OsteoArthritis and Cartilage (2005) **13,** 575–581

doi:10.1016/j.joca.2005.02.012

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Treatment of knee osteoarthritis with pulsed electromagnetic fields: a randomized, double-blind, placebo-controlled study

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Summary

Objective: The investigation aimed at determining the effectiveness of pulsed electromagnetic fields (PEMF) in the treatment of osteoarthritis (OA) of the knee by conducting a randomized, double-blind, placebo-controlled clinical trial.

Design: The trial consisted of 2 h daily treatment 5 days per week for 6 weeks in 83 patients with knee OA. Patient evaluations were done at baseline and after 2 and 6 weeks of treatment. A follow-up evaluation was done 6 weeks after treatment. Activities of daily living (ADL), pain and stiffness were evaluated using the Western Ontario and McMaster Universities (WOMAC) questionnaire.

Results: Within group analysis revealed a significant improvement in ADL, stiffness and pain in the PEMF-treated group at all evaluations. In the control group there was no effect on ADL after 2 weeks and a weak significance was seen after 6 and 12 weeks. Significant effects were seen on pain at all evaluations and on stiffness after 6 and 12 weeks. Between group analysis did not reveal significant improvements over time. Analysis of ADL score for the PEMF-treated group revealed a significant correlation between less improvement and increasing age. Analysis of patients <65 years using between group analysis revealed a significant improvement for stiffness on treated knee after 2 weeks, but this effect was not observed for ADL and pain.

Conclusions: Applying between group analysis we were unable to demonstrate a beneficial symptomatic effect of PEMF in the treatment of knee OA in all patients. However, in patients <65 years of age there is significant and beneficial effect of treatment related to stiffness.

Key words: Pulsed electromagnetic fields, Osteoarthritis, Placebo-controlled clinical trial.

Introduction

Osteoarthritis (OA) has a very high prevalence among middle-aged and elderly people and the disease is responsible for substantial direct and indirect socioeconomic costs and the treatment options are few and unsatisfactory. Recently a number of papers have appeared suggesting pulsed electromagnetic fields (PEMF) as a technique for treatment of osteoarthrosis in which technique was applied one or a few times a day for up to a month[1–5]. The assumption that PEMF promotes beneficial effects was further substantiated by a recent *in vivo* study demonstrating a disease-modifying effect of PEMF in an animal model of OA[6]. European League Against Rheumatology has now rated PEMF treatment for OA as a 1B of evidence and it received a B rating for strength of recommendation. This was decided since no effect sizes were calculable from previous data, poor practicality of delivery to the patient population in most cases, and due to economic considerations[7]. Beneficial therapeutic effects of PEMF have also been documented with increasing frequency for a variety of bone and cartilage related diseases since 1973[8–11]. So far, the use of PEMF for treating bone fractures is, however, the only condition that has received approval by the Food and Drug Administration in the US.

The mode of action of PEMF is based on creating small electrical fields in tissue and thereby promoting biological effects. When current changes in coils attached to the body an increasing magnetic field appears in the tissue that, in turn, creates an electrical gradient with a magnitude that depends on the rate by which the magnetic field changes according to Faraday's law. The electrical fields induced in tissue are of a small magnitude, usually 1–100 mV/cm and the way by which these fields activate cell biological processes is not clarified. We therefore aimed at studying the efficacy of PEMF treatment in a group of patients suffering from OA in the knee by using an electrical pulse pattern frequently applied of 50 Hz and by constructing placebo devices that made it essentially impossible for the patients to assess whether or not they were assigned to an active or a placebo device.

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Received 22 December 2004; revision accepted 21 February 2005.

Materials and methods

STUDY POPULATION

Patients were recruited from the out-patient clinic at the Department of Rheumatology, Copenhagen University Hospital in Glostrup from March through to December 2001. Patients older than 45 years with painful knee OA of the femorotibial compartment fullfilling the combined clinical and radiological criteria of the American College of Rheumatology were included[12]. Exclusion criteria were inflammatory joint disease, acromegaly, Charcot's arthropathy, haemochromatosis, Wilson's disease, ochronosis, terminal illnesses/malignancies, pregnancy or lack of contraception use in women of childbearing age, and use of pacemaker or any implanted electrical device. Furthermore, patients were excluded if they were unable to understand/fill out the questionnaires, had received intra-articular glucocorticoid or hyaluronic acid injection 1 month prior to study entry, or had hip and/or lumbar spine OA with referred pain to the study knee. All participants gave written informed consent. The study was approved by the local Ethics Committee of Københavns Amt (KA00040g).

