PULSED ELECTROMAGNETIC FIELDS "PEMF"
CTU – MEDICAL DEVICE *PERISO sa*,
for the
THE ROLE OF PEMF IN KNEE OSTEOARTHRITIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY.

Abstract

Background:
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 OA.

Study Objective:
the purpose of this study was to evaluate the efficacy of PEMF (Pulsed Electromagnetic Field, CTU Medical Device - Periso sa) for the treatment of patients with KNEE OSTEOARTHRITIS.

Methods:
This was a 1:1 randomized, controlled, double-blind study. The duration of the study was 14 weeks and the patients met for five visits. The trial consisted of 30 minutes 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 STIFNESS 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 CTU 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.

Search strategy:
databases used to identify studies for this clinical study include Medline, Embase and Cochrane.

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

MD. Pietro Romeo (Annex 1)

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 OA in which technique was applied one or a few times a day for up to a month. 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. 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.
Beneficial therapeutic effects of PEMF have also been documented with increasing frequency for a variety of bone and cartilage related diseases since 1973.
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 CTU Medical Device – PERISO sa, treatment in a group of patients suffering from OA.

DEVICE DESCRIPTION

PULSED LOW-FREQUENCY ELECTROMAGNETIC FIELDS: The pulsed low-frequency (< 50Hz; ~7Hz) electromagnetic fields (1b) belong to the class of non ionizing radiations, that is, they are characterized by an associated energy below 12 eV (electron-Volt). Such an energy is insufficient both to turn on ionization phenomena in molecules and to break even very weak chemical bonds. For this reason in the last decades these radiations have not been considered able to interact with biological systems and, as a consequence, the studies on this subject were scarce and information poor, especially when compared with the great amount of knowledge concerning the interactions among ionizing radiations and biological systems (2b). Only recently, due to the more and more common use of electromagnetic fields of different intensity and frequencies (3b), a vast research activity (4b-5b-6b-7b-8b-9b-10b-11b) has started, addresses to the definition of their main biological and therapeutic effects, on which are based the exposition thresholds currently recommended.
DIAMAGNETISM: The diamagnetism works on hydrogen atoms. Indeed, when a hydrogen atom is covalently bound to a strongly electronegative atom, as for example the oxygen, the bond electrons tend to move toward the latter. As a consequence, the H atom assumes a partial but consistent positive charge. This charge, distributed in a small volume, lead to a high electric charge density. At this point, the hydrogen atom tends to bind with a partially negatively charged atom (the oxygen atom of a different water molecule) in this way acquiring a greater stability neutralizing its electric charge.
A single water molecule does not feel any net force, since it is subject to the action of the surrounding molecules that are uniformly distributed in any direction of the three-dimensional space. The liquid water consists in a disordered network of molecules, bound together by relatively weak chemical bonds. Such a network is continuously subject to fluctuations that randomly break and create new bonds among the molecules. Due to these characteristics the

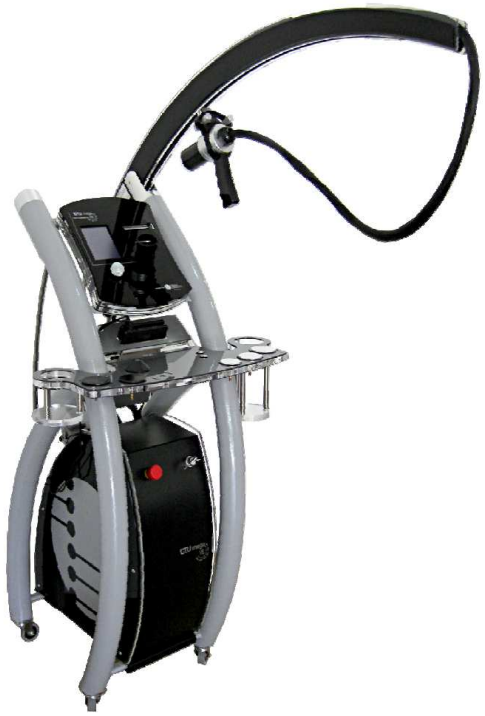
water does not have a proper dipole magnetic moment and it is repelled by an external magnetic field (diamagnetism). The PEMF - CTU PERISO sa (Fig. 1), is a device of molecular diamagnetic acceleration. It uses an energy of up to 200 Joule, generating high power (2 Tesla), pulsating fields and developing a water-repulsive force with the following main therapeutic aims:

- liquids transport;
- tissue biostimulation.

