogenesis of peripheral hypersensitivity in chronic muscle pain via activating acid-sensing ion channels<sup>34</sup>. In addition, the viscoelasticity of myofascia was reported to modify activation of the neuronal transducers (e.g., mechanoreceptors respond to surrounding tissue viscoelasticity) within myofascia<sup>35</sup>. Peripheral afferent in a muscle was responding to noxious stimuli to the myofascia<sup>16,36</sup>. Accordingly, we speculated that low pH, algescic substances, and mechanoreceptors in the interfascial space might be involved in the pathophysiology of MPS.

#### **Possible action mechanism of interfascial injection for MPS**

Little is known about the action mechanism of interfascial injection on MPS. We speculated the following mechanisms of interfascial injection by MH, PS and BRS: 1) Na channel block by a local anesthetic; 2) acid stimuli by injection of low pH solution; 3) puncture stimuli by needle injection (same as acupuncture); 4) mechanical stimuli to myofascia by solution injection; 5) washout of the various algescic substances in the interfascial space; 6) decreasing of the viscosity of interfascial fluid by injected solution; and 7) separation of the myofascial layers which reduces muscular friction resulting in smooth movement.

Our first trial indicated that Na channel block by a local anesthetic did not have any factor affecting the analgesic effect of the interfascial injection for MPS because PS was more effective than MH (a local anesthetic). The strong pain intensity on PS injection might be related to the low pH because the pH of the PS we used was about 6.0.

Some studies indicated that the stronger the intensity of pain related to injection, the greater its analgesic effect<sup>7,8</sup>. However, our second trial showed that the strong intensity of pain related to injection and/or acid stimuli was not a factor related to its analgesic effect, because BRS (pH 7.4 and similar osmotic pressure to PS) was as effective as PS (pH 6.0). Therefore, we speculated in light of these considerations that the factors contributing to the

analgesic effect of interfascial injection are themselves stimuli to mechanoreceptors by needle puncture, mechanical stimuli by solution injection, the washout of various algescic substances in interfascial space which might stimulate hypersensitive nociceptors, decrease of the viscosity of interfascial fluid, and/or the separation of the myofascial layers which reduces friction. These possible affecting factors associated with the injection might produce the analgesic effect on MPS via normalizing the physiological function of interfascial space.

#### **Conclusion**

This study examined the effects of interfascial injection of PS, MH and BRS on MPS. The results suggested that the interfascial injection of PS had a greater analgesic effect on MPS but produced stronger pain related to injection compared to MH. BRS was equivalent to PS in analgesic effect and produced less pain related to injection compared to PS. Thus BRS would be the appropriate solution by interfascial injection for local therapy to MPS patients. The benefits of BRS are as follows: 1) effective, 2) less pain related to injection, and 3) no anesthetic side-effects. The action mechanisms may not be proportionate to the strong pain related to injection nor the pharmacological anesthetic effect.

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