DESIGN

This was a 1:1 randomized, controlled, double-blind add-on study. The duration of the study was 14 weeks and the patients met for five visits. Patients were included at baseline (Visit 1) and met 2 weeks later for randomization and start of treatment (Visit 2). Treatment was then given for 6 weeks for 2 h daily every 5 of 7 days at the discretion of the patient. Patients met for a check of compliance after 1–2 weeks of treatment (Visit 3) and met at the end of treatment (Visit 4). A follow-up and final visit was scheduled 6 weeks after the end of treatment (Visit 5). At all visits a Western Ontario and McMaster Universities (WOMAC) questionnaire was filled in and weight, height, and a physical examination of study knee was done. The physical examination included measurement of range of movement (goniometer) and examining for periarticular tendernes (yes/no) and swelling of the joint (yes/no). Patients were allowed to continue analgesic medication all through the study. The radiological features at baseline were examined according to the Kellgren and Lawrence grading system of OA[13].

TREATMENT WITH PEMF

Two sets of two adjacent coils were placed on the medial and lateral regions of the study knee, respectively, with the interspace between the coils being at the level of the joint line. The coils were placed on an insulating bandage of 3–5 mm thickness that could be tightened by use of Velcro material. The coils were constructed to ensure a fast rise time and fast declining phase for current. The use of adjacent coils creates an amplified and focused electromagnetic field. A pulse generator from *Biofields Aps*, Copenhagen, Denmark was used that yields ± 50 V in 50 Hz pulses changing voltage in 3 ms intervals (Fig. 1). This set up results in a maximal electrical gradient sensed by charged particles in tissue of 1–100 mV/cm depending on the distance from the coils[14]. This value was obtained by measurements with a differential amplifier in low conducting media but can also be assessed by integrating the current density using vector calculus[14]. A diode flashes in front of the pulse generator when current is provided for the coils.

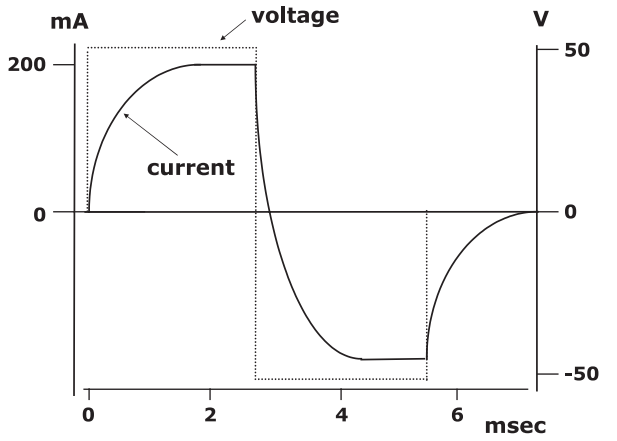

Fig. 1. Changes in current and voltage in coils used for PEMF treatment. The pulse is initiated by applying $+50$ V to the coil and after 3 ms $-$ 50 V whereby coils are exposed to a 100 mV potential change. After 6 ms the voltage is zero. Pulses occur with 50 Hz frequency. Changes in electromotoric force (EMF) on charged particles in tissue is proportional to: EMF $= \mathrm{d}B/\mathrm{d}t$, where B is the magnetic field proportional to the current (A) and t is the time. It was calculated and measured that the electrical field 1 cm from the coil amounted to approximately 10 mV/cm.

The patients were instructed to notice that the flashing light was indicative of current flowing in coils. The device was constructed in such a way that resistance in the circuitry (composed of coils) was measured and therefore the light was flashing only when current was flowing in a fully intact device for treatment. The current in coils that create PEMF causes the coils to become slightly warmer than the surroundings after 30 min (28–35 °C). For the group of patients not receiving active treatment, DC current was applied to coils yielding a permanent magnetic field that does not evoke changing electrical potentials in tissue. We calculated the effect delivered to the active coils (PEMF) and delivered the same effect (in DC current) to the placebo coils. Thereby the coils in the active and placebo groups had the identical increase in temperature. The patients were instructed that coils from both groups would exhibit a slight increase in temperature. The diode on the pulse generators flashes in a similar fashion in both cases when current is flowing. Thus, by use of this set up, patients in the two groups could detect the exact same heat from the coils and were unable to determine to which group they were assigned. There was no transfer of heat from coils to the knee due to the insulating material.

