Clinical Results of Pulsed Signal Therapy on Patellofemoral Syndrome With Patellar Chondropathy

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This study was designed to evaluate the effect of pulsed signal therapy (PST) on patellofemoral pain syndrome associated with patellar chondropathy. A prospective randomized double-blind placebo controlled trial included 25 patients (41 knees) between 20 and 50 years with pain due to isolated patellofemoral syndrome with chondropathy. PST group received nine 60-min daily sessions of PST treatment. Control group received the same protocol of blinded placebo treatment. The main outcome was change from baseline Kujala score at 3 months. After 3 months, patients in the control group received effective treatment (placebo post-treatment). All patients were then followed, for up to 12 months. Seventeen knees (5 males and 12 females, mean age 36.7 ± 7.9) received placebo and 24 knees (8 males and 16 females, mean age 35.5 ± 8.9) received PST. By the third month, PST group exhibited a mean change from baseline of 9.63 ± 7.5 Kujala points, compared to 0.53 ± 1.8 in the placebo group ($P < 0.001$). A significant progressive improvement was seen in the PST group between the 3rd and 6th and between the 6th and 12th month ($P < 0.016$). Patients initially allocated in the control group also improved at 3 months ($P < 0.001$) and 6 months ($P = 0.005$) post-effective treatment. In conclusion, PST in patellofemoral pain syndrome with chondropathy was effective compared to placebo at 3 months, showing an important improvement of Kujala score. The improvement was progressive and maintained up to 12 months. PST is safe and should be considered as a non-invasive option for management of this condition. Bioelectromagnetics. 40:83–90, 2019. © 2019 Bioelectromagnetics Society.

Keywords: patellofemoral syndrome; pulsed electromagnetic field; pulsed signal therapy; patellar chondropathy

INTRODUCTION

Pulsed signal therapy (PST) is an extension of pulsed electromagnetic field therapy (PEMF) consisting in a patented pulse frequency for bones and soft tissue (PST MOBIL, Bio Magnetic Therapy Systems, Munich, Germany). PST has been used empirically to treat various diseases, including arthrosis of various joints, spine pain syndromes, tendinopathy, sports injuries, and even as an adjunct in rheumatic diseases [Moretti et al., 2012; Massari et al., 2015; Collarile et al., 2018].

The biological effect of electromagnetic fields on different tissues has been a focus of research in

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Conflicts of interest: None; this work was not sponsored by the PST's manufacturer or distributor.

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some studies, with cartilaginous tissue being the most studied. This treatment has been shown to increase proteoglycan and collagen synthesis in vitro [Liu et al., 1996; Ongaro et al., 2011; Veronesi et al., 2015; Anbarasan et al., 2016]. Electromagnetic stimulation generates electrical signals in chondrocytes, simulating a mechanical force. This effect is similar to physiological electrical behavior when cartilage receives a load [Bassett and Pawluk, 1972]. Specifically, during compression, hydrogen ions (positively charged) are expelled along with the fluid, leaving glycosaminoglycans (negatively charged) in the matrix. In theory, this electrical signal stimulates chondrocytes to produce matrix components. Electromagnetic stimulation has been used successfully in patients with arthrosis, where the physiology of the cartilage has changed [Trock et al., 1993, 1994; Nelson et al., 2013; Wuschech et al., 2015; Bagnato et al., 2016]. This alteration decreases the activity of the compression system that generates electrical stimulation, in turn leading to increased matrix synthesis. The proposed PST's mechanism of action generates pulses with lower frequencies (in comparison to traditional pulsed electromagnetic fields; PEMF) with variable frequency and amplitude; thus, cell signaling would be more biological, eliciting more physiological responses. Electromagnetic stimulation has been shown to reduce pain in randomized, controlled, and double-blind studies [Trock et al., 1993, 1994; Nelson et al., 2013; Wuschech et al., 2015; Bagnato et al., 2016]. However, there are no studies in the literature analyzing the effect of electromagnetic fields on patellar cartilage disorders (the thickest hyaline cartilage in the human body) and their associated pain syndromes.

A prospective randomized double-blind placebo controlled clinical trial was therefore developed aiming to evaluate the effect of PST therapy on patellofemoral pain syndrome associated with patellar chondropathy. The hypothesis was that knees treated with PST would show functional Kujala score improvement in comparison to placebo at 3 months of follow-up.

