

A randomized, double-blind, sham-controlled study of static electric field therapy by high voltage alternating current for active rheumatoid arthritis

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Static electric field therapy by high voltage alternating current (EF-HVAC) is a traditional complementary Japanese medicine used for headache, shoulder stiffness, chronic constipation and insomnia. Open-label studies and clinical experience in Japan have suggested that this electric field therapy is safe and effective in treating chronic arthritis. We evaluated the efficacy of EF-HVAC therapy in a randomized, double-blinded, sham-controlled trial in patients with active rheumatoid arthritis (RA) in community-based general physician centers. Thirty patients fulfilling American College of Rheumatology (ACR) criteria for RA were treated with EF-HVAC therapy with the LEGACIS PLUS System (COCOROCA Corp., Tokyo, Japan) or sham therapy for 12 weeks and followed for 4 weeks without treatment. The disease activity score 28 (DAS28-CRP), visual analogue scale for pain (VAS), modified health assessment questionnaire (MHAQ), and inflammatory parameters were used as the outcome variable. Twenty four patients ($n = 12$ in each group) were analyzed by a per protocol analysis. Although a significant reduction in DAS28-CRP was observed in EF-HVAC group at 8 and 12 weeks compared to before treatment, there were no significant differences in DAS28-CRP scores during treatment between two groups. The scale of VAS was also significantly decreased by the treatment with EF-HVAC compared to before treatment, in addition, the scale of VAS in EF-HVAC group was significantly lower than sham group at 8 and 12 weeks. Changes in another parameters including MHAQ were not significant between before and after treatment, or by all comparative study between two groups. There were no adverse events related the treatment. In conclusion, the EF-HVAC therapy has a beneficial effect on the improvement to subjective pain of RA.

Key Words: static electric field, rheumatoid arthritis, disease activity score, visual analogue scale

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that has a global distribution. Over recent years, the development of highly effective biological agents, such as anti-tumor necrosis factor- α antibody therapy, has led to a paradigm shift towards the goal of disease remission.^(1,2) Nevertheless, due to the chronic nature of the disease and its effects on quality of life, especially chronic pain, patients commonly try

complementary methods of treatment for RA.⁽³⁾ Complementary and alternative medicines (CAMs) are more popular among patients who are suffering from disease for which conventional therapies have failed to offer a cure or satisfactory control. However, recent systematic reviews have concluded that there was not good evidence for efficacy for any of CAMs taken orally or applied topically for RA,^(3,4) osteoarthritis⁽⁵⁾ or fibromyalgia.⁽⁶⁾ Given the popularity of CAMs, it is important that patients and physicians have accessible and clear evaluation of the efficacy and safety of these treatments by a prospective randomized placebo-controlled trial.

In Japan, an electric field therapy has been developed in disciplines of CAM and has been utilized since 1972, which was approved by the Ministry of Health, Labour and Welfare. The electric field therapy, placing a living body in a static electric field by high voltage alternating current (EF-HVAC), has been believed to affect the nervous and endocrine system, and has been used for patients with headache, shoulder stiffness, chronic constipation, and insomnia in Japan,^(7,8) although little is known about the precise molecular mechanism of these actions. Recently, we have demonstrated that the exposure to EF-HVAC inhibited the development of experimental collagen-induced arthritis in mice via the inhibition of interleukin-1 β expression in joints.⁽⁹⁾ In 2009, a small scaled preliminary study was performed for evaluating the efficacy for RA, and it was shown the improvement of the disease activity score and visual analogue score (VAS) for pain in these patients. The aim of the present study was to evaluate the efficacy of EF-HVAC therapy in a randomized, double-blinded, sham-controlled trial in patients with active RA in community-based general physician centers.

Patients and Methods

Study design and participants. This was a randomized, double-blind, sham-controlled study assessing EF-HVAC therapy for active RA. Patients were recruited from four rheumatology clinics in the cities of Tokyo and Saitama. Selected patients

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presented RA and fulfilled the ACR 1987 criteria for diagnosis of RA.⁽¹⁰⁾ Inclusion criteria considered patients aged at least 30 years old and less than 70 years old with active RA (defined as more than 4 items of ACR score set). Patients were allowed to take stable dose of non-steroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, or disease modifying anti-rheumatic drugs (DMARDs) for at least one month before screening, and were instructed not to make any changes in their background therapies during the study. Patients were excluded from the study if they received biological therapies for RA, were diagnosed with another inflammatory disease or experienced uncontrolled or clinically significant systemic diseases other than RA. Ethical approval was obtained from the Ethical Committee at Tsukiji Futaba Clinic. All patients gave written and informed consent at the time of enrolment.