OUTCOME MEASURES

Symptoms of knee OA were assessed by the WOMAC OA index[15], a questionnaire addressing severity of joint pain (five questions), stiffness (two questions), and limitation of physical function (17 questions). The version using verbal rating scales of the WOMAC index was used – i.e., with the patient assessing each question by none (1), mild (2), moderate (3), severe (4), and extreme (5). A higher WOMAC score thereby represents worse symptoms severity.

WOMAC subscore of joint pain was the primary outcome measure (0–25). WOMAC subscores of stiffness (0–10), activities of daily living (ADL) (0–85), and scintigraphic results were secondary outcome measures.

Since PEMF is expected to modify and enhance cellular processes in particular in younger patients we designed the trial in such a way that a separate estimate should be performed on patients <65 years after all data were accumulated.

STATISTICAL METHODS

Specially designed case report forms were used to collect data. Blinding was maintained until the final database was cleaned and locked. Baseline values were calculated as the mean value for the first two visits. An analysis based on intention to treat with last observation carried forward as well as an analysis of patients who finished per protocol was done. Parametric or non-parametric statistical tests were used depending on whether the data followed a Gaussian or non-Gaussian distribution. Comparisons within groups were done by Student's paired *t* test and comparisons between groups were done by a two-way repeated measures ANOVA (one factor repetition). A *P*-level of ≤ 0.05 was considered as revealing significance. Based on an SD of 3.5, we calculated that a sample size of 90 patients would give a power of 90% in detecting a more than 2.5 (10%) difference in the WOMAC subscore of joint pain at the 5% level of significance. Data are given as mean (SD) unless indicated otherwise.

BONE SCINTIGRAPHY

Late phase bone uptake was recorded 180 min after the injection of 500 MBq ^{99m}Tc-MDP. Three 6 min frames were recorded in anterior, posterior and lateral views using a high-resolution collimator on a dual-head gamma camera (Forte, ADAC Laboratories, Milpitas, USA). Matrix size was 256×256. Images of the relevant study knee were displayed on a high-resolution computer screen using a monochrome color scale and a standard display software package (Pegasys Ultra, ADAC Laboratories). Quantification was performed blindly by placing pre-defined rectangular regions of interest (ROI) over the knee joint (covering a field from 1.4 cm proximal to 1.4 cm distal to the joint line) (Knee Joint), the whole knee region (Whole Knee), and a reference ROI placed over the femoral bone 19 cm proximal to the knee[16]. Knee to reference ROI ratios (Ratios) were calculated without background subtraction.

Results

CHARACTERISTICS AT BASELINE

One hundred and fifty-five patients were screened and 90 fulfilled the study criteria and were randomized to study treatment. Eighty-three patients completed the study without protocol violations after finishing the protocol they were included in the analysis and the results are given below. An analysis based on the intention to treat principle with last observation carried forward gave similar results as all non-completers left the study before Visit 3. Patients were randomized into the active PEMF group (45 patients) and into the control group (45 patients). Before ending treatment three withdrew from the PEMF group and four from the control group. Thus, 42 completed in the PEMF group and 41 in the control group. The patient characteristics from the two groups are shown in Table I. There were no significant differences between the groups with respect to age, body mass index (BMI), gender, disease duration, and Kellgren and Lawrence score.

Table I
Baseline demographics and clinical characteristics in two groups of patients with knee OA randomized to receive PEMF ($n = 42$) or placebo ($n = 41$) in a therapeutic study

	PEMF	Placebo
Age (years)	60.4 (8.7)	59.6 (8.6)
BMI (kg/m^2)	27.0 (4.0)	27.5 (5.7)
Females (*n*)	20	25
Males (*n*)	23	16
Disease duration (years)	7.5 (5.2)	7.9 (7.7)
Kellgren and Lawrence score (0–4)	2.5 (1.2)	2.8 (1.1)
Analgesic medication (*n*)	28	29

At baseline 23 of 42 patients in the PEMF group used analgesic medication (55%) – eight patients used non-steroidal anti-inflammatory drug (NSAIDs), 10 patients used analgesics (paracetamol or weak opioids), and five patients used both NSAIDs and analgesics. At baseline 25 of 41 patients in the placebo group used analgesic medication (61%) – 13 patients used NSAIDs, seven patients used analgesics (paracetamol or weak opioids), and five patients used both NSAIDs and analgesics. At the end of treatment in the PEMF group two patients had increased and one patient had decreased consumption of analgesic medication whereas in the placebo group one patient had increased and three patients had decreased consumption of analgesic medication.

