Effects of Adjuvant Hydrotherapy on Functional Status and Mental Relaxation in Patients with Knee Osteoarthritis: Preliminary Study

Eun Young Han, MD¹, Bo Ryun Kim, MD¹, Sang Hee Im, MD²,
Jun Hwan Choi, MD¹, Sun Mi Kim, MD¹

¹Department of Rehabilitation Medicine, Jeju National University Hospital, Jeju,

²Department of Rehabilitation, Catholic Kwandong University International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Korea

Background: The aim of this study is to test if adjuvant hydrotherapy with viscosupplement is beneficial on management of pain, stiffness, function, and mental relaxation in knee osteoarthritis (OA).

Methods: Nineteen patients with OA were randomly assigned to hydrotherapy or control groups. All patients received viscosupplement injections once a week for 3 weeks. Hydrotherapy group (n=9) had a spa containing green tea, 3 days a week for 2 weeks. The control group (n=10) received only injections. All patients were assessed at baseline and after the third injection. All were assessed for pain (visual analog scale, VAS), pain severity, and functional status (Western Ontario and McMaster Universities osteoarthritis index, WOMAC), emotional status, quality of life (Euro quality of life health-related quality of life inventory five dimension, EQ-5D), and relative spectral power of alpha waves in electroencephalography (EEG).

Results: Both groups reported a statistically significant reduction of pain at the end of treatment and detailed assessment of pain, and function in WOMAC and the relative power of alpha in electroencephalogram showed statistical significant difference only in the hydrotherapy group. However, there were no significant intergroup differences, except for VAS score.

Conclusion: Adjuvant 2-week hydrotherapy to viscosupplement might have a modest role in the management of pain and functional disability and the mental relaxation in patients with knee OA. Larger, randomized controlled trials with intervention of long term period to determine efficacy in treating knee OA are warranted.

Key Words: Osteoarthritis, Green tea extract, Hydrotherapy, Electroencephalography, Viscosupplement

INTRODUCTION

Osteoarthritis (OA) is the most common form of chronic arthritis¹⁾, causing pain, stiffness, edema, and dysfunction of the involved joint. It has pathologic characteristics

of both focal loss of articular cartilage and marginal and central formation of new bone²⁾. OA is strongly associated with aging, and is a major disability in elderly people in Korea. It also causes various psychological problems, including depression, a sense of alienation, and apathy, reduces quality of life (QoL), and increases the risk of additional morbidity and mortality^{2,3)}.

The objectives of the management of knee OA are to relieve pain, maintain or improve mobility, and minimize disability. Although there are several guidelines on the conservative treatment of OA, most are based on the evidence from pharmacological therapy. However, pharmacological treatments based on symptomatic drugs provide

► Received: July 5, 2014 ► Revised: August 1, 2014

► Accepted: August 27, 2014

Address for correspondence: Bo Ryun Kim, MD, PhD
Department of Rehabilitation Medicine, Jeju National University
Hospital, 15 Aran 13-gil, Jeju 690-767, Korea
Tel: +82-64-717-1671, Fax: +82-64-717-1131
E-mail: brkim08@gmail.com

only short-term pain relief, and their effects are probably too small to be meaningful to patients⁴⁾. Furthermore, many nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with considerable side effects⁵⁾. In addition, intra-articular injection of long acting corticosteroid is indicated for flares of knee pain, especially if accompanied by effusion⁶⁾; however, many practitioners avoid the long-term use of these injections because repeated use may cause cartilage destruction or systemic infection.

On the other hand, hyaluronan is a highly coiled molecule which acts as viscous lubricant, resists compressive forces, and reduces friction between opposing cartilage surfaces⁷⁾. Hyaluronan is associated with a low incidence of local adverse events and is well tolerated, and is therefore recommended for treating less-advanced knee OA of patients⁷⁾. However, patients receiving intra-articular hyaluronic acid (HA) products are known to complain of pain and/or swelling of the injected joint, and systemic hypersensitivity reactions may occur occasionally.

On the other hand, hydrotherapy or spa is one of the most commonly used nonpharmacological approaches for OA⁸⁾ and various recently published systematic reviews and meta-analyses on spa therapy for rheumatic diseases have encouraging evidence of the effect of balneotherapy on knee OA^{8,9)}. However, balneotherapy has a regional limitation and cannot be widely utilized in general. Furthermore, despite the long history and popularity of hydrotherapy, the evidence for its benefit in OA is not clear and it is being challenged to prove its worth.