Randomization. Investigators were screened and the candidates were registered. Randomized allocation of apparatus was distributed by minimization method by Pocock *et al.*⁽¹¹⁾ procedure. Sites distributions were performed by Zelen *et al.*⁽¹²⁾ procedure.

Interventions. EF-HVAC therapy group: Patients were exposed to EF-HVAC with a high voltage value for 20 min a day until 2 weeks, and then were treated 60 min a day to 12 week using a LEGACIS PLUS System (COCOROCA Corp., Tokyo, Japan). The voltage and other level of apparatus were not changed during the study. Sham therapy group: Patients were exposed to sham-apparatus by the same protocol. In particular, controlled diary was recorded by subjects every day, and subjects had to contact immediately to the investigators when they had any trouble.

Outcome assessment. Assessments at baseline, 4, 8, 12, and 16 weeks included clinical and laboratory assessment. The primary efficacy endpoint is the improvement of the activity of subjects by 28-joints disease activity score based on CRP (DAS28-CRP, range 0–10).⁽¹³⁾ Scores for DAS28-CRP are reportedly lower than the original DAS28 assessments using the erythrocyte sedimentation rate⁽¹⁴⁾ and were defined as follows: ≥ 4.1 , high activity; ≥ 2.7 to < 4.1 , moderate activity; ≥ 2.3 to < 2.7 , low activity; and < 2.3 , remission. The secondary endpoints were patient's VAS for pain (0 indicating no pain and 10 indicating worst pain imaginable), swollen joint score, tender joint score, modified health assessment questionnaire (MHAQ)⁽¹⁵⁾ for arthritis functioning, and changes in laboratory measures of biomarkers: erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), matrix metalloproteinase-3 (MMP-3), and C-reactive protein (CRP). MHAQ items include question about dressing and grooming, rising, wating, walking, hygiene, reaching, grip and activities. The MHAQ is one of the most widely recognized measures of patients functioning, with acceptable reliability and validity.⁽¹⁵⁾

Safety. All adverse events (AE) any clinical adverse sign, symptom, syndrome, or illness that occurs or worsens were collected. And also abnormal value and worsened value of clinical studies were collected as AE. All AEs were collected during the study after the treatment of apparatus.

Statistical analysis. Number of subjects was calculated under the 5% level of significance in both sides and 80% of statistical power referred with the results of DAS28-CRP and VAS of preliminary study. Based on the calculation, subject

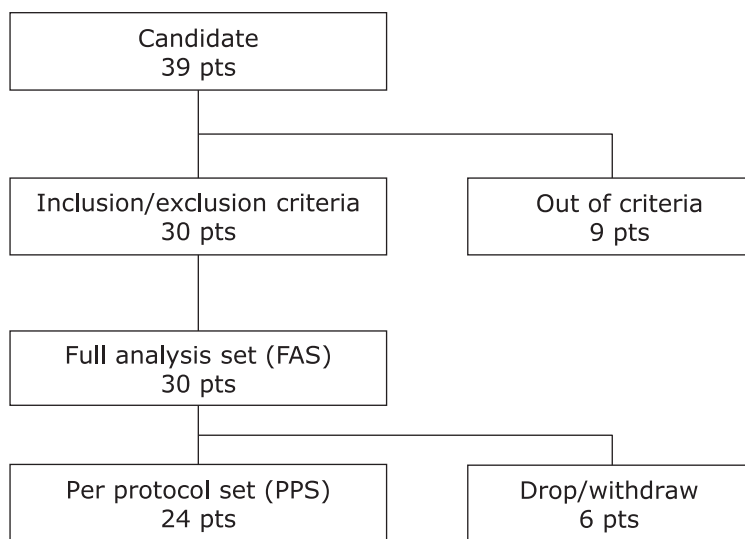


Fig. 1. Trial profile.

