The effects of radiofrequency hyperthermia on pain and function in patients with knee osteoarthritis: a preliminary report

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Abstract

Background The clinical evidence of the efficacy of hyperthermia on osteoarthritis (OA) has not yet been clearly established. In addition, the application of a modality that can control the temperature inside the joints has not been reported. The purpose of this study was to investigate the effect of percutaneous radiofrequency hyperthermia, which could safely raise the temperature of the body core, in patients with OA knees.

Methods Temperature changes inside the knee joint without OA were measured during exposure to radiofrequency. Radiofrequency hyperthermia was performed on 12 OA knees by exposure to 8 MHz and 200 W for 20 min, 3 times, at 1-week intervals. The clinical outcome was evaluated by use of the Lequesne index (LI) and the Japan Orthopaedic Association (JOA) scale. The osteoarthritis research society international (OARSI) responder criteria were also analyzed.

Results Radiofrequency hyperthermia of 8 MHz and 200 W for 20 min increased the temperature inside the joint from 34.4 to 39.4°C. The LI decreased by 3.55 points from baseline during the 3 weeks. The JOA scale improved significantly during the period, reaching 86.25 points at the final examination from baseline of 67.5 points. 67% of patients had a response to the therapy according to OARSI criteria. No side effects were observed.

Conclusions Radiofrequency hyperthermia can safely increase the temperature inside the knee joint. Radiofrequency hyperthermia on OA knees provides a remarkable pain relief effect and can improve the patients’ daily life. In the future, clinical studies should be performed with a protocol containing more cases, with appropriate control groups.

Introduction

Osteoarthritis (OA) results from gradual degeneration of the articular cartilage and the number of patients with symptoms has been increasing in this aging society [1]. Because it causes significant damage to joint function, it restricts daily life and social activity. When joint deformity progresses, surgical procedures, including total joint replacement or corrective osteotomy, are normally selected for treatment. Because medical therapy such as oral administration of non-steroidal anti-inflammatory drugs can neither change the natural course of OA nor greatly suppress the progression of OA, it is necessary to establish a treatment strategy taking into consideration different aspects, for example developing effective physical therapy and combining such therapy with drug treatment. Hyperthermia is commonly used for clinical treatment of OA; currently a hot pack or ultrashort-wavelength irradiation is generally used, although clinical evidence of efficacy is not yet adequate [2]. In addition, application of a modality that
can affect the temperature of articular cartilage and subchondral bone deep inside the joint structure has not been reported.

Radiofrequency waves are electromagnetic waves with a frequency of from 3 to 30 MHz. These can heat the body from inside by utilizing thermogenesis caused by the dielectric loss. Radiofrequency hyperthermia has been primarily used as an adjunct therapy for malignant tumors and is known for its effectiveness both in removing cancer pain and in minimizing tumors. In orthopaedics, the analgesic effect of percutaneous radiofrequency hyperthermia has been reported for sacroiliac arthralgia [3]. Arthroscopic ablation of degenerating cartilage by radiofrequency treatment, by inserting a single or bipolar electrode into the joint, has been reported [4]. Nonetheless, to date, no cases in which radiofrequency hyperthermia was applied noninvasively for OA have been demonstrated. The purpose of this study was therefore to examine whether radiofrequency hyperthermia could safely increase the temperature inside joints by exposing knees percutaneously. We also attempted to clarify the therapeutic potential of percutaneous radiofrequency hyperthermia in patients with OA knee.

**Subjects and methods**

This study was approved by the local Ethics Committee of Nippon Medical School. The purpose and method, and the risk of side effects, for example burns and their countermeasures, and the method of protecting personal information, were explained to patients, and written informed consent was obtained from them. One of the authors became a subject by agreeing to temperature measurement inside the joints.