Liquids transport: as a result of diamagnetic repulsion, the free water in the extracellular compartments is fiercely pushed away from the field application site. The transport of extracellular liquids helps the oedema and post-traumatic effusions reabsorption and the scoriae removal, and stimulate the lymphatic circulation and related phenomena also thanks to the vasodilatation draining action produced by the diathermia coupled with PEMF (CTU – PERISO sa). In addition, the magnetic field works on the intracellular liquids, increasing their mobility. The increase of the thermal molecular excitation supports the cells biochemical activity as well as the mitochondrial and phagic-lysosomal metabolic mechanisms. The result is a beneficial acceleration of all energetic, metabolic and cellular activities like ionic transport, scoriae removal and cellular breathing.

Tissue biostimulation: a variable magnetic field crossing a conductor induces an electric current. The human body is a conductor, that when it is crossed by a magnetic field the phenomenon of biostimulation occurs. The action of magnetic fields is well described in terms of bioelectric parallelisms existing among cells (12b), since it acts on the difference of electric potential on the membrane sides as well as on the orientation af the circulating atoms that behave as elementary magnetic dipoles (13b, 14b).

Fig. 1



SEARCH STRATEGY

Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from the inception of each database from 18 January 2013 to 13 December 2013. The Medline and Embase databases were searched together via www.embase.com

The search was conducted using the keywords knee, osteoarthritis, OA, PEMF, radiographic evidence, bone scintigraphy, and it was limited to RCTs (List 1). Additionally, all of the available reviews related to knee osteoarthritis were manually screened for any additional possibly relevant studies. No language limit was applied.

List 1 Search Strategy used in www.embase.com (step by step):

1 'osteoarthritis' OR 'OA'/exp
2 'knee' OR 'knee OA'/exp
3 'bone scintigraphy' OR 'knee bone scintigraphy'/exp
4 'knee x-rays' OR 'knee x-rays'/exp
5 'knee PEMF'
6 'OA PEMF'
7 #1 OR #2 OR #3 OR #4 OR #5
8 random: ab,ti OR factorial: ab,ti OR crossver: ab,ti OR placebo :ab,ti OR control :ab,ti OR trial:ab,ti OR group: ab,ti OR 'crossover procedure'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp
#1 #2 #3 #4 AND #5.

MATERIALS AND METHODS

This was a 1:1 randomized, controlled, double-blind study. The duration of the study was 14 weeks and the patients met for five visits.

STUDY SELECTION CRITERIA

TYPES OF STUDIES, PARTICIPANTS AND INTERVENTIONS INCLUDED

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. Furthermore, patients were excluded if they were unable to understand/fill out the questionnaires, had received intraarticular 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.

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 30 minutes daily every 5 days. 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 treatment commenced immediately after enrolment:

Once included in the study, the patient was blindly assigned into the PEMF treatment group (Group 1) or the control group (Group 2) according to randomly generated numbers. The treatment commenced immediately after enrollment.

- In Group 1, PEMF using a real (Magnetic Field=2 Tesla; Intensity=90 J; frequency of impulses=7Hz; duration=30minutes/session). The handpiece of CTU Medical Device – PERISO sa, was placed 3 cm over the region of the study knee
- In Group 2, the coil was applied for 30min/day with a sham signal generator from the same manufacturer.

All patients were requested to record their potential discomfort and the duration of the treatment. They were also asked to refrain from smoking, alcohol abuse, or additional forms of therapy during the study period. Biweekly contact through phone calls was performed by two research assistants to exclude patients with poor compliance.

EXCLUSION CRITERIA

Before performing the treatments with PEMF CTU Medical Device – PERISO sa, all the patients received a clinical evaluation to exclude patients with: Open Physis, 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 and ferromagnetic parts.

BENEFIT/RISK

No Risks, Dangers, Adverse Reactions have been associated with the use of the CTU Medical Device – PERISO sa, even outside the protocols used. The CTU Medical Device PERISO sa, respects all CLINICAL SAFETY Standards.

TYPES OF OUTCOME MEASURES

The physical examination included measurement of ROM (range of movement) (goniometer) and examining for periarticular tenderness (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.

METHODS

Symptoms of knee OA were assessed by the WOMAC OA index, 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.

STATISTIC ANALYSIS

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 99mTc-MDP. Three 6 min frames were recorded in anterior, posterior and lateral views using a high-resolution collimator on a dual-head gamma camera. 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. 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. Knee to reference ROI ratios (Ratios) were calculated without background subtraction.