ADL, PAIN AND STIFFNESS

WOMAC subscores of ADL are given in Table II(a). In the PEMF group there was a significant fall in the WOMAC subscore of ADL during treatment, at the end of treatment, and at follow-up. In the placebo group there was a significant fall at the end of treatment and at follow-up, but not during treatment. At the end of treatment there was a fall in

Table II
WOMAC data on ADL, pain and stiffness

Week	PEMF			Placebo			Two-way ANOVA
	Mean	SE	*P* value	Mean	SE	*P* value	
	(a) WOMAC data on ADL from patients treated with or without PEMF						
0	43.83	1.93		46.49	2.21		
2	40.46	2.05	0.010*	44.54	2.25	0.29	0.524
6	37.63	1.73	0.00004*	42.44	2.38	0.05*	0.619
12	37.89	2.14	0.00007*	41.37	2.27	0.02*	
	(b) WOMAC data on pain from patients treated with or without PEMF						
0	13.15	0.57		14.49	0.54		
2	11.93	0.53	0.12	13.20	0.54	0.12	NS
6	11.68	0.48	0.05*	12.36	0.66	0.14	NS
12	11.40	0.57	0.03*	12.24	0.63	0.01*	
	(c) WOMAC data on stiffness from patients treated with and without PEMF						
0	5.74	0.29		5.85	0.28		
2	5.10	0.27	0.11	5.49	0.32	0.40	0.620
6	4.90	0.25	0.03*	5.32	0.32	0.21	0.567
12	4.81	0.32	0.04*	5.15	0.30	0.09	

NS, not significant; *$P \leq 0.05$.

WOMAC subscore of 14% in the PEMF group and of 8.7% in the placebo group. Between group analysis using a two-way ANOVA with replication revealed no significant difference between the PEMF-treated group and the placebo group. WOMAC subscores of pain are given in Table II(b). In both groups there was at the follow-up a significant fall in the WOMAC subscore of 15%. There were no significant differences between the two groups at any time point using the two-way ANOVA.

Regarding stiffness there was a significant fall in the PEMF-treated group at the end of treatment and at the follow-up which was not observed for the placebo group. At the follow-up there was a decrease of 16% in the PEMF-treated group and 12% in the placebo group. The two-way ANOVA revealed no significant difference between groups at any point.

ADL, PAIN AND STIFFNESS FOR PATIENTS <65 YEARS

Since effects of PEMF is expected to initiate growth and differentiation of living tissue we anticipated that PEMF might have more effect in patients with a larger growth potential for osteoblasts, chondrocytes, and possibly able to evoke an enhanced blood flow in a relatively young population. In the design we therefore decided to evaluate patients <65 years. We analyzed the relation between age and changes in ADL WOMAC score as measured by difference between the score before treatment and the score measured after 6 weeks of treatment (end of treatment). When plotting the differences in ADL WOMAC scores vs age we found that there was a significant correlation between increase in age and decrease in reported improvement ($P = 0.05$) of the PEMF-treated group as shown in Fig. 2. This correlation was not observed for the control group ($P = 0.57$). Kellgren scores for patients <65 years were 2.50 ± 1.00 (SD) for the PEMF-treated group and 2.57 ± 1.14 (SD) for the placebo group. Average ages were 56.7 years and 55.3 years, respectively. We analyzed the effects of treatment on ADL, pain and stiffness for the treated and placebo groups <65 years. There were 31 patients in each group (PEMF-treated and placebo). The data analysis revealed that there were significant improvements for ADL, pain and stiffness for the PEMF-treated groups and that the effect was only observed in the placebo group at the follow-up for ADL [Table III(a–c)]. With regard to stiffness a highly significant difference was seen between baseline and 2, 6, and 14 weeks for the PEMF-treated group. There was a 19% improvement in the PEMF-treated group at the follow-up which only amounted to 8% for the placebo group. Between group analysis using a two-way ANOVA on stiffness revealed a significant improvement after 2 weeks ($P = 0.032$) and a smaller significance level ($P = 0.072$) was observed after 6 weeks. Thus, PEMF treatment reduces stiffness of joints for patients <65 years when evaluated using in between group analysis.