Measuring the temperature changes inside knee joint resulting from radiofrequency hyperthermia

After sterilizing the normal left knee of a healthy subject (one of the authors) with isodine, a sterilized thermocouple was inserted from the lateral side between the patella and the femur. The Thermotron-RF8 (Yamamoto Vinita, Osaka, Japan) which can expose the human body to radiofrequency irradiation of 8 MHz was used for hyperthermia. The subject lay down in a lateral position with the corresponding knee downwards, and the knee was then tightly sandwiched by applicators at the center of the internal and external condyle of the femurs (Fig. 1). Cyclic water in the applicator was set at 25°C, and the skin of the contacting part was cooled. In a preliminary experiment that involved healthy subjects (three of the authors), the knee was exposed to radiofrequency irradiation, and the output at which none of the subjects felt heat around the knee was determined. As a result, the output of the radiofrequency irradiation was found to be 200 W. Radiofrequency hyperthermia of 8 MHz and 200 W was performed for 20 min, and the temperature inside the joint was measured with a thermocouple at 1-min intervals. The temperature of the skin surface of the medial side of the knee was measured at the same time. The radiofrequency hyperthermia used in the experiment below was performed at the same position, frequency, and output.

**Radiofrequency hyperthermia of knee OA**

The subjects comprised 12 joints of 11 patients (1 male and 10 females) enrolled from outpatient orthopaedic clinics at Hara Orthopaedic Hospital and Hashimoto Clinic, aged 62–81 years (mean 70.4 ± 6.4 years) who were diagnosed as having knee OA on the basis of American College of Rheumatology (ACR) criteria. According to Kellgren–Lawrence grade [5], grades were: II, 6 joints; III, 5 joints; VI, 1 joint, and an early to advanced stage of OA was prevalent. For all cases, knee pain had not improved despite administration of anti-inflammatory drugs or intra-articular injection of hyaluronic acid for 3 months. More than a month after the last intra-articular injection of hyaluronic acid or corticosteroid, radiofrequency hyperthermia was started. The hyperthermia was performed by use of radiofrequency irradiation at 8 MHz and 200 W for 20 min, 3 times, at 1-week intervals.

**Clinical evaluation**

Outcome was evaluated using the Lequesne index (LI) [6], the Japan Orthopaedic Association (JOA) scale [7], the Western Ontario and McMaster Universities Osteoarthritis
Index (WOMAC) [8], and pain on a 100-mm visual analogue scale (VAS). For a comparison among the trial periods, the variables of the LI, JOA scale, WOMAC pain subscale, WOMAC function subscale, and VAS scores were measured at baseline and at weeks 1 (1 week after the first hyperthermia) and 3 (1 week after the last hyperthermia). Urine for OA biomarker CTX-II was collected at baseline and week 3. Urine samples were assayed by use of a specific competitive ELISA using a mouse monoclonal antibody (Urine CartiLaps EIA kit, Immunodiagnostic Systems, UK). Concentration of CTX-II in the urine (ng/ml) was divided by the concentration of creatinine in the urine (mmol/dl) for adjustment purposes. Repeated-measures analysis of variance (ANOVA) was applied. Tukey’s post hoc tests were performed when significant differences between trial periods were found. Paired t tests were used to compare the difference in CTX-II concentration between baseline and 3 weeks after the first exposure. P < 0.05 was regarded as significant. Values were expressed as mean ± the standard deviation of the mean (SD). The osteoarthritis research society international (OARSI) responder criteria was analyzed according to the WOMAC (OMERACT–OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited) [8].

Results

Exposure to radiofrequency irradiation for 20 min at 200 W linearly increased the temperature inside the joint from 34.4 to 39.4°C (Fig. 2). The temperature of the skin remained consistent at approximately 30°C. In the 5 min after terminating exposure to radiofrequency irradiation, the temperature inside the joint dropped approximately 0.3°C every minute; subsequently, the drop in temperature became gradual (data not shown). The experiment below was performed under these conditions.