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

	PEMF CTU	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 (0e4)	2.5 (1.2)	2.8 (1.1)
Analgesic medication (*n*)	28	29

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. At baseline 23 of 42 patients in the PEMF group used analgesic medication (55%) e eight patients used nonsteroidal 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%) e 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.

Table II
WOMAC data on ADL, pain and stiffness

Week	PEMF CTU			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 % 0.05.

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 WOMAC subscore of 14% in the PEMF CTU 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.

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	

*$P \leq 0.05$.

Bone Scintigraphy

The results of the bone scintigraphic examinations are given in Table IV. To distinguish activity in the patellofemoral compartment from that in the tibio-femoral compartment, ratios obtained with the lateral view are given separately (Whole Knee-lateral, Knee Joint-lateral). 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 CTU 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 e 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.

Table IV

Bone scintigraphic results for study knee at baseline and at the end of treatment (6 weeks) with PEMF CTU (n Z 18) or placebo (n Z 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)
	PEMFCTU	2.8 (1.8)	2.7 (1.5)
Knee Joint	Placebo	2.0 (0.5)	2.0 (0.8)
	PEMFCTU	1.8 (0.9)	1.8 (0.7)
Whole Knee-lat	Placebo	3.2 (1.2)	3.1 (1.1)
	PEMFCTU	3.1 (1.9)	3.0 (1.7)
Knee Joint-lat	Placebo	2.0 (0.6)	1.9 (0.5)
	PEMFCTU	1.7 (0.8)	1.8 (0.8)

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.

Our findings are in some respects in accordance with previous observations 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. 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.

Recently, Pipetone and Scott reported a significant improvement within groups treated with PEMF e 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. 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.

Conclusion

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.

Improvement on stiffness could be envisioned as being due to an enhanced blood circulation in the periarticular compartment, improved growth of chondrocytes or 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) and synthesis of NO in endothelial cells could be involved in enhancing blood flow.
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.

CONFLICTS of INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.
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Device References

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DATE: 21/02/2018

SIGNATURE: MD Pietro Romeo

ANNEX 1

FORMATO EUROPEO PER IL CURRICULUM VITAE

INFORMAZIONI PERSONALI

Nome	Pietro Romeo
Indirizzo	Via E. Cernuschi 59 21100, VARESE (VA), ITALIA.
Telefono	(039) 0332.281099- 347.6651575
Fax	---
E-mail	romeo.p@libero.it
Nazionalità	Italiana
Data di nascita	05/11/1958

ESPERIENZA LAVORATIVA

• Date (da – a)

Aprile 2010 – oggi
Istituto Ortopedico Galeazzi – IRCCS – Via Riccardo Galeazzi 4, Milano.
Dipartimento di Clinica Ortopedica Università degli Studi Milano
(Direttore Prof. V. Sansone)
Dirigente Medico (Rapporto LP)

Ottobre 2004 - oggi
Eurocentro Polispecialistico – V.le Milano 18 - Varese
Convenzionato Servizio Sanitario Regione Lombardia
Specialista Ortopedico – Terapia con Onde d'Urto (Rapporto LP)

Da Aprile 2000 - Marzo 2015
INAIL – Istituto Nazionale Assicurazione Infortuni sul Lavoro
V.le Aguggiari, 6 . 21100 Varese
Specialista Ortopedico Convenzionato

Dal 1993 al 2000
Azienda Sanitaria Locale della Provincia di Varese- Via O. Rossi 9- Varese
Dirigente Medico - Organizzazione Servizi Sanitari di Base – Incarico in Ambulatorio Infortuni Traumatologia

Dal 1993 al 2000
Ministero di Grazia e Giustizia – Dipartimento dell'Amministrazione Penitenziaria- Casa Circondariale di Busto Arsizio (VA)
Specialista Ortopedico Convenzionato

1990
Azienda Sanitaria Locale della Provincia di Varese- Via O. Rossi 9- Varese
Ospedale Filippo Del Ponte
Assistente Medico Supplente – Chirurgia Generale (Incarico a Termine)

Dr. PIETRO ROMEO
MEDICO CHIRURGO
Specialista in Ortopedia e Traumatologia
[illegible] 59 - 21100 VARESE
[illegible] RMO PTR 58S05 L452X
Partita IVA 01227940129

1990
Azienda Sanitaria Locale della Provincia di Varese- Via O. Rossi 9- Varese
Igiene Pubblica
Assistente Medico Supplente (Incarico a Termine)