Table III
WOMAC data on ADL, pain and stiffness

Week	PEMF			Placebo			Two-way ANOVA
	Mean	SE	*P* value	Mean	SE	*P* value	
	(a) WOMAC data on ADL from patients <65 years treated with or without PEMF						
0	43.26	2.35		47.90	2.35		
2	39.64	2.42	0.0242*	45.13	2.42	0.18	0.742
6	35.58	1.91	0.0001*	42.87	1.91	0.02*	0.581
12	37.06	2.37	0.0034*	41.23	2.37	0.002*	
	(b) WOMAC data on pain from patients <65 years treated with or without PEMF						
0	13.34	0.73		14.67	0.70		
2	11.80	0.65	0.014*	13.68	0.80	0.003*	0.476
6	11.43	0.59	0.008*	12.81	0.83	0.0005*	0.715
12	11.37	0.69	0.007*	12.80	0.77	0.0006*	
	(c) WOMAC data on stiffness from patients <65 years treated with or without PEMF						
0	5.65	0.37		5.81	0.36		
2	4.81	0.33	0.09	5.68	0.40	0.81	0.032*
6	4.65	0.32	0.04*	5.52	0.40	0.59	0.071
12	4.55	0.37	0.04*	5.35	0.38	0.39	

*$P \leq 0.05$.

PHYSICAL EXAMINATION

The results of the physical examinations were comparable in the two study groups at baseline. There were no changes in the results of the physical examinations, in weight or in height within or between the groups during study treatment or follow-up (data not shown).

ADVERSE EFFECTS

There were no serious adverse effects and there were no drop outs from the study for reasons related to the

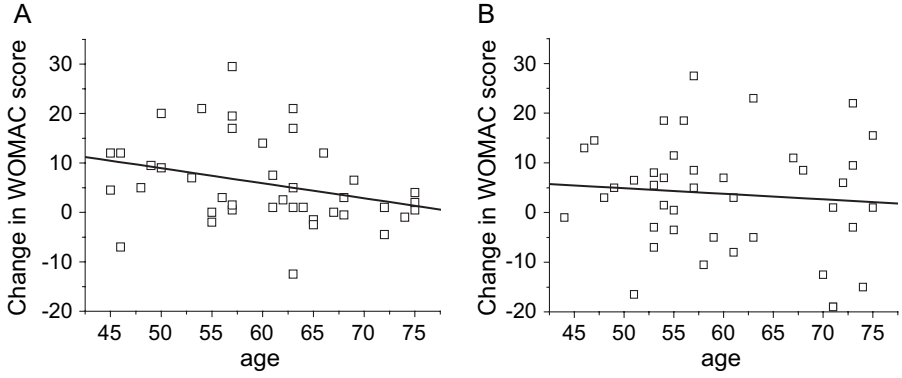

Fig. 2. Changes in ADL WOMAC score as a function of age for the PEMF-treated (A) and placebo (B) group. Ordinates show differences between initial scores before treatment and scores measured after 6 weeks (end of treatment). Linear regression analysis of data reveals a slope of -30 ± 0.15 ($P = 0.05$) for the PEMF-treated group and -0.09 ± 0.19 ($P = 0.57$) for the placebo group.

treatment. In the PEMF group four patients reported a grumbling or throbbing sensation, six patients reported a warming sensation, and two patients reported an aggravation of the osteoarthritic pain in the study knee. In the control group the corresponding figures were four, one, and one, respectively. In all cases the adverse effects took place within the first 2 weeks of treatment and were mild and transient.

BONE SCINTIGRAPHY

The results of the bone scintigraphic examinations are given in Table IV. To distinguish activity in the patello-femoral compartment from that in the tibio-femoral compartment, ratios obtained with the lateral view are given separately (Whole Knee-lat, Knee Joint-lat). The ratios in the two study groups were comparable at the start of treatment. There were no changes within or between the groups that could be attributed to the study treatment.