The current study addressed several objectives. First, as a preliminary study, we evaluated the therapeutic effect of hydrotherapy on pain, stiffness, and function in the elderly patients with OA of knee as an adjuvant treatment method after viscosupplementation. Second, we objectively confirmed the beneficial effects of adjuvant hydrotherapy on mental relaxation using electroencephalography (EEG) and might propose hydrotherapy to create a high-value medical product.

MATERIALS AND METHODS

1. Subjects

Twenty two outpatients who visited the Physical Medicine and Rehabilitation Clinic in Jeju National University between October 26, 2011, and February 28, 2012,

for knee pain for at least 3 months and were diagnosed as having bilateral knee OA according to the American College of Rheumatology Classification Criteria¹⁰⁾ were recruited in this study. All patients had symptomatic knee pain >30 mm as measured by visual analog scale (VAS) for at least 3 months prior to inclusion in the study. Radiological staging was carried out using the Kellgren-Lawrence method¹¹⁾, and patients with a radiological score of I–III were included in the study.

Patients with severe OA (Kellgren score IV), psychiatric disease, impaired cognition (Mini-Mental Status Examination <24), and severe radiating pain in the upper extremities, or with peripheral neuropathy were excluded from the study. Patients who had undergone thermal treatments, joint lavage, arthroscopy, or treatment with intra-articular HA or steroid during the previous 3 months were also not eligible for inclusion. Other exclusion criteria were as follows: allergic reaction to green tea, abnormal neurologic signs, previous spinal or musculoskeletal fracture or surgery, pregnancy, or serious medical illness including comorbidity of the heart or brain, varices, systemic bleeding disease, and neoplasm. This study protocol was reviewed and approved by the Jeju University of Institutional Review Board, and that written informed consent for this research project was obtained from all participants.

1) Group assignment

The patients were randomly assigned to a hydrotherapy group (n=11) or a control group (n=11). Simple randomization was done using a computer-generated table of random numbers. But, after first injection, three participants (two in the spa group and one in the control group) refused evaluation at baseline and were withdrawn.

2. Intervention

1) Ultrasound-guided intra-articular knee injection of HA

HA preparations were administered into the patients' knee joints bilaterally while observing the suprapatellar pouch filling under live ultrasound guidance. The patients reported minimal pain during the procedure and complete injection-related pain relief immediately after the

injection. All patients in both groups received injections once a week for 3 weeks and were allowed to carry out their daily routines during the study period. The use of symptomatic drugs such as analgesics or NSAIDs and physical modalities were discontinued during the intervention period.

2) Hydrotherapy

The patients in the hydrotherapy group ($n=9$; 2 males and 7 females; average, 66.89 ± 7.41 years) immersed their body, up to the xiphoid level, in a whirlpool bath containing 1 kg of green tea leaves at $34\text{--}36^\circ\text{C}$ for 30 minutes. The Jesetter whirlpool bath (Hot Spring Spas N.Z Ltd, Auckland, New Zealand) included 14 jets (two sets of one Motor-Massage DX jet, one Jetstream jet, two rotary Hydromassage jets, one directional Hydromassage jets, four Hydro Stream jets, four directional Precision jets). The treatment room ambient temperature was maintained at around $28\text{--}30^\circ\text{C}$ to prevent patient body heat loss. Hydrotherapy was performed for 30 minutes a day, 3 days a week for a total duration of 2 weeks. The control group ($n=10$; 2 males and 8 females; average, 63.40 ± 7.46 years) received only viscosupplement injection without any other interventions.

3. Evaluation

In this study, a blind researcher for group assignment gave instructions to the patients for the questionnaires and collected the outcome measurements. All participants were assessed before treatment (at baseline) and after treatment (at the end of the third week). All tests were performed within 48 hours after 1st and 3rd injection.

1) Pain severity and functional assessment

The variables evaluated were as follows: pain severity was evaluated using a VAS¹²⁾. The VAS for pain consisted of three 100-mm lines, each of which was labeled with 'no pain' at the left-hand end (0 mm) and 'very severe pain' at the right-hand end (100 mm)¹²⁾. Patients were asked to draw a vertical mark on each line, one on the upper line for their current pain, one on the middle line for the pain at their best (least painful) period during the previous week, and one on the lower line for the pain at their worst (most painful) period during the previous week.