• Nome e indirizzo del datore di lavoro

Dal 1988 al 1993
Ministero di Grazia e Giustizia – Dipartimento dell'Amministrazione Penitenziaria- Casa Circondariale di Busto Arsizio (VA)
Medico del Servizio di Assistenza Sanitaria Integrativa

• Tipo di azienda o settore
• Tipo di impiego
• Principali mansioni e responsabilità

ISTRUZIONE E FORMAZIONE

• Date (da – a)

2008
Bologna – Scuola di Ecografia Muscolo Scheletrica
Corso Avanzato
2006 e 2007
Bologna – Scuola di Ecografia Muscolo Scheletrica
Corso Base
1992
Diploma di Specializzazione in Ortopedia e Traumatologia
Università degli Studi di Milano
1984
Abilitazione Professionale
Università degli Studi di Pavia
1984
Diploma di Laurea in Medicina e Chirurgia
Università degli Studi di Pavia
1977
Diploma di Maturità Scientifica
Liceo "F.lli Vianeo" Tropea (CZ)

• Nome e tipo di istituto di istruzione o formazione
• Principali materie / abilità professionali oggetto dello studio
• Qualifica conseguita
• Livello nella classificazione nazionale (se pertinente)

Dr. PIETRO ROMEO
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CAPACITÀ E COMPETENZE ORGANIZZATIVE

ULTERIORI INFORMAZIONI

Affiliazione a società scientifiche
SIOT (Società Italiana Ortopedia e Traumatologia)
ASON (Associazione Specialisti Osteoarticolari Nazionale) – Referente regionale per la Lombardia biennio 2015-2017
SITOD (Società Italiana di Terapia con Onde d'Urto).
Componente del Consiglio Direttivo biennio 2008-2010, biennio 2010-2012 biennio 2012-2014 , biennio 2014-2016 , biennio 2016-2018
ISMST (International Society for Medical Shock Wave Treatment)

Il sottoscritto è a conoscenza che, ai sensi dell'art. 76 del DPR 445/2000, le dichiarazioni mendaci, la falsità negli atti e l'uso di atti falsi sono puniti ai sensi del codice penale e delle leggi speciali. Inoltre, il sottoscritto autorizza al trattamento dei dati personali, secondo quanto previsto dalla Legge 196/03.

CITTA' __Varese_____

DATA___07/08/2017 _____

NOME E COGNOME (FIRMA)

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CAPACITÀ E COMPETENZE PERSONALI

Acquisite nel corso della vita e della carriera ma non necessariamente riconosciute da certificati e diplomi ufficiali.

Italiano

Dal 1995 al 2016 interesse e competenze specifiche nel campo dell' Ortopedia applicata alla Medicina Legale quale consulente di compagnie assicurative (1995 – 2008) dell' Istituto Nazionale Assicurazione Infortuni sul Lavoro (INAIL) , consulente tecnico per la branca di Ortopedia presso il Tribunale di Varese sino al mese di ottobre 2015.

Dal 2004 interesse nella Terapia con Onde d'urto Extracorporee utilizzando apparecchiature focalizzate piezoelettrica ,elettromagnetica ed elettroidraulica . Esperto in trattamenti ecoguidati ed eco-assistiti *manu medica*, per il trattamento delle principali patologie muscolo scheletriche, inclusi i ritardi di consolidazione delle fratture , la patologia vascolare e metabolica dell'osso le osteocondropatie e il trattamento delle ulcere cutanee . Dal 2010 attività di ricerca clinica e sperimentale presso il Dipartimento di Ortopedia e Traumatologia dell'Università degli Studi di Milano dell' Istituto Ortopedico Galeazzi (Direttore prof V. Sansone) che riguardano l'impiego delle energie fisiche nella patologia metabolica , degenerativa e vascolare dell'osso , gli effetti su colture di cellulari (Centro di Ricerca Applicata sulla Stimolazione Biofisica dei Tessuti Muscolo-Scheletrici)

Coautore di pubblicazioni in materia su riveste nazionali e internazionali indicizzate . Relatore – moderatore in congressi e corsi di formazione

PRIMA LINGUA	Italiano
ALTRE LINGUE	
	Inglese
• Capacità di lettura	Buona
• Capacità di scrittura	Buona
• Capacità di espressione orale	Discreta

Ha maturato negli anni capacità di lavoro individuale e in equipe

CAPACITÀ E COMPETENZE RELAZIONALI

Vivere e lavorare con altre persone, in ambiente multiculturale, occupando posti in cui la comunicazione è importante e in situazioni in cui è essenziale lavorare in squadra (ad es. cultura e sport), ecc.