METHODS

The study was approved by the Research Ethics Committee of the Clinical Hospital (Hospital das Clinicas), University of São Paulo (Universidade de São Paulo – USP) under number 0253/11 and was registered at ClinicalTrials.gov under number NCT02012413. All patients who participated in this study signed the terms of free and informed consent. The study was designed as a prospective randomized double-blind controlled study.

Patients aged between 20 and 50 years and presenting patellofemoral pain syndrome and patellar chondropathy confirmed by magnetic resonance imaging (MRI) were eligible for this study. Exclusion criteria included: tibiofemoral and trochlear chondral degeneration according to MRI; established arthrosis of the tibiofemoral joint; use of drugs with direct action on the cartilage or bone in the last 6 months (such as disease modifying osteoarthritis drugs—DMOADs—for example, chondroprotective drugs and bisphosphonates); prior surgery on the studied knee; knee invasive procedures, such as knee infiltration, in the previous 12 months; disease in the contralateral limb that would cause an excessive burden on the studied limb (such as limb shortening, angular deformity $>10^{\circ}$, and articular loss of motion); and contraindications to performing PST, including a pacemaker, cancer, infectious disease activity, severe heart failure, arrhythmias, angina, epilepsy, and pregnancy.

The presence of all of the following criteria was required for diagnosis of patellofemoral pain syndrome: typical complaint of anterior knee pain with a duration longer than 3 months (when going up or down stairs, squatting, remaining for long periods with bent knees), pain on palpation of the patellar articular surface, and pain on patellar compression (reproducing the patient's complaint) [Nunes et al., 2013].

Enrollment of patients occurred between 2013 and 2014. A total of 40 patients who had been diagnosed with patellofemoral pain syndrome were assessed for eligibility. The final patient population was comprised of 25 patients with a total of 41 knees, since 10 patients did not meet the inclusion criteria and 5 declined to participate (see CONSORT flowchart, Fig. 1).

Patients were randomized by a computer-generated list allocated in enclosed envelopes into two groups, the placebo-control and PST groups. Patients with both knees included in the study received randomization for the right knee, and the left was automatically allocated into the other group (patients were unaware of this fact). Since 16 patients had both knees included, the final distribution of patients into groups was not equalized. This method in bilateral cases was selected to best demonstrate any differences between groups (same patient could perceive differences if they existed). Twenty-four knees were allocated to PST group and 17 to the placebo group. Group allocation was performed by one of the authors (ALPS).

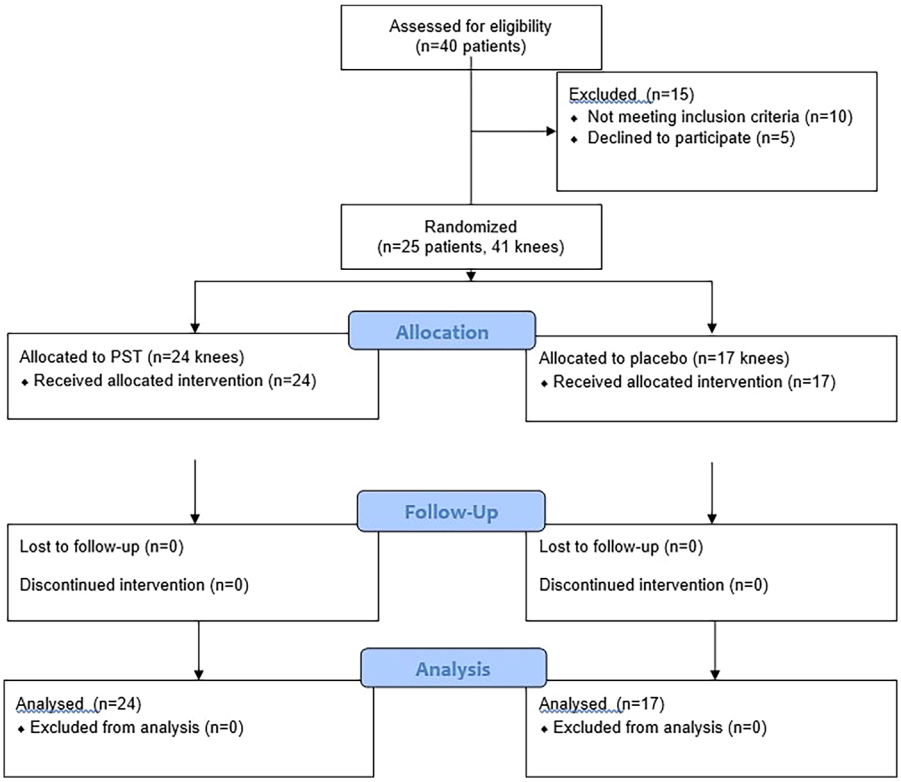

Fig. 1. CONSORT enrollment flowchart.

