Is There a Role of Pulsed Electromagnetic Fields in Management of Patellofemoral Pain Syndrome? Randomized Controlled Study at One Year Follow-Up

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Patellofemoral pain syndrome (PFPS) is a common cause of recurrent or chronic knee pain in young adults, generally located in the retropatellar region. Etiology is controversial and includes several factors, such as anatomical defects, muscular imbalance, or joint overuse. Good results have been reported with exercise therapy, including home exercise program (HEP). Joint inflammation with increase of pro-inflammatory cytokines levels in the synovial fluid might be seen especially when chondromalacia becomes evident. Biophysical stimulation with pulsed electromagnetic fields (PEMFs) has shown anti-inflammatory effects and anabolic chondrocyte activity. The purpose of this randomized controlled study was to evaluate if the combination of HEP with PEMFs was more effective than HEP alone in PFPS treatment. Thirty-one PFPS patients were enrolled in this study. All patients were instructed to train with HEP. Patients in the PEMFs group associated HEP with PEMFs. Function and pain were assessed with Victorian Institute of Sport Assessment score (VISA), Visual Analog Scale (VAS), and Feller's Patella Score at baseline at 2, 6, and 12 months of follow-up. Drug assumption was also recorded. Increase in VISA score was significantly higher in PEMFs group compared to controls at 6 and 12 months, as well as the increase in the Feller's Patella Score at 12 months. VAS score became significantly lower in the PEMFs group with respect to control group since 6 month follow-up. Pain reduction obtained with PEMFs enhanced practicing therapeutic exercises leading to a better recovery process; this is extremely important in addressing the expectations of young patients, who wish to return to sporting activities. Bioelectromagnetics.

Key words: rehabilitation; knee pain; regenerative medicine; home exercise; electromagnetic stimulation

INTRODUCTION

Patellofemoral pain syndrome (PFPS) [Cutbill et al., 1997] is a common cause of knee pain in young adults, especially females [Taunton et al., 2002] who practice sport activities [Devereaux and Lachmann, 1984]. Particularly, runners and endurance athletes are high risk for developing this condition. PFPS etiology is controversial and includes several factors, such as anatomical defects, altered biomechanics of lower limbs, muscular imbalance, or joint overuse [Thomee et al., 1999; Duffey et al., 2000]. Pain is generally located in retropatellar or peripatellar regions and occurs mainly during squatting, walking up stairs, running, or sitting for extended periods of time.

Alarmingly, 70–90% of individuals with PFPS have recurrent or chronic pain. However, it is still debated if PFPS may lead to early development of knee arthritis [Hinman et al., 2013].

Conflicts of interest: Dr. Matteo Cadossi owns 10% of IGEA spa shares, the manufacturer of devices used in the present study. All other authors declare not to have any conflict of interest.

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Received for review 18 June 2015; Accepted 12 December 2015

DOI: 10.1002/bem.21953
Published online XX Month Year in Wiley Online Library (wileyonlinelibrary.com).

The normal sliding mechanism of patellofemoral joint is controlled by different static and dynamic factors [Elias et al., 2014]. Static factors include size of patella and femoral condyles, trochlear groove, alignment of lower limbs and patella height. Vastus lateralis and vastus medialis oblique muscles mainly represent the dynamic component [Brownstein et al., 1985].

Patients with anterior knee pain have to be examined carefully with regard to functional causes for PFPS. PFPS treatment is generally non-operative and should address functional causes [Petersen et al., 2014].

The principal goal of treatment is to obtain a better position of the patella on the trochlea. Different conservative approaches have been reported in literature [Kannus and Niittymaki, 1994; Brody and Thein, 1998; Powers, 1998; Juhn, 1999; Thomee et al., 1999; Baker and Juhn, 2000; Clark et al., 2000], with exercise therapy being widely accepted and routinely applied as the main treatment strategy with good results, especially in pain reduction [Heintjes et al., 2003].