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2012 TORINO XI CONGRESSO NAZIONALE SOCIETA' ITALIANA TERAPIA CON ONDE D'URTO EXTRACORPOREE (SITOD)
P. Romeo. La terapia con onde d'urto extracorporee. L'Operatore. Figure professionali coinvolte e specificità operative

2012 TORINO XI CONGRESSO NAZIONALE SOCIETA' ITALIANA TERAPIA CON ONDE D'URTO EXTRACORPOREE (SITOD) CONVEGNO SATELLITE: LE ONDE D'URTO IN PATOLOGIA ORTOPEDICA
P. Romeo. La Terapia con Onde d'Urto. Indicazioni Controindicazioni Aspetti Medico Legali.

2012 – ROMA 4° CONGRESSO NAZIONALE C.O.R.T.E
P. Romeo – MC D'Agostino, Onde d'Urto e Rigenerazione tissutale, il ruolo dell'Angiogenesi

2012- INNSBRUCK 2nd ISMST Basic Research Meeting
MC D'Agostino. P. Romeo. Early angiogenic response to shock waves in a three – dimensional model of microvascular endothelial cell culture (HMEC-1)

2011 - SANTA MERGHERITA LIGURE (GE) INDICAZIONI E LIMITI DELLA TERAPIA CON ONDE D'URTO: DAL MEDICO DI MEDICINA GENERALE ALLO SPECIALISTA.
- P. Romeo. Indicazioni Controindicazioni e modalità di somministrazione della terapia con onde d'urto. Linee guida

2011 VARESE AGGIORNAMENTO DEL MEDICO DI MEDICINA GENERALE
- L'Edema Osseo Midollare nelle patologie Osteoarticolare. Aspetti prognostici e Terapeutici

2011 BERGAMO TERAPIA CON ONDE D'URTO: DALLA RICERCA ALLA PRATICA CLINICA. INDICAZIONI
- P. Romeo Effetti Biologici delle Onde d'Urto Extracorporee. I Meccanismi della risposta cellulare.

2010/2011 MILANO – I CORSO AVANZATO SULL'UTILIZZO DELLE ONDE D'URTO EXTRACORPOREE IN ORTOPEDIA-FISIATRIA E MEDICINA RIGENERATIVA

-P. Romeo, V. Sansone Effetti Biologici della Stimolazione con Onde d'Urto. I meccanismi dell'azione terapeutica.
-P. Buselli, P. Romeo. Aspetti Medico Legali delle Terapia e raccolta del consenso informato.
- P. Romeo, V. Sansone. Onde d'Urto extracorporee e patologie vascolari dell'osso. Il razionale terapeutico
-P. Romeo, V. Sansone Le Onde d'Urto nella patologa dell'Achilleo. Dalla biologia alla pratica clinica.

2010 BARI. X CONGRESSO NAZIONALE SOCIETA' ITALIANA TERAPIA CON ONDE D'URTO EXTRACORPOREE (SITOD)
- P. Romeo, Indicazioni Controindicazioni, Utilità, Inutilità nelle applicazioni cliniche (o routinarie) delle onde d'urto focalizzate.

2010 SANTA MARGHERITA LIGURE (GE) NUOVE FRONTIERE NEL TRATTAMENTO DELLE PATOLOGIE ORTOPEDICHE CON ONDE D'URTO ED INGEGNERIA TISSUTALE ON LINE
- P. Romeo. V. Sansone. M.C. D'Agostino Onde d'Urto e Angiogenesi, Considerazioni clinico sperimentali.

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2010 VIENNA 1 th ISMST (International Society for Medical Shock Waves Treatments) BASIC RESEARCH MEETING
M.C. D'Agostino – P. Romeo. Osteogenesis and Bone Turnover

2009 CAMPOBASSO XXXVII SIMFER. SOCIETA' ITALIANA MEDICINA FISICA E RIABILITAZIONE
M. C. D'Agostino, P. Romeo. V. Sansone
Onde d'Urto Extracorporee dalla litotripsia alla rigenerazione tissutale. Sessione Poster

2007 VII CONGRESSO NAZIONALE SOCIETA' ITALIANA TERAPIA CON ONDE D'URTO EXTRACORPOREE (SITOD)
L. Polo – P. Romeo
Effetti secondari e applicazioni "off label "delle Onde d'urto. Sperimentazione e aspetti Medico Legali

Varese 07/08/2017

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