PST application was directed to the patellofemoral joint (Fig. 2). The PST application protocol was as follows: nine daily 1-h applications, with five in the first week, a break for the weekend, and four more the following week. The PST application was to position the device PST MOBIL (Bio Magnetic Therapy Systems, Munich, Germany) around the area that was to receive the magnetic fields, leaving the patient in a comfortable position and connecting the device, which emitted pulsatile signals that were imperceptible to the patient. Each application was controlled by a card provided by the manufacturer and lasted for 1 h. The applications were all performed by the same physiotherapist (ALPS). The PST proprietary patented signal consisted of a pulsed direct current magnetic field of 0.28 W, predominantly 5–15 gauss (max 20 gauss), pulsed modulated frequency of 5–24 Hz (with six frequency sources) with a quasirectangular (not sinusoidal) waveform. Various frequency/amplitude combinations were switched over automatically and transmitted under continuous control during the treatment period. Every session had the exact same signal pattern, therefore, being totally reproducible. Induction of treatment took place during the first 10 min, followed by a proprietary patented protected configuration of pulsed signals that delivered the therapy over the remaining 50 min. The protocol of nine sessions was defined and suggested by the manufacturer [Markoll, 2001].

The control group patients underwent sham PST treatment with the device connected using a placebo card that did not generate magnetic pulses. Patients in the PST group received the nine applications on the knee with the device connected and the treatment card generating pulses. The device operated silently, and it was not possible for the patient to determine whether they were receiving the placebo or treatment, thus maintaining patient blinding. For patients with both knees included, nine sessions of the treatment were performed on one side and nine more sessions of the placebo on the other. These protocols were performed in sequence rather than simultaneously.

All of the patients were instructed (for the duration of the study) not to use drugs that directly acted on the cartilage (e.g., chondroprotectors, such as glucosamine and chondroitin) in order to avoid confounding biases regarding the effects of the treatments and to maintain their usual level of physical activity. Neither group received physiotherapy exercises in the follow-up period. All of the participants were instructed not to change their usual level of physical activity.

Fig. 2. Patient receiving PST treatment directed to patellofemoral joint.

Kujala score questionnaire [Kujala et al., 1993] was obtained at baseline and after 3, 6, and 12 months in both groups. If significant clinical superiority of the PST group was proven at any time point, it was decided for ethical reasons that the placebo group should receive the effective PST treatment and would again be followed up for 1-year post-treatment, with the Kujala score ascertained at 3, 6, and 12 months; after receiving effective PST treatment, the placebo group was referred as placebo post-treatment group in results. The Kujala score is commonly used for anterior knee pain, and consisted of 13 questions that addressed patient pain and limitations of performing activities such as walking, sitting, stairs, squatting, running, and jumping, and swelling, atrophy, patellar stability, and range of motion.

Statistical Analysis

A sample size calculation used the following parameters: alpha of 5% (probability of incorrectly claiming statistical significance—type I error), beta of 20% (probability of incorrectly concluding no statistical significance—type II error), Kujala baseline standard deviation in the population between 9 and 13. To adequately detect a minimum Kujala improvement of 8–10 points (effect size) that was previously established as a significant clinical superiority by the authors [Van Der Heijden et al., 2016], approximately 20 knees in each group were needed. This effect size in Kujala score was equivalent to improving from not being able to climb stairs to being able to without any difficulty. The IBM software Statistical Package for the Social Sciences (SPSS 23, IBM, Armonk, NY) for Mac was used for statistics. The main hypothesis test was two-sided and used level of significance of 5%. The primary outcome was the change from baseline in the Kujala score at 3 months and was tested with Kolmogorov–Smirnov. For comparison between groups (PST vs. Placebo), the Mann–Whitney test was used based on the resulting data distribution. The outcome was chosen to be the change from baseline value instead of total Kujala score, because of the relatively small sample size (although adequately powered for the outcome) that could cause a false negative test when comparing the baseline Kujala between groups. To study the total Kujala score behavior inside each group during follow-up at 3, 6, and 12 months, ANOVA-repeated measures with post hoc contrast analysis was used in the placebo post-treatment group. In the PST group, this analysis was made with Friedman test based on Shapiro Wilk distribution testing. Because this post hoc analysis used 3 tests (comparison between 3 months and baseline, 6 months and 3 months, and finally 12 months and 6 months), significance was corrected with Bonferroni and was considered 0.05 divided by 3, therefore 0.016.