Discussion

The aim of the study was to evaluate the efficacy and applicability of the PEMF technology for improving the conditions for patients suffering from OA. We chose to evaluate for global assessment, ADL, stiffness and pain. The important design in this study was firstly, that patients were treated for 6 weeks and the final evaluation was conducted after 6 more weeks to evaluate if improvements would sustain over time. The results in this study showed that there was a rapid improvement in ADL, pain and stiffness for the PEMF-treated group – an effect not as pronounced in the placebo group. Between group analysis using a two-way repeated measures ANOVA did not show a significant difference between the PEMF-treated and placebo groups. However, when the patient group was reduced to <65 years of age there was a significant improvement at early time points for stiffness but not for ADL and pain.

There were no obvious flaws in the conduct of our study. At baseline the PEMF-treated and the control patients did not differ in any significant respect. As assessed from the diaries, the compliance was high, and we have no reasons to believe that the patients did not adhere to treatment. We used the WOMAC questionnaire, which is a validated, disease specific, and sensitive measurement of symptoms related to knee OA[12]. The number of patients enrolled in the study was sufficient to ensure a high probability of detecting a clinical relevant improvement in the PEMF-treated patients. An add-on design was chosen, and therefore patients continued their individual analgesic medication (paracetamol, NSAID, or weak opioids). Only a few patients changed their analgesic medication in the study period. More patients in the placebo than in the PEMF group decreased the analgesic medication, and less patients in the placebo than in the PEMF group increased the analgesic medication. It is, therefore, unlikely that a possible analgesic effect of PEMF was affected by a counter regulatory decrease in the analgesic medication. Furthermore, coils for the placebo device were constructed in such a way that they were indistinguishable from the active coils for the PEMF-treated group by releasing the same amount of heat. Thus, patients were unable to determine to which group they were assigned.

Table IV
Bone scintigraphic results for study knee at baseline and at the end of treatment (6 weeks) with PEMF (n = 18) or placebo (n = 18) in patients with OA of the knee. The values are given as mean (SD). No significant differences within or between groups. For explanation of Site and Ratios, see Methods and Results sections

Site	Treatment	Ratio	
		Baseline	End of treatment
Whole Knee	Placebo	3.0 (1.0)	2.9 (1.3)
	PEMF	2.8 (1.8)	2.7 (1.5)
Knee Joint	Placebo	2.0 (0.5)	2.0 (0.8)
	PEMF	1.8 (0.9)	1.8 (0.7)
Whole Knee-lat	Placebo	3.2 (1.2)	3.1 (1.1)
	PEMF	3.1 (1.9)	3.0 (1.7)
Knee Joint-lat	Placebo	2.0 (0.6)	1.9 (0.5)
	PEMF	1.7 (0.8)	1.8 (0.8)

We observed a placebo effect in most outcomes of 8–14% which is expected in this type of trials, in particular since the control device, like the active device, generated some heat. Thus, patients in both groups could to the same extent get the impression that they were being treated although information about these factors was given at the onset of the trial.

Our findings are in some respects in accordance with previous observations[1–3] describing improved functional performance of PEMF-treated patients both in relation to OA of the knee as well as OA of cervical spine. Our data differ from the data by Zizic *et al.*[4], in our finding, that pain score is not significantly improved when data are analyzed between groups. Our improvement on mobility is also somewhat smaller than that reported by Trock *et al.*[2] Recently, Pipetone and Scott[5] reported a significant improvement within groups treated with PEMF – a finding that was not observed in the placebo group. They, however, did not perform between group analysis. We could by using between group analysis demonstrate improvement with regard to stiffness which was not demonstrated in the study by Pipitone and Scott[5]. Thus, it appears that in group analysis of PEMF treatments consistently gives the result that there is an improvement on ADL and mobility which is slightly better than that seen for the placebo groups when they are evaluated based on their significance levels. Therefore, in between group analysis is essential in order to demonstrate whether or not improvements have occurred based on treatment. Although we found a much better significance level on PEMF treatments for ADL and stiffness compared to placebo for all patients we could not demonstrate improvements based on treatment from between group analysis. However, when evaluating patients <65 years of age we did find a significant improvement on the stiffness of the knee revealing a possible improvement in mobility of the joint treated.