Good clinical results have been reported with quadricep strengthening and both open and closed kinetic chain exercises [Irish et al., 2010]. A more specific physiotherapeutic approach has been presented by McConnell [2002]. This rehabilitation program is comprehensive with quadricep strengthening, patellar taping [Osorio et al., 2013], and weight-bearing exercises to influence timing of contraction and strength of hip and thigh musculature. Bily et al. [2008] obtained good results in short and long-term PFPS treatment from a 3-month supervised exercise program. In their review, Kooiker et al. [2014] reported strong evidence for use of quadriceps strengthening exercises, with or without other interventions, for PFPS treatment.

Many medical treatments have been proposed to integrate and enhance the exercise program [Collins et al., 2013]. Anti-inflammatory drugs are often useful for a few days in the acute phase to decrease inflammation and pain [Heintjes et al., 2004]. Nonsteroidal anti-inflammatory drugs (NSAIDs) applied directly to the knee may be a valid option whereas corticosteroid injections should be reserved for patients who suffer from severe inflammation and do not respond to NSAIDs, local ice, and rest [Heintjes et al., 2004]. Radiologic evidence of chondromalacia of the patella in patients who did not respond to the conservative approach may be an indication for hyaluronic acid injections [Kannus et al., 1992].

Other interventions, such as foot orthotics, can be extremely helpful in appropriate patients [Saxena and Haddad, 2003; Swart et al., 2012]. A patellar taping technique to control patellar subluxation and tilt could be considered to reduce anterior knee pain [Paoloni et al., 2012].

Different physical therapies have been proposed to increase effectiveness of therapeutic exercise but scientific evidence of their usefulness does not exist [Crossley et al., 2001].

Arthroscopic treatment is usually reserved to those patients in which conservative treatments have failed; nevertheless clinical outcome is not always satisfying [Kettunen et al., 2007].

PFPS is sustained by joint inflammation; an increase of pro-inflammatory cytokines levels such as IL-6 can be measured in the synovial fluid especially when a progression of the disease to chondromalacia becomes evident [Vaatainen et al., 1998].

Pulsed electromagnetic field stimulation (PEMFs) is a physical treatment most commonly used in orthopedics for treatment of non-union or delayed union [Griffin et al., 2011].

Biophysical stimulation with cartilage specific PEMFs has been shown to promote anabolic chondrocyte activity, to stimulate proteoglycan synthesis [Varani et al., 2008; De Mattei et al., 2009], and to reduce release of the most relevant pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and PGE_2 by immune cells through upregulation of A_{2A}-adenosine receptors [Revell et al., 1988; Sakkas et al., 1998; Nakamura et al., 1999; De Mattei et al., 2003, 2004, 2007; Jahns et al., 2007; Stolfa et al., 2007; Benazzo et al., 2008].

The purpose of this randomized controlled study was to evaluate if the combination of home exercise program (HEP) with PEMFs was more effective than HEP alone in treatment of PFPS in terms of knee function and pain reduction.

MATERIALS AND METHODS

The trial was approved by the Federico II "C. Romano" Ethic Committee (Napoli, Italy).

Inclusion criteria were: presence of at least three of the following symptoms: pain when walking up or down stairs, pain when squatting, pain when running, pain when cycling, pain when sitting with knees flexed for a prolonged time, grinding of patella, and a positive clinical patellar test (such as Clarke's test or patellar femoral grinding test); untreated pain lasting for more than 3 months; age between 15 and 45 years; and informed consent given.

Exclusion criteria included the following: knee capsular ligament or meniscus tears; previous knee surgery; severe knee varus/valgus deformities ($>10°$);

lower limb prosthesis; corticosteroid therapy; body mass index > 30 kg/m^2; infections, rheumatoid arthritis, or autoimmune diseases; malignancy; systemic diseases; and plateau-patella angle <20° or >30° according to Portner and Pakzad [2011].

Primary endpoint was to evaluate if association of PEMFs with HEP leads to better function of the knee, evaluated with Victorian Institute of Sport Assessment score (VISA), compared to only HEP in patients affected by PFPS. Secondary endpoint was to evaluate the effect of PEMFs on pain, measured through Visual Analog Scale (VAS) and on NSAID consumption.