RESULTS

Patient groups were homogenous in terms of age, lower limb side, trochlea type, or patellar height at baseline (Table 1). At the end of the third month, all knees allocated in the PST group showed improvement. Among patients with bilateral knee allocation, all but one exhibited greater improvement in the PST-treated knee. Thirteen of the placebo group knees showed no change in score, three showed little improvement, and one worsened.

TABLE 1. Baseline Patient Characteristics in PST and Placebo Groups

	PST ($n = 24$)	Placebo ($n = 17$)	P-value
No. (%) with data	24 (100)	17 (100)	
Age, mean ± SD, years	35.5 ± 8.98	36.8 ± 7.99	0.64*
Side, No. (%)			0.23**
Right	13 (54.2)	6 (35.3)	
Left	11 (45.8)	11 (64.7)	
Trochlear dysplasia, No. (%)			0.5**
Absent	11 (45.8)	6 (35.3)	
Type A	13 (54.2)	11 (64.7)	
Patellar height, mean ± SD, Caton-Deschamps	1.08 ± 0.12	1.1 ± 0.12	0.67*
Chondral lesion, No. (%)			
Outerbridge grade I	4 (16.7)	6 (35.3)	
Outerbridge grade II	8 (33.3)	6 (35.3)	
Outerbridge grade III	7 (29.2)	2 (11.8)	
Outerbridge grade IV	5 (20.8)	3 (17.6)	
Kujala score, mean ± SD	74.04 ± 13.03	80.29 ± 9.39	0.14***

*t-student test.
**Chi-square test.
***Mann–Whitney.

The Kujala score change from baseline to the third month (Table 2, Fig. 3) was 9.63 (±7.5) points in the PST group, compared to 0.53 (±1.8) points in the placebo group, which was significantly different ($P < 0.001$).

With a clear superiority of the PST group established at the third month (improvement of 8–10 points in the Kujala score), the blinding was removed and patients from the placebo group started receiving the PST treatment, as previously pre-determined in the methodology, and were followed for 12 more months. The results for each group over time are shown in Table 3. An improvement was also observed in the third month after PST treatment of the placebo group (Table 3). In addition to being maintained up to 12 months, the improvement was progressive, with statistically significant improvements from the third month to the sixth month in both groups, and from the sixth month to the 12-month follow-up endpoint in the PST group. The improvement in the Kujala score at the last follow-up endpoint was 15.67 and 10.12 for the PST and placebo post-treatment groups, respectively.

DISCUSSION

The main finding of this study was that there was clinical improvement obtained from PST treatment compared to placebo in patients with patellofemoral pain syndrome with patellar chondropathy at 3 months.

The improvement in patients treated with PST was progressive and maintained throughout the 12 months of study, with a mean change from baseline of 9.63 at the third month and 15.67 at the 12th month, which is clinically relevant. As an example, a 10-point difference in Kujala represents the change from a patient who is able to climb stairs without difficulty to a patient that cannot climb stairs. Moreover, 94% (16) of patients that had one knee included in the PST group and a contralateral knee included in the control group reported greater improvement in the knee treated with PST at the third month. Similarly, patients initially allocated to placebo group also showed improvement at the third month after effective treatment, sustained up to 12 months.