The Western Ontario and McMaster Universities osteoarthritis index (WOMAC) is a multidimensional measure of pain, stiffness, and physical functional disability as an indicator of self-reported disability⁵⁾. WOMAC parameters were scored using the Likert scale (0, no pain; 1, mild; 2, moderate; 3, severe; and 4, very severe pain), which is recommended by the OMERACT (Outcome Measures in Rheumatology Clinical Trials). The sum of the scores was obtained by adding the scores of five parameters of pain (WOMAC total pain score, W-TPS), two parameters of stiffness (WOMAC total stiffness score, W-TSS), and 17 parameters of physical function (WOMAC total physical function score, W-TPFS)^{5,13,14)}. The total subscore for W-TPS and W-TSS ranged from 0 to 20 and from 0 to 8, respectively. W-TPFS rated the degree of difficulty experienced in performing each of 17 activities in the preceding 48 hours, with the total subscore ranging from 0 to 68. Higher scores indicate greater levels of difficulty⁵⁾.

2) Emotional status and QoL

Emotional status and QoL evaluation included depressive mood, which was measured using the Korean version of the Beck Depression Inventory (K-BDI)¹⁵⁾. Anxiety status was measured using the Korean version of the Beck Anxiety Inventory (K-BAI)¹⁶⁾ and QoL was scored using Euro QoL health-related QoL inventory five dimension (EQ-5D). The BDI is a 21-item scale that gathers information on different symptoms of depression^{15,17)}. Each item on the scale is scored from 0 to 3. It provides information on both the presence and severity of depression; higher scores indicate the presence of more severe depression.

The BAI consists of 21 anxiety symptoms, with respondents being asked to indicate the extent to which they were bothered by each item "during the past week, including today"^{16,18)}. Each responses is scored on a 0–3 scale ranging from "not at all" to "severely", the inventory has a score range of 0 to 63. As a recommended scoring and interpretation system for the BAI, scores of 10–18 points are classified as mild-moderate anxiety, 19–29 points as moderate-severe, and 30–63 points as severe anxiety^{16,18)}.

QoL of the patients was assessed using the Korean version of the EuroQoL EQ-5D Index¹⁹⁾. The EQ-5D Index is a widely used measurement of general health status. The instrument comprises a questionnaire with five dimensions: mobility (M), self-care (SC), usual activities (UA), pain/

discomfort (PD), and anxiety/depression (AD). Each dimension is represented by one question with three severity levels (no problems, some or moderate problems, and extreme problems)¹⁹⁾. Scores were transformed by using utility weights derived from the Korean general population¹⁹⁾ and ranged from -1 to 1, with higher scores indicating better overall health status. The formula producing the EQ-5D Index was as presented in Kim et al.¹⁹⁾.

3) Electroencephalography

(1) EEG recordings and experimental conditions²⁰⁾

The participants were seated in a comfortable arm chair in a sound-attenuated, dimly lit EEG room at different day with injection. After having become accustomed to the atmosphere, the participants were checked for 5 minutes resting EEG collection with eyes closed. To avoid any disturbances and interferences, the recording room was shielded with copper. EEG were recorded using silver-silver chloride cup electrodes (Ag-AgCl) attached by collodion, on Fp1 and Fp2 (prefrontal), on F3 and F4 (frontal), on P3 and P4 (parietal), and on T3 and T4 (temporal) scalp regions of the 10–20 international system²¹⁾. All electrode impedances were below 5 kX. The EEG-measurement-device (LEX3208, LAXTHA Inc., Daejeon, Korea) settings were as follows: 256-Hz sampling rate, 12-bit analog-to-digital converter, 0.6-Hz high-pass filter, 46-Hz low-pass filter, and 60-Hz notch filter. The EEG data were visually inspected for artifacts. Data contaminated with artifact were discarded.

(2) Relative spectral power and topographic mapping²²⁾

The raw EEG data were used without any prenormalization. The raw data were used as such except that a 60-Hz notch filter was applied to remove possible artifacts related to power line noise. To estimate the relative power of the EEG data we used a 5-second nonoverlapping sliding window approach. In each window, we computed the relative power in the different subbands: delta (0.1–4 Hz), theta (4–7 Hz), alpha (7–14 Hz), beta (14–30 Hz) and gamma (30 Hz to Nyquist frequency). The relative power can be described as the average of the squared coefficients of the fast Fourier transform in the defined frequency range¹³⁾. To obtain the topographic maps, the relative power was computed for all the electrodes and subbands.