The mean LI score decreased progressively during 2 weeks of treatment and at the final examination 1 week after the last hyperthermia, relative to the baseline value of 9.55 points. The reductions were significant throughout the period. LI reduction of 3 points or more is reported to be indicative of clinically clear effects. In this study, mean absolute score reductions reached 3.55 points at the final examination (Fig. 3).

JOA scale improved significantly over time, reaching 86.25 points at final examination from a baseline average score of 67.5 points (Fig. 4). Five joints (62%) reached 95 points or more and almost all of the symptoms were eradicated. The VAS scores for pain also improvement.
significantly 3 weeks after starting the treatment (65.4 ± 14.8) compared with the baseline value (36.5 ± 29.5) (Fig. 5).

Of the patients, 67% (8 joints out of 12) had a response to therapy according to OMERACT–OARSI criteria; this is considered to be a high percentage, in comparison with other conservative therapies (Table 1) [9–11].

The baseline amount of CT-XII in urine was 509 ± 278 (ng/mmol) and this dropped to 465 ± 290 (ng/mmol) 3 weeks later; however, this change was not significant. Among the 12 cases, it increased in 6 cases and decreased in another 6 cases; however, there was no relationship with symptoms.

During the study, no side effects such as exacerbation of swelling, burning, or parasthesia were observed to result of exposure to radiofrequency irradiation.

Discussion

In clinical settings, hyperthermia is widely used in physical therapy for motor system disorders [12]. For joint disorders, for example OA and rheumatoid arthritis, especially, physical rehabilitation combining therapeutic exercise with hyperthermia by using a hot pack or ultrashort-wavelength irradiation is generally performed. The local thermal effects of these modalities on soft tissues are reported to include increased extensibility of collagen fibers [13], analgesic effect because of increased pain threshold [14], hypotonia action because of reduced extension receptivity in the muscle spindles [15], increased regional blood flow [16], and accelerated effects of tissue metabolism. Hyperthermia for treatment of joint disorders has been considered to be effective in joint range-of-motion exercises because it reduces pain and tenseness in the muscles, although so far few clinical studies have been reported. In this study, the following 2 aspects have become clear:

1 exposure to radiofrequency irradiation can safely increase the temperature inside the knee joint; and
2 radiofrequency hyperthermia on the OA knee provides remarkable pain relief effect and can improve the patients’ daily life.

Table 1 Reported OMERACT–OARSI response to conservative treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OMERACT–OARSI response (%)</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Insole or brace</td>
<td>17</td>
<td>[9]</td>
</tr>
<tr>
<td>Hyaluronic acid (molecular weight 6 million)</td>
<td>54</td>
<td>[10]</td>
</tr>
<tr>
<td>Radiofrequency hyperthermia</td>
<td>67</td>
<td>This study</td>
</tr>
</tbody>
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Fig. 5 Effect of radiofrequency irradiation as evaluated on a visual analogue scale (VAS). The mean value of VAS (100 mm scale) ± SD is shown for three chronological points, specifically at baseline, week 1, and week 3. A statistically significant decrease was observed at both week 1 and week 3 (P < 0.05).

Table 1 Reported OMERACT–OARSI response to conservative treatments

The Thermotron-RF8, which was used for thermotherapy for the OA knees in this study, causes less burden on the entire body because only the part sandwiched between the electrodes is heated. It raises the temperature of the body core by use of intermittent radiofrequency oscillators that reduces the feeling of heat experienced by the patient. Moreover, it has another unique characteristic that prevents heat burn—combination with the use of a surface-cooling system to inhibit heating of the fat tissue. This study verified that exposure to a radiofrequency irradiation of 200 W for 20 min causes the temperature inside the joint to increase to approximately 40°C. It did not exacerbate the swelling of OA, and, according to biochemical examination of the blood, it did not cause an inflammation reaction (data not shown).