PEMF therapy has been used clinically for over 30 years, and although it has achieved interesting results in some studies, it is still not widely used for any pathology. The in vitro results of PEMF used on chondrocytes have shown increased cell viability [Anbarasan et al., 2016], decreased cellular degeneration [Tan et al., 2015], upregulation of adenosine receptors [Varani et al., 2008], changes in chondrocyte morphology [Jahns et al., 2007], and a chondroprotective effect against IL-1 and increased proteoglycan synthesis [Ongaro et al., 2011; Veronesi et al., 2015; Anbarasan et al., 2016]. The effect seems to be lost in arthritic chondrocytes [Sadoghi et al., 2013]. Randomized controlled studies on PEMF used for arthrosis showed improvement in joint stiffness,

TABLE 2. Kujala Score Improvement From Baseline to the Third Month in the PST and Placebo Groups

	PST ($n = 24$)	Placebo ($n = 17$)	P-value
Kujala pre, mean ± SD	74.04 ± 13.03	80.29 ± 9.39	
95% confidence-interval	(68.53–79.54)	(75.47–85.12)	
Kujala post 3-months, mean ± SD	83.67 ± 9.38	80.82 ± 9.52	
95% confidence-interval	(79.59–87.89)	(75.93–85.72)	
Mean change from baseline to 3 months ± SD	9.63 ± 7.48	0.53 ± 1.81	<0.001

Significance test were made with Mann-Whitney U-test.

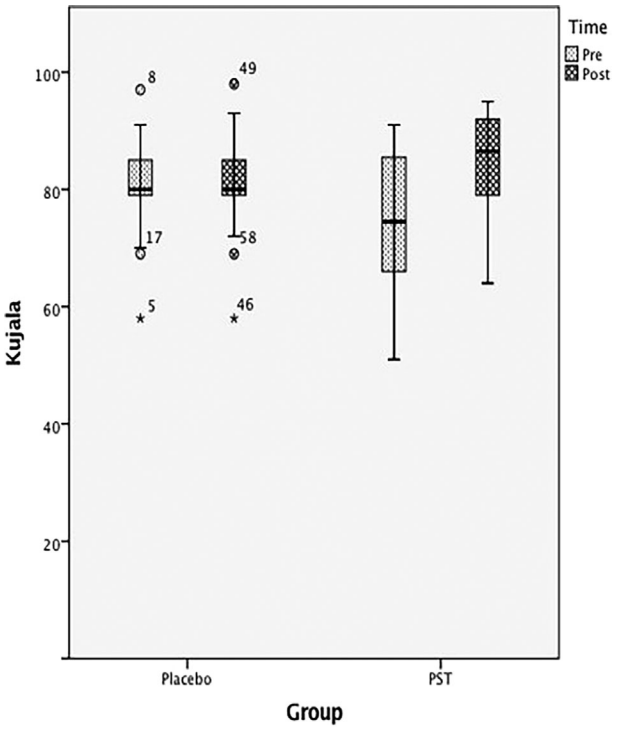

Fig. 3. Kujala scores pre-intervention and 3 months post-intervention in the PST and placebo groups.

but no improvement in pain relative to the placebo [Thamsborg et al., 2005; McCarthy et al., 2006; Ay and Evcik, 2009; Ozguclu et al., 2010]. More recent studies have reported significant improvements on visual analog scale (VAS) with the use of PEMF therapy, including a systematic review with studies employing high quality methodologies that showed PEMF to be more effective than placebo for pain at 4 and 8 weeks and for function at 8 weeks [Ryang We et al., 2013]. Improvement in pain, stiffness, and physical function has also been found in elderly cases with knee osteoarthritis [Iannitti et al., 2013; Cadossi et al., 2014; Collarile et al., 2018].

PEMF is the generic term used when referring to electromagnetic field therapy and can be performed at variable frequencies. It appears that better efficacy in terms of the histological effect on chondrocytes is achieved when a higher frequency is used, that is, 75 Hz as opposed to 37 Hz [Veronesi et al., 2014]. These heterogenous frequencies used may explain some of the variability found in the results reported in the literature. It is unclear which electromagnetic field application parameters are the most effective. Further studies are required to determine the most appropriate frequency to be used in selected groups of patients. On the other hand, PST therapy has a patented variable low-frequency field application that is known only to the manufacturer, so it may be considered a PEMF-type therapy but it cannot be modified. This fact may be regarded as a disadvantage (i.e., it may not be the ideal frequency) or as an advantage (i.e., the procedures are homogenous and the reproducibility is maximal).

A study comparing PEMF associated with a home exercise program to the program alone for patellofemoral pain syndrome showed that in the PEMF group, both function and pain were significantly better at 6 and 12 months [Servodio Iammarrone et al., 2016]. This was the only other study with electromagnetic fields for patellofemoral pain syndrome found in the literature. The present study is the first to use PST in a similar setting, demonstrating that PEMF treatment can be effective to treat patients with this clinical condition.