4. Statistical analysis

We analyzed the data using the SPSS ver. 12.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics such as mean±standard deviation were calculated from the data collected. Chi-square tests were used to compare the demographic factors between two groups. In cases where the anticipated frequency was lower than five, a Fisher exact test was applied. We analyzed the changes of the described test items, including the evaluation of VAS, BAI, EQ-5D, and the relative power in the different subbands before and after treatment within the spa and control groups using the Wilcoxon signed rank test. We compared the differences of above test items before and after treatment between the spa and control groups using the Mann-Whitney test. We calculated Spearman correlation coefficients to examine the relationship between independent and dependent variables using the data from baseline measurements. A p-value <0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics of the patients in the two groups

The baseline characteristics of the patients are summarized in Table 1. Baseline comparison of the two groups showed no statistically significant differences in age, gender, mean body mass index, number of patients, baseline severity of pain and anxiety status, QoL, and WOMAC scores ($p>0.05$). The majority of the OA patients were women. At baseline, the median parameters of BAI and BDI were within normal range.

2. Changes in parameters after the 3-week intervention

Both groups reported a statistically significant reduction in VAS pain scale scores at the end of treatment (Table 2) ($p<0.05$). VAS pain scores were reduced more in the hydrotherapy group than in the control group ($p=0.04$).

At the end of treatment, detailed assessment of pain (W-TPS), physical function (W-TPFS) and total scores in

the WOMAC parameters had improved only in the hydrotherapy group. By contrast, in the control group, none of these parameters had changed (Table 2).

At the end of the treatment, the patients' QoL had not changed significantly in either group (Table 2).

The relative power of alpha waves in P4 decreased in the spa group ($p=0.02$) and additionally, the relative power of alpha waves in Fp1, F3, F4, T3, and P3 tended to be reduced in the spa group ($0.05 < p < 0.1$). However, in the control group, the relative power of alpha waves did not change significantly in any EEG region examined (Table 3).

DISCUSSION

This study evaluated the therapeutic effect of adjuvant hydrotherapy with the HA injection on pain and functional disability and mental relaxation in the patients with knee OA for the first time. For the beneficial effects of intra-articular HA injection, previous research reviewed it as an effective treatment for early to moderate OA of the knee on pain, function and patient global assessment, especially at the 5- to 13-week post injection period²³⁾. And another recent systematic review reported that its effects peak around 6–8 weeks following administration of 1st hyaluronan, but it concluded that this injection only has ordinary effects on mild to moderate knee OA. Indeed, the clinical guidelines issued by the American Academy of Orthopedic Surgeons²⁴⁾ and Korean Knee Society Subcommittee⁶⁾ recently don't recommend for or

against the use of intra-articular HA for patients with mild to moderate symptomatic OA of the knee.

However, our results revealed the beneficial effects of intra-articular HA on pain reduction of symptomatic knee OA and also demonstrated that the adjuvant hydrotherapy had modest influence on the reduction of pain,

Table 1. Baseline general characteristics of the hydrotherapy and control groups

Characteristic	Hydrotherapy	Control	p-value
Number	9	10	
Gender			
Male:female	2:7	2:8	0.67
Age (yr)	66.9±7.4	63.4±7.5	0.24
K-L grade			0.93
I:II:III	2:3:4	3:3:4	
Body mass index (kg/m ²)	24.86±1.92	24.40±1.34	0.72
K-BDI	6.78±6.59	8.90±12.31	0.91
K-BAI	8.89±7.04	7.90±7.81	0.55
EQ-5D	0.78±0.09	0.82±0.08	0.31
Visual analogue scale	40.0±13.2	33.0±10.6	0.28
WOMAC (pain)	8.7±5.5	10.7±8.2	0.97
WOMAC (stiffness)	3.9±1.5	3.8±3.7	0.78
WOMAC (function)	18.1±12.3	19.8±15.8	0.84
WOMAC (total)	31.8±19.5	34.6±26.9	0.99

Values are presented as mean±standard deviation.

K-L grade, Kellgren-Lawrence grade; K-BDI, the Korean version of the Beck Depression Inventory; K-BAI, the Korean version of the Beck Anxiety Inventory; EQ-5D, Euro quality of life health-related quality of life inventory five dimension; WOMAC, The Western Ontario and McMaster Universities osteoarthritis index.