The intensity and duration of hyperthermia used in a clinical setting are determined on the basis of experience, and their effects are rarely scientifically based. In this study, duration and output of the exposure to radiofrequency irradiation was intended to raise the temperature inside the joint to 40°C because of data from some previous basic studies. Hojo et al. [17] evaluated proteoglycan metabolism by applying heat stimulation to cultured chondrocytes. According to the results, metabolism rose at 39 and 41°C but decreased at 43°C. The longer the duration of the heat stimulation, the greater the decrease in metabolism at 43°C. On the other hand, Tonomura et al. [18] employed a clinically used 2.45-GHz microwave applicator on the knee joint of a rabbit for 20 min. Expression of proteoglycan and type II collagen in the articular cartilage increased significantly when the temperature inside the joint was increased to approximately 40°C. Moreover, heat shock protein 70 (HSP 70) accumulated in chondrocytes when the articular cartilage was heated to 40°C in vivo.
Effects of HSP 70 are to inhibit apoptosis of chondrocytes [19] and to accelerate proteoglycan metabolism [20]. Taking into account these data, heating at 40°C became the target temperature in our study during exposure to radiofrequency irradiation because it is advantageous to cartilage metabolism. The limited margin of error is an issue, because even a small difference in the temperature can result in different effects. With the 2.45-GHz microwaves often used in clinical settings, it was difficult to adjust the temperature inside the joint and it exceeds 40°C in some parts. In addition, the joint can only be exposed for a short duration because the temperature of the skin rises and this increases the risk of a heat burn at the same output that increases the temperature inside the joint (publication in preparation). With the Thermotron-RF8, radiofrequency hyperthermia can be performed for 20 min to heat the entire joint without any side effects, for example heat burn.

In clinical research there is only a small amount of evidence that supports the efficacy of hyperthermia for treatment of OA. In a systemic review of the literature, treatment with hyperthermia by using hot packs did not have any significant beneficial effect when used to treat OA [21]. Recently, clinical improvement of OA has been reported when a heat-retaining knee sleeve [22] or heat-generating sheet [23] is used for a long time. Yet, hot packs or these types of sheet have little effect in heating the body core, because they only increase the temperature of the skin or under the skin. Our study is the first to report relief of the symptoms of OA by use of equipment that can heat the core of the joint.

The mechanism of how pain occurs in OA joints has long been unknown. When OA progresses, subchondral bone resorption pits invade from the subchondral bone beyond the tidemark [24]. Recently, in the pits, calcitonin gene-related peptide (CGRP) immunoreactive nerve fibers have been observed in addition to concentric vascular factors and expression of the nerve growth factor (NGF), which could induce nerve fibers in the pits [25]. The details of the OA symptom-relief effects of radiofrequency hyperthermia remain unknown; however, it will be interesting for future studies to perform research on the effects of radiofrequency irradiation on the expression of NGF [26].

The primary objectives of contemporary therapy for OA are to reduce pain, improve joint function, and improve quality of life, because there is no structure-modifying therapy for OA that has gained consensus at this point. Yet, there is concern regarding OA treatments that just improve the pain of the joint without improving function and structure, because they might accelerate the progression of OA by applying more non-physiological mechanical stress to the articular cartilage. Hyperthermia does not simply relieve the symptoms but also offers the possibility of becoming a disease-modifying therapy, because the beneficial effects of hyperthermia for OA on the articular cartilage has been proved by both cellular and animal research [17–19]. In addition, heat shock proteins induced by mild heat stress are now understood to be involved in processes of chaperon-mediated autophagy, which is essentially a cellular homeostasis mechanism. Abnormal autophagy or decreased stress response could lead to accelerated development of aging-related diseases [27]. The biological effects of radiofrequency irradiation, except for its heating effect, remain unresolved. For future research, it is necessary to analyze the effects of radiofrequency irradiation on the bone and the articular cartilage. In this study, it was difficult to select a placebo that does not involve exposure to radiofrequency irradiation. The extent of the placebo effect of radiofrequency hyperthermia on OA is unclear. Moreover, suitable frequencies and intervals remained to be elucidated. Therefore, further clinical studies should be performed with a protocol containing more cases and appropriate control groups.

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References