Table 1. Demographics and current medications of patients with RA

	EF-HVAC treatment (n = 16)	Sham treatment (n = 14)
Age, mean \pm SD years	51.3 \pm 10.0	50.7 \pm 14.8
Disease duration, mean \pm SD years	7.3 \pm 6.1	4.3 \pm 4.5
Male:Female	6:10	3:11
Rheumatoid factor positive, n (%)	62.5	71.4
Erosion on X-rays (%)	93.8	85.7
Current medication		
NSAIDs, n (%)	6 (37.5)	3 (21.4)
Steroids, n (%)	3 (18.8)	3 (21.4)
DMARD, n (%)	13 (81.3)	8 (57.1)

number of each group was calculated in 12 subjects, 24 subjects on both groups. The change or significant of primary and secondary endpoints was evaluated by Student's *t* test between before treatment and after treatment. Level of significance was 5% of both sides.

Results

Baseline characteristics and compliance with the protocol.

Of 39 eligible patients, 30 patients were randomized as shown in Fig. 1. Patient characteristics of both groups were shown in Table 1. Twelve and 12 patients from the EF-HVAC and sham groups, respectively, completed the study at 16 weeks. Drop or withdraw by subject request were 3 cases, protocol deviations were 2 case and other reason was 1 case.

Endpoints. Primary endpoint as DAS28 score (DAS28-CRP) was shown in Table 2, and time course changes in DAS28 score shown in Fig. 2. The DAS28 score of the EF-HVAC group was significantly decreased at 8 and 12 weeks after treatment compared with those of baseline. The score of the sham group did

not change during the treatment. However, the DAS28 score comparison between two groups at 12 weeks after treatment was not significant. In each assessment for swollen and tender joints, the number of tender joints was significantly decreased in the EF-HVAC group, not in the sham group at 12 weeks after treatment.

Secondary endpoints as swollen and tender joints, VAS and MHAQ scorings, and serum markers were shown in Table 2. The numbers of swollen joints (ACR) were significantly decreased after the treatment in both groups, however, these numbers between groups at baseline or 12 weeks after treatment were not significantly different. In contrast, the numbers of tender joints (ACR) were significantly decreased in the EF-HVAC group, not in the sham group.

Time course changes in VAS scoring for pain was shown in Fig. 3. The scale of the EF-HVAC group was significantly decreased at 8 weeks and 12 weeks after treatment ($p = 0.05$) compared to that of the baseline. The VAS scoring of the sham group did not change before and after the treatment. There were significant differences in the VAS scoring between two groups at 8 weeks and 12 weeks after treatment, respectively. There were

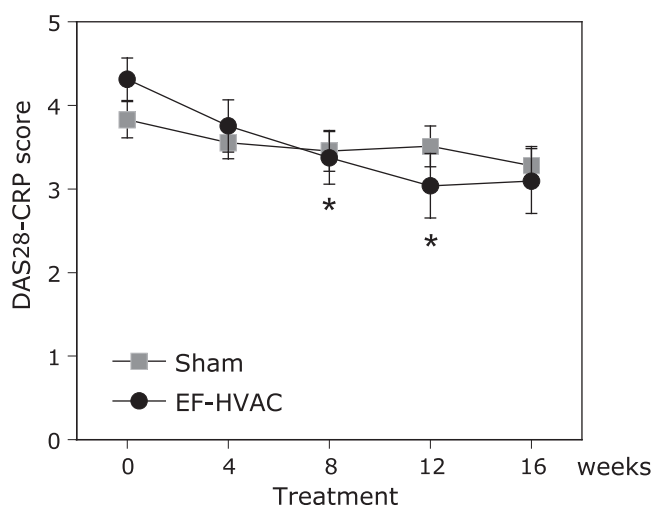


Fig. 2. Time-course changes of DAS28-CRP score. The primary efficacy endpoint was evaluated by the improvement of the activity of subjects by 28-joints disease activity score based on CRP (DAS28-CRP, range 0–10). * $p < 0.05$ vs before the treatment.