It is necessary to compare the improvement obtained in the present study with treatment commonly used for this condition. Muscle rehabilitation

TABLE 3. Kujala Scores Over Time Inside PST and Placebo Post-Effective PST Treatment Groups

	PST ($n = 24$)	Placebo post-effective treatment ($n = 17$)
Kujala baseline, mean ± SD	74.04 ± 13.03	80.82 ± 9.52
95% confidence-interval	(68.53–79.54)	(75.47–85.12)
Kujala at 3-months, mean ± SD	83.67 ± 9.38	87.88 ± 6.11
95% confidence-interval	(79.59–87.89)	(84.74–91.03)
P value pre × 3 months	<0.001	<0.001
Kujala post 6 months, mean ± SD	88.75 ± 7.44	89.82 ± 6.62
95% confidence-interval	(85.61–91.89)	(86.42–93.23)
P value 3 months × 6 months	<0.001	0.005
Kujala post 12 months, mean ± SD	89.71 ± 6.56	90.94 ± 5.98
95% confidence-interval	(86.94–92.48)	(87.86–94.02)
P value 6 months × 12 months	0.016	0.058

Significance tests with post hoc contrast analysis were made with Friedman test for PST group and ANOVA for placebo post-effective treatment.

physiotherapy is the primary tool currently used to treat such patients when surgery is ruled out. The results of 6 weeks of physiotherapy show Kujala scores improved by 20 points over 12 months [Petersen et al., 2016], which is very close to the results obtained with PST. A Cochrane systematic review investigated the effect of exercise as a treatment for patellofemoral pain syndrome. Pooled data from seven studies, including 483 patients, showed improvement in the functional range (Kujala equivalent) of 12.21 after 3 months. Data from 3 studies with 274 patients showed an improvement of 17.98 after 12 months [Van Der Heijden et al., 2016]. The clinical improvement obtained in the present study in patellofemoral pain syndrome with PST is therefore very close to the improvement found when using exercise therapy (9.63 after 3 months and 15.67 after 12 months), which supports the clinical significance of the findings. Although electromagnetic field therapy is more expensive, it is passive and does not demand patient adherence to an active protocol of exercises, which are demanding in time. Besides, it has been shown that PEMF therapy enhances therapeutic exercise outcomes [Servodio Iammarrone et al., 2016]. Future studies should combine PST and physiotherapy to ascertain the potential benefits of combining both therapies.

The limitations of the study include the unblinding in the placebo group after the 3-month evaluation, the absence of proof of PST's action mechanism, and the relatively small number of patients despite the statistical significance. We must emphasize that the unblinding in the third month was pre-determined as part of the study design if preliminary analysis showed a clear superiority of one of the groups. The number of patients enrolled was small; however, the required estimated number of patients to be included based on the a priori sample size calculation was fulfilled. The study randomized each knee of 16 patients with bilateral chondropathy to a different group. It could be argued that this could impair adequate analysis of the Kujala score, because one knee limitation could affect the score of the other. But all patients were actively participating in physical exercises at a gym, and their disability consisted mainly of pain, which could be unilaterally assessed in the score, as long as the patients did not have a significant functional limitation such as not being able to use stairs, running, etc., which was the case in our study. Moreover, although the lack of a physiotherapy group may be considered a weakness, the objective of this study was to clearly test the isolated effect of PST treatment. Another study in the future comparing PST and physiotherapy is needed. MRI evaluation of the knee at the 12-month follow-up period would provide useful information regarding the patellar cartilage status following the PST treatment. However, due to insufficient funding this was not possible to perform.

Further studies are necessary to define how PST generates clinical improvement and to determine whether structural change of the patellar cartilage occurs. Notwithstanding the above, in terms of being a short-term noninvasive therapy that has clinically significant effects for up to 12 months, PST is an interesting tool for the treatment of this complex syndrome.

CONCLUSION

PST therapy in patients with patellofemoral pain syndrome and patellar chondropathy was effective compared to placebo at 3 months, showing an important improvement of Kujala score. The improvement was progressive and maintained up to 12 months. PST is safe, effective, and should be considered as a non-invasive option for the management of patellofemoral pain syndrome and patellar chondropathy.

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REFERENCES

Anbarasan S