Table 2. Changes in pain, stiffness, function and quality of life scores of the hydrotherapy and control groups before and after intervention

Variable	Hydrotherapy (hydrotherapy + injection)			Control (injection only)			Intergroup difference
	Before	After	Intragroup difference	Before	After	Intragroup difference	
WOMAC (pain)	8.7±5.5	6.6±5.8	0.02*	10.7±8.2	8.0±5.0	0.47	0.32
WOMAC (stiffness)	3.9±1.5	2.6±2.4	0.07	3.8±3.7	2.9±1.7	0.44	0.55
WOMAC (function)	18.1±12.3	14.2±10.5	0.02*	19.8±15.8	12.8±10.5	0.84	0.45
WOMAC (total)	31.8±19.5	23.4±16.6	0.008**	34.6±26.9	26.2±15.4	0.96	0.36
VAS (cm)	40.0±13.2	25.6±10.1	0.006**	33.0±10.6	26.0±9.6	0.02*	0.04*
EQ-5D	0.78±0.09	0.79±0.09	0.67	0.82±0.08	0.82±0.11	0.72	0.13

Values are presented as mean±standard deviation.

WOMAC, The Western Ontario and McMaster Universities osteoarthritis index; VAS, visual analogue scale; EQ-5D, Euro quality of life health-related quality of life inventory five dimension.

* $p < 0.05$. ** $p < 0.01$.

Table 3. Electroencephalography parameters of the hydrotherapy and control groups before and after therapy

RA	Hydrotherapy			Control		
	Before	After	p-value	Before	After	p-value
Fp1_RA	0.48±0.11	0.44±0.08	0.09	0.42±0.13	0.40±0.17	0.39
Fp2_RA	0.49±0.11	0.44±0.10	0.17	0.40±0.15	0.39±0.18	0.65
F3_RA	0.51±0.14	0.46±0.11	0.09	0.45±0.12	0.42±0.16	0.29
F4_RA	0.51±0.14	0.42±0.12	0.07	0.45±0.13	0.42±0.17	0.51
T3_RA	0.48±0.10	0.44±0.09	0.05	0.40±0.14	0.41±0.15	0.72
T4_RA	0.45±0.13	0.39±0.11	0.17	0.44±0.16	0.40±0.20	0.17
P3_RA	0.58±0.10	0.53±0.08	0.07	0.52±0.15	0.49±0.19	0.45
P4_RA	0.57±0.12	0.51±0.10	0.02*	0.53±0.15	0.50±0.20	0.45

Values are presented as mean±standard deviation.

RA, relative power of alpha wave; Fp, prefrontal; F, frontal; T, temporal; P, parietal.

*p<0.05.

functional disability and the mental relaxation of the patients with mild to moderate knee OA at 2–3 weeks after administration of 1st hyaluronan.

Several trials have demonstrated the favorable influence of spa therapy in patients with knee OA, with beneficial effects on the painful symptomatology and functional capacities^{25,26}. Most of these trials used thermal mineral water (spa water) which definition and classification are based on its chemical composition²⁵. The temperature of the natural spring or well water must be at least 20°C and balneotherapy is traditionally given as bi-daily thermal water baths at temperatures of 34–38°C during a spa therapy course that usually lasts 10–15 days²⁷. In addition to thermal and mineral components, other factors such as buoyancy, immersion and resistance also play important roles in balneotherapy.

In our hydrotherapy protocol, immersion and buoyancy in water, which provides more resistance than air, and a hydro-massage jet might relax muscles, increase tendon extensibility, and facilitate blood circulation²⁸. According to the gate theory, pain relief may be due to the pressure and temperature of the water on skin, and the heat stimuli may also influence muscle tone and pain intensity, helping to reduce muscle spasm and to increase the pain threshold¹⁴.

Interestingly, after 2-week hydrotherapy, the relative power of alpha waves has decreased in various brain areas (Fp1, F3, F4, T3, P3, and P4) in the hydrotherapy group. The alpha rhythm is thought to filter the processing of irrelevant sensory inputs in the primary sensory cortex and is inversely correlated with spatial attention²⁹.

The patients with chronic pain demonstrate the attentional bias that leads them to attend excessively to the painful area³⁰, resulting in both hypersensitivity in the painful area and hypoesthesia with deficits in tactile perceptual processing³¹ in other areas, and in the ability to modulate alpha. Moreover, alpha oscillations likely have a very important function in a variety of cognitive processes because inhibitory mechanisms contribute to diverse biological and behavioral phenomena. Kerr et al.³² reported that meditation enhanced top-down regulation of a 7- to 14-Hz (alpha) cortical oscillation. Furthermore, decreased alpha power is associated with relaxation induced by autogenic training³³, and is observed after performing the yoga high-frequency breathing technique³⁴ and receiving massage therapy³⁵. Therefore, hydrotherapy using hydromassage might have a slight positive influence on mental relaxation, which induces improvements of the patient's pain and physical function temporarily, but adequate intervention period with 6 to 8 weeks should be required for increasing the pain threshold or acquiring long-term therapeutic effect on mental relaxation.