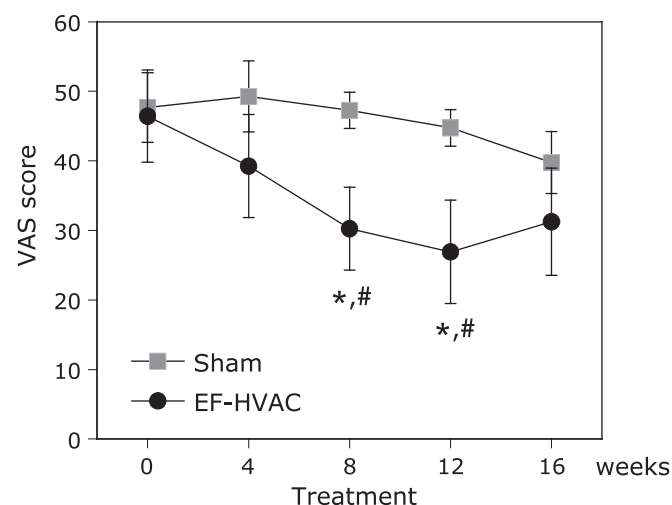


Fig. 3. Time-course changes of VAS score. The secondary endpoint was evaluated by the improvement of patient's VAS for pain (0 indicating no pain and 10 indicating worst pain imaginable). * $p < 0.05$ vs before the treatment, # $p < 0.05$ vs sham group.

Table 2. Changes in the American College of Rheumatology (ACR) components, DAS28-CRP, patient's VAS, Modified Health Assessment Questionnaire (MHAQ), and serum biomarkers.

	EF-HVAC treatment (mean ± SD n = 12)		Sham treatment (mean ± SD n = 12)	
	Baseline	Week 12	Baseline	Week 12
Primary endpoint				
DAS28-CRP score	4.31 ± 0.89	3.04 ± 1.34**	3.83 ± 0.75	3.51 ± 0.85
(Swollen joints, EULAR)	5.08 ± 3.32	2.50 ± 2.97*	4.58 ± 2.61	2.17 ± 1.85
(Tender joints, EULAR)	9.83 ± 6.70	3.33 ± 3.80**	6.83 ± 5.29	6.75 ± 5.94
Secondary endpoints				
Swollen joints (ACR)	5.17 ± 3.83	2.75 ± 3.39*	4.75 ± 2.70	2.25 ± 1.86**
Tender joints (ACR)	10.25 ± 6.77	4.50 ± 5.60**	6.17 ± 5.22	6.67 ± 6.40
Patient's VAS	46.42 ± 22.96	26.92 ± 25.8*,#	47.67 ± 17.37	44.75 ± 9.07
MHAQ	3.08 ± 5.26	1.58 ± 3.50	1.50 ± 1.62	1.08 ± 2.11
ESR (mm/h)	12.58 ± 12.51	15.75 ± 17.22	15.33 ± 14.87	12.00 ± 7.58
CRP (mg/dl)	0.433 ± 0.512	0.658 ± 0.821	0.363 ± 0.776	0.219 ± 0.381
RF (U/ml)	65.1 ± 72.3	65.3 ± 76.4	83.3 ± 101.7	78.5 ± 104.9
MMP-3 (ng/ml)	125.5 ± 110.0	154.5 ± 170.4	90.7 ± 92.4	91.8 ± 75.3

* $p < 0.05$ and ** $p < 0.01$ vs baseline, # $p < 0.05$ vs sham treatment.

no significant differences observed in MHAQ or the serum biomarkers of RF, MMP-3, CRP, or ESR between the two groups at any time points, or within the groups from baseline to after treatment.

Adverse events. One subjective symptom was reported as AE on 12 cases in EF-HVAC group at 8, 12 and 16 weeks on the treatment but this case was not related apparatus. Three objective symptoms were diagnosed before treatment but no symptom was during the study. In the sham group, it was diagnosed one objective symptom before treatment and three objective symptoms during the study (There were plural report by same subjects). All reports were not related the apparatus. Eight AEs in 24 cases were reported by the physiological tests, but there were no abnormal changes and not related the apparatus. In the clinical tests, 18 events in 178 events were positive as abnormal, but all events were not related the apparatus. There were no memorable events under safety evaluation.

Discussion

This is the first reported randomized, controlled trial on the efficacy and tolerability of the electrical field therapy compared with sham apparatus in patients with active RA. Although the primary outcome determined by DAS28-CRP score did not differ between the two groups at any points, the score of the EF-HVAC group was significantly decreased compared with that of baseline at 8 and 12 weeks after the treatment. In addition, the significant decline of VAS for pain was observed by the EF-HVAC treatment compared with sham apparatus group.