Considerable amount of experimental data have now emerged demonstrating an anabolic effect of PEMF on osteoblasts and chondrocytes[10,17–19]. A putative positive effect of PEMF on bone and cartilage metabolism in knee OA may not necessarily improve symptoms within the short duration of the present study. To detect subtle short-term changes in remodeling of the subchondral bone in the study knee, we therefore performed bone scintigraphies using a semiquantitative measurement. Unfortunately, we were unable to demonstrate an effect of PEMF on bone metabolism. No reliable and sensitive method exists to detect and monitor subtle changes in cartilage metabolism

in a similar way. Therefore, we do not know whether PEMF affected cartilage metabolism.

It is relevant to compare the effects of PEMF treatment with the improvement in stiffness due to treatment with ibuprofen evaluated on a similar WOMAC scale[12]. These data show that with regard to stiffness there is a strong effect after 2 and 4 weeks treatment with ibuprofen (2.4 g/day) amounting to 24% and 40% improvement. For ADL the effects were 25% and 33%. This is a stronger effect than that seen in this study, but it should be noted that the improvement in stiffness of 19% on the WOMAC scale seen in our study occurred on patients (<65 years) who were already under medications.

Recently, a number of papers have appeared from studies on cell cultures as well as animal studies that attempt to explain how PEMF activates cells and induce proliferation and differentiation. It has been suggested that cytoplasmic tyrosine kinases of the Src family like Lyn becomes activated[14,20–22]. On endothelial cells as well as chondrocyte cell cultures (ATDC5) we have recently found that our pulsed fields activate the cytoplasmic Src kinase by phosphorylating the activation site and dephosphorylating the inhibitory site (data not shown). Recently it was shown[6,23] that low frequency PEMF regulates chondrocyte differentiation and the expression of matrix proteins in immature male rats and that in rabbits PEMF stimulates cartilage differentiation and endochondrial ossification which was coincident with an increase in transforming growth factor (TGFα) expression. Within the last 10 years a considerable amount of literature describing PEMF activated biological processes have been focusing on the fact that existing biochemical processes becomes facilitated by the pulsed fields – especially in relation to cell proliferation of chondrocytes[17,18]. In relation to enhanced growth and differentiation of chondrocytes and function of joints the two growth factors TGFα and insulin-like growth factor (IGF) are essential activators of chondrocytes. It is therefore interesting that expression of TGFα proteins are enhanced following PEMF treatment[20] and that the receptor type for TGFα is facilitated presumably through activation of cytoplasmic tyrosine kinases. Thus, PEMF activation as used in this study can activate cellular processes although the mechanism by which it occurs is far from clarified. Improvement on stiffness could be envisioned as being due to (1) an enhanced blood circulation in the periarticular compartment, (2) improved growth of chondrocytes or (3) positive effects on cartilage differentiation. A possible explanation for the improved mobility on the treated joint on a short basis of 2 weeks could be an enhanced blood flow. Support for this idea could be found in the observation that PEMF activates synthesis of nitric oxide (NO)[19] and synthesis of NO in endothelial cells could be involved in enhancing blood flow. Furthermore, it was recently shown that PEMF increases *in vivo* and *in vitro* angiogenesis through endothelial release of fibroblast growth factor-2, an important angiogenic factor[24]. Thus, there are data indicating that improved blood circulation in the periarticular compartment could occur following treatment. Recent data from several laboratories have suggested that PEMF activates cellular signaling processes rapidly within 5–10 min[14,20–22] and signaling is largely blunted after 30 min. Thus, future studies could benefit from applying a shorter duration of PEMF-stimulation, that is, less than 1 h but several times a day.

In conclusion, there was for all patients with knee OA a tendency towards an initial transient improvement and in group analysis revealed a high significance level when compared to baseline. Between group analysis of all patients did however not show a significant effect of treatment. When the group was reduced to those <65 years there was still a tendency towards a rapid improvement on ADL, pain and stiffness on the WOMAC scale and there was furthermore a significant effect on stiffness using between group analysis. Thus, improved mobility of joints exposed to PEMF is a possible outcome of the treatment. In order to fully characterize a possible useful clinical effect of PEMF treatment further analysis should be performed on patients of different age groups and using different durations of treatment.

Acknowledgements

We appreciate economical support from IMK Almene Fond and from Københavns Amts Erhvervskontor.

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