Unexpectedly, the control group only showed improvement in the VAS pain score. This might be because the peak effect did not occur within the 3 weeks after the first injection, as mentioned above, which previous studies reported that the peak effects are observed 5- to 6-week postinjection. And counter to our expectations, the study patients with mild to moderate OA did not express a depressive mood, anxiety, or low QoL at baseline. This result was contrary to our previous study in chronic myofascial pain syndrome³⁶. That might be due to the

pain severity. Most of the patients in our previous study had more severe pain and their anxiety was mild to moderate in severity, and their QoL was relatively low, but the patients in this study expressed relatively mild pain, and that is why the therapy might not have improved scores on the psychological inventories.

Overall, our results indicate that the intra-articular injection of HA may be considered to be effective in controlling pain in mild to moderate OA when performed soon after HA injection but provide only limited evidence of adjuvant hydrotherapy for managing functional disability and mental relaxation.

On the other hand, our research has several notable findings. It was the first study that aimed to provide objective evidence of mental relaxation induced by hydrotherapy using EEG. Second, we used hydrotherapy which it is also more easily utilized than balneotherapy that is only accessible regionally. In addition, spa therapy is very popular and does not have disastrous adverse effects. As the elderly population has been increasing rapidly, it can be applied easily to elderly OA patients without special equipment.

This study had several limitations. First of all, this was a pilot study including a small number of patients that aimed to evaluate the effect of adjuvant hydrotherapy on knee OA. The sample size of this study limited the interpretation of the findings and the precise psychophysiological mechanisms of adjuvant hydrotherapy, which remain unknown. Therefore, further study should include more than 28 participants. Secondly, although there was no significant intergroup difference in pain score, the pain score of hydrotherapy group was higher than that of control at baseline and it might affect more reduction in pain score of hydrotherapy group.

Thirdly, chronic inflammation is the leading cause of connective tissue remodeling and destruction in OA, we used green tea as a bath salt. The polyphenols in green tea (GTPs) comprise a mixture that offers promising new options for the development of more effective strategies for the prevention of inflammation associated diseases, including OA³⁷⁾ and a recent study indicates that Epigallocatechin-3-gallate (EGCG), the major and most active component of GTPs, protects human chondrocytes from interleukin-1 α -induced inflammatory responses, and supports the potential of EGCG in OA treatment/prevention³⁸⁾. However, we did not compare the sole effects of green

tea spa with hydrotherapy and did not perform an analysis of the water composition because of technical problems and because the absorption rate of the diluted components was thought to be very low, use of EGCG as effective bath salts might be considered. Further studies about the adequate concentrations of quantified green tea should be conducted. Fourthly, OA studies have high rates of placebo response when patient expectations are high³⁹⁾ and adjuvant hydrotherapy may cause the improvements that were seen in pain and functional indexes in the hydrotherapy group and not in the control group. Lastly, we did not compare the two groups during the period during which the effects of HA injection reportedly peak, and we did not verify how long the effects of hydrotherapy last. Finally, our patients did not perform water-based aerobic or strengthening exercise⁴⁰⁾ because we only wanted to know the sole effect of hydrotherapy.

Further well-designed randomized clinical trials with adequate sample size and with long-term interventional period are warranted to evaluate the effectiveness of water-based exercise in OA.

In conclusion, the results of this pilot study indicate that viscosupplement therapy is effective on pain reduction in mild to moderate OA and a 2-week course of adjuvant hydrotherapy may have modest role in the management of pain, disability and mental relaxation in knee OA during the period soon after the injection. In spite of invasive treatment, adjuvant hydrotherapy to viscosupplementation might apply easily to the patients with knee OA, especially to elderly patients with comorbidities. However, further steps must be taken to enforce these results by conducting a larger, randomized controlled study and following study with estimating number of patients required to evaluate the treatment of knee OA combined with water-based exercise.

ACKNOWLEDGEMENTS

Following are results of a study on the “Human Resource Development Center for Economic Region Leading Industry” project, supported by the Ministry of Education, Science & Technology and the National Research Foundation of Korea. The authors gratefully acknowledge Dae Soo Ko for the consultation of green tea materials.

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