The lack of differences in DAS28-CRP between two groups was disappointing. Slightly higher score at the baseline in the EF-HVAC group (mean 4.31) than that in sham group (mean 3.83) may affect the results at 12 weeks after the treatment. In the EF-HVAC group, the DAS28-CRP score decreased gradually during 12 weeks of treatment and tended to reverse after stopping treatment, in contrast, the score did not change in the sham group during the study, indicating the possibility that the decrease in DAS28-CRP in the EF-HVAC group would be derived from the efficacy of the treatment with EF-HVAC. Among two parameters (swollen and tender joints) including in DAS28-CRP, the EF-HVAC treatment decreased the numbers of tender joints more effectively than those of swollen joints. The usefulness of the EF-HVAC treatment to reduce the tenderness was also observed by the evaluation with ACR criteria, by which the number of tender joints was significantly decreased in the EF-HVAC group, but not in the sham group. Although our previous study demonstrated the inhibitory effect of static electric field therapy on pro-inflammatory cytokine expression in the cartilage tissue in mice with collagen-induced arthritis,⁽⁹⁾ the EF-HVAC treatment neither affect the inflammatory parameters including ESR and CRP nor the disease activity markers including RF and MMP-3 in the present study. Further studies will be necessary to demonstrate the mechanism by which this therapy could reduce tenderness of joints.

A noteworthy finding is that the VAS scale of the EF-HVAC group decreased significantly at 8 and 12 weeks after the therapy compared to that of the baseline, and that there were significant differences in the VAS scoring between two groups at 8 weeks and 12 weeks after treatment, respectively. As shown in the evaluation of joints, the reduction of tender joints by the EF-HVAC treatment could affect the decrease in VAS scale. The decreased VAS scale at 12 weeks after the treatment tended to reverse after the stopping of the treatment, indicating that it would be necessary to continue the treatment to maintain the decrease in VAS scale. To investigate the health-related quality of life in RA, Garip *et al.*⁽¹⁶⁾ have compared RA quality of life (RAQoL) with other scales in terms of disease activity, severity of pain, and functional status. They have concluded that pain evaluated by

VAS-pain ranked the first among the variables that influenced RAQoL, and this was followed by disease activity and functional status. In addition, a combination of disease-modifying anti-rheumatic agents (DMARDs) and the biological agents has aggressively initiated for RA in the recent clinical field. However, this is not sufficient to retard the underlying progression of the disease and hence the disease-associated pain persists. Therefore, complementary and alternative medicines are needed and more popular among patients to improve the RAQoL. This is the first study to confirm the effectiveness of EF-HVAC therapy for pain by a prospective randomized placebo-controlled trial.

Otherwise, MHAQ was not significant between groups in the index of motion functional activity. Considering insignificant result between intra/inter group of MHAQ, it was clear that the improvement of pain did not conduct the improvement of motor function. It may be thought that there was small part of the subjects who was severity motion disability in this study.

There were no adverse effects related apparatus in all 24 subjects. This study is prospective and scientific study for the possible evaluation of application enlargement. In these result, it is thought that this apparatus is safe and produce the sufficient efficacy of subjective impression and could be evaluated the improvement of the pain.

Conclusions

The results of the first randomized study demonstrated that significant and clinically meaningful reduction in the DAS28-CRP score and VAS scale of RA were achieved and sustained throughout 12 weeks of treatment with EF-HVAC added to a background regimen, with a generally manageable safety profile. This study supports the decision to use EF-HVAC for 60 min a daily during 12 weeks.

Abbreviations

ACR	American College of Rheumatology
CAM	complementary and alternative medicines
EF-HVAC	electric field therapy by high voltage alternating current
MHAQ	modified health assessment questionnaire
RA	rheumatoid arthritis

Conflict of Interest

Yuji Naito received scholarship funds from Otsuka Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. Toshikazu Yoshikawa has an affiliation with a donation-funded department from AstraZeneca Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., MSD K.K., Dainippon Sumitomo Pharma Co., Ltd., Chugai Pharmaceutical Co., Ltd., FUJIFILM Medical Co., Ltd. and Merck Serono Co., Ltd. The other authors declare that there are no competing interests.

Authors' Contributions

Yuji Naito and Yutaka Kawahito participated in the design of the study, and helped to draft the manuscript. Shinnichi Yamaguchi, Yasuhiro Mori, Koji Nakajima and Sanhiro Hashimoto performed clinical study. Masakazu Tomaru, Yoshihiko Satoh and Yuji Hitomi analyzed clinical and laboratory data and performed the statistical analysis. Masakazu Karita and Tomoaki Hiwatari helped the clinical setting of the static electric field therapy by high voltage alternating current. Toshikazu Yoshikawa provided overall supervision. All authors read and approved the final manuscript.

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