The smallest difference in VISA score considered clinically relevant is at least 10 points. The sample power calculation was made using the superiority test on the hypothesis that VISA score will be superior at 12 months in the active group of 12 units with a standard deviation for the population of 12 units. If alpha value is 0.05 and statistical power is set to 80%, the sample size for each sample is 13 per group. Considering a dropout percentage of about 10%, resulting sample size is 15 per group. Calculation was performed using the PASS 13.0 software (PASS 13, NCSS Statistical Software, Kaysville, UT, www.ncss.com.).

From May 2010 to March 2011, 31 patients (9 males, 22 females) with a mean age of 22.5 years were enrolled in this study at Federico II University Hospital (Napoli, Italy).

Written informed consent was obtained from all patients enrolled in the study. In cases of minors, written informed consent was collected from their guardians.

Patients were randomly assigned by a sealed envelope technique to the PEMF intervention group ($n = 14$) or to the control group ($n = 17$). Function and pain were assessed with VISA Score [Visentini et al., 1998], VAS, and Feller's Patella Score [Feller et al., 1996] at baseline, at 2, 6 and 12 months of follow-up. Drug assumption was also recorded. The physician who assessed functional scores was blinded regarding treatment, and functional scores were self-assessed by each patient.

Both groups were instructed to train with HEP. This consisted of an initial 5 min warm up running in place followed by static and dynamic muscular exercises for quadriceps, adductor, and gluteal muscles. It also included balance and stretching exercises to loosen tight structures like hamstrings, iliotibial tract and patellar retinaculum. Patients exercised for about 25 min daily for 6 weeks. Every 2 weeks they were seen by the therapist to ensure they were practicing exercises correctly and to enhance the load of exercise protocol by increasing number of repetitions or intensity of exercises, being guided by pain reaction upon exertion. To enhance compliance, patients received a tutorial with photographs, a text explaining exercises and a diary to register amount of exercising.

Patients in the intervention group were conservatively treated with self-administered PEMF therapy (I-ONE, IGEA, Carpi, MO, Italy) for 4 h per day for 6 weeks. The battery-operated device produced a pulsed signal with a square waveform, a peak magnetic field intensity of 1.5 mT, an active pulse duration of 1.3 ms with a frequency of 75 Hz and a duty-cycle of 10%. The area of applied magnetic field was like a sphere of 7 cm diameter covering the whole joint homogeneously; peak intensity of induced electric field inside knee tissue was 0,045 mV/cm. The coil was placed on affected knee, avoiding direct contact with skin. Coil was kept in place by means of provided strap. No heat or vibration was felt by patient during treatment.

All devices were provided by manufacturer at no cost.

The stimulator had a timer to record the hours of therapy, allowing patient compliance to be monitored.

Statistical analyses were conducted with Statistical Packages for Social Sciences software (IBM, Armonk, NY). Mean values and standard deviation were calculated to continuous variables. Comparison between groups was performed by heteroschedastic 2 tailed Student *t*-test, while comparison among follow-up visit on same patients of each group was performed by coupled 2 tailed Student *t*-test.

RESULTS

Of 31 patients enrolled, one patient in the PEMF group was lost to follow-up because he did not return to scheduled visits for unknown reasons; therefore 30 patients were available for analyses.

At baseline there were no significant differences between the two groups regarding age, weight, height, VAS, Feller's Patella Score and VISA Score (Table 1). The compliance was good, with mean usage of stimulator of 4.2 ± 2.0 h (mean ± standard deviation) per day.

VISA score was not significantly different between the 2 groups during the whole study, but when we calculated mean VISA score variations from baseline in the 2 groups we could see a significantly different trend at 6 and 12 months. Increase in VISA score was significantly higher in PEMF intervention group compared to control group ($P = 0.010$ at 6 months and 0.001 at 12 months) (Fig. 1).

TABLE 1. Patients' Characteristics in PEMF Intervention Group and Control Group at Baseline

	CONTROL 5M, 12F		PEMFs 3M, 10F		
Patients' characteristics at baseline	Mean	St.dev.	Mean	St.dev.	*t*-test
Age (yrs)	24	8	21	7	0.369
Weight (kg)	61	16	70	16	0.159
Height (cm)	170	7	168	8	0.704
VAS	6.2	1.1	7.0	1.2	0.112
VISA SCORE	53.5	22.7	40.3	21.2	0.122
PATELLA SCORE	17.5	4.4	16.4	6.1	0.614

Feller's Patella score was similar in both groups when considering absolute mean values. A significant difference between groups was observed only when calculating mean Feller's Patella score variations from baseline, being score increase at 12 months higher in the PEMF intervention group with respect to control one ($P = 0.030$) (Fig. 2).

VAS score became significantly lower in the PEMF intervention group at 6 and 12 months with respect to control group ($P = 0.052$, 0.010, respectively). The different trend in pain intensity in the 2 groups is clearer when analyzing pain variation in single patients with respect to baseline. Mean pain decrease with respect to baseline is significantly higher in PEMF group even at 2 months follow-up ($P = 0.012$ at 2 months, 0.015 at 6 months, and 0.003 at 12 months) (Fig. 3).

We recorded a minor percentage of patients still consuming drugs to control pain: in fact, at baseline 41% of patients in the control group and 50% in PEMF intervention group used NSAIDs (Table 2), while 12 months later, only 6% in control and 0% in PEMF intervention group used NSAIDs. Differences between groups are not statistically significant ($P = 0.716$ at baseline and 1.000 at last follow-up).

DISCUSSION

PFPS generally affects young athletes whose primary desire is to resume sporting activity as soon as possible. Pain may be caused both by increased subchondral bone stress in the patellofemoral joint or cartilage lesions on the patella or distal femur [Besier et al., 2005; Gerbino et al., 2006]. Concern over long-term consequences of anterior knee pain in adoles-

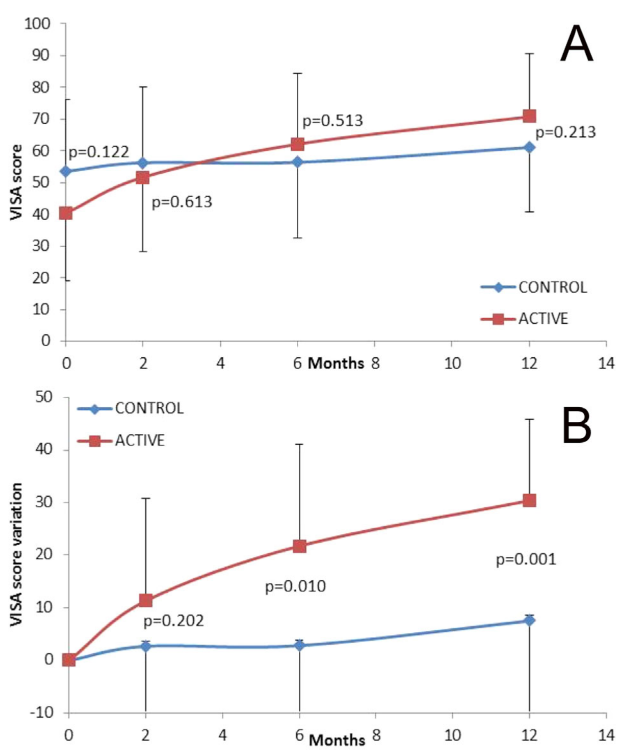

Fig. 1. Mean VISA score (**A**) and VISA score variation: difference between follow-up and baseline (**B**) in PEMF's intervention group and control group, respectively. Error bars represents standard deviations.

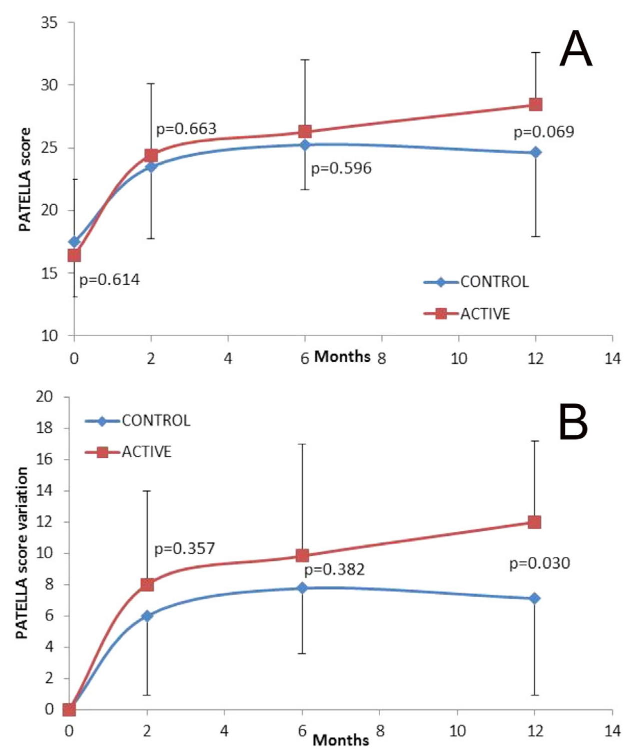

Fig. 2. Mean Feller's Patella Score (**A**) and Feller's Patella Score score variation difference between follow-up and baseline (**B**) in PEMF's intervention group and control group, respectively. Error bars represents standard deviations.

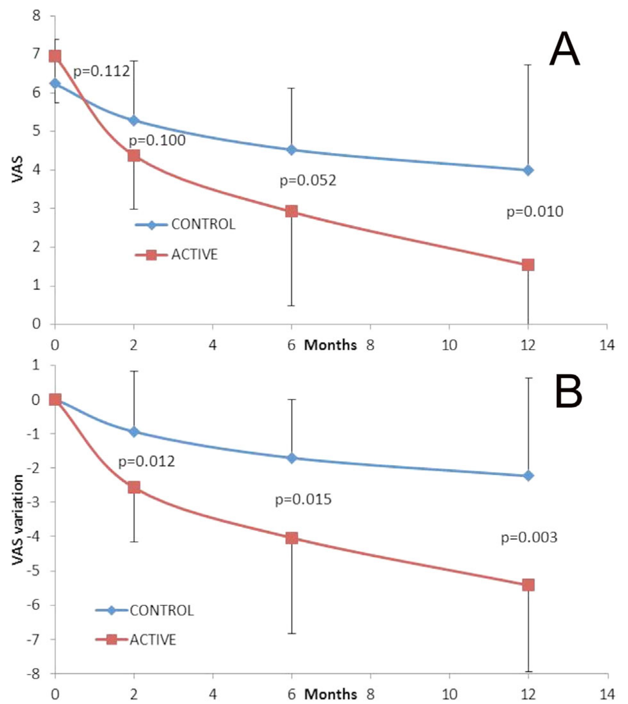

Fig. 3. Mean pain (**A**) and pain variation difference between follow-up and baseline (**B**) evaluated with VAS score in PEMF's intervention group and control group, respectively. Error bars represents standard deviations.

cence and young adulthood includes a predisposition to patellofemoral osteoarthritis in later life. Rehabilitation exercises can restore patellofemoral joint homeostasis reducing pain and preventing cartilage damage [Witvrouw et al., 2005].

Non-operative treatments are generally used. Exercises remain the treatment of choice in PFPS. Results obtained with stretching and muscular rebalancing are generally satisfactory. However, the positive outcome of this treatment is extremely dependent on patients' compliance.

Evidence suggests that physiotherapy can reduce pain associated with PFPS in short term; nevertheless, at long-term a mild pain may persist.

This might be due to a chronic inflammatory state in knee joint, with possible association of early stage patello-femoral cartilage lesion.

TABLE 2. Number of Patients Consuming NSAIDs at Baseline and at Different Follow-Ups

Evaluation time	CONTROL ($n = 17$) (%)	PEMFs ($n = 13$) (%)
Baseline	41	50
2 Months	12	15
6 Months	0	0
12 Months	6	0

Biophysical stimulation with PEMFs has been demonstrated to have an anti-inflammatory and chondroprotective activity [Zorzi et al., 2007; Benazzo et al., 2008], leading to improvement of analgesic effect, both at short and long term follow-up.

In PEMF intervention group, a significant reduction in pain was already observed at two month follow-up. Pain reduction enhanced practicing therapeutic exercises, allowing an early increase in HEP intensity. Triggering this virtuous circle is of paramount importance to ameliorate recovery process.

According to results of this study, HEP was demonstrated to generate amelioration in all functional scores tested, even not statistically significant.

Knee function assessed with Feller's Patella Score improved in both groups until 6 months with respect to baseline; a further amelioration at 12 month follow-up was observed only in PEMF intervention group ($P = 0.030$). VISA score, which is focused on sporting activities, showed a different trend, with a constant increase over time in PEMF group, compared to a flat curve in control.

The association of PEMFs with HEP might be particularly indicated to address expectations of young patients, who wish to promptly return to sporting activities.

Several studies reported the chondro-protective effect of biophysical stimulation [Zorzi et al., 2007; Benazzo et al., 2008]. Differences between the two groups observed at 12 month follow-up might be partially explained according to preservation of knee cartilage from degeneration that may be present in chronic disease.

Some authors hypothesized that PFPS might be due to insufficient stabilization of the pelvis with a secondary involvement of the patello-femoral joint [Schneider et al., 2001].

Ismail et al. [2013] performed a randomized control study to compare two different rehabilitation protocols for PFPS: closed kinetic exercises alone or associated with hip muscle reinforcement. Additional hip strengthening was found to be more effective for both knee function and pain reduction than closed kinetic exercises alone at 6 week follow-up. According to Ismail et al. [2013], our HEP consisted of a 6-week protocol that associated adductor and gluteal muscles strengthening to quadricep exercises.

Moyano et al. [2013] reported in a randomized control trial that a proprioceptive neuromuscular facilitation intervention protocol combined with aerobic exercise showed a better outcome than a classic stretching approach.

Specific electric stimulation of vastus medialis obliquus or general quadricep strengthening have attained widespread acceptance but evidence for efficacy of these interventions is not well established. Bily et al. [2008] demonstrated no clinical advantage of electric stimulation added to muscle exercises; therefore, we did not included electric stimulation in our rehabilitation protocol.

Many studies investigated effectiveness of physiotherapy in PFPS at short-term follow-up (4–12 weeks) [Crossley et al., 2001].

In our study we observed a clinical improvement in the PEMF's intervention group still present at 1 year follow-up.

As demonstrated through upregulation of A_2A adenosine receptors and decrease of release of the most relevant pro-inflammatory cytokines [Fini et al., 2008; Varani et al., 2008; Vincenzi et al., 2012] we can hypothesize that PEMFs are able to control inflammation, ultimately resulting in chondroprotection, thus leading to these long-term positive results.

Few study limitations must be addressed. One of the major limitations of this study is lack of sham devices in the control group. Patients, therefore, were not blinded regarding treatment. A placebo effect must certainly be considered. We believe extremely unlikely that this effect was still present 10 months after biophysical stimulation was over. Rossini et al. [2010] in a double blind study observed a placebo effect that started decreasing after 6 weeks, while biophysical stimulation was still administered.

Moreover, the physician who assessed functional scores was blinded regarding treatment, and functional scores were self-assessed by each patient.

Another limitation is the small number of patients. Nevertheless, the power analysis performed and study design were adequate to verify the primary endpoint.

Further studies with larger sample size and cartilage evaluation with high quality MRI are needed to confirm effectiveness of PEMFs in cartilage preservation in PFPS.

Based on our results, biophysical stimulation with PEMFs should be considered as an effective tool for conservative treatment of PFPS with encouraging results still lasting at 12-month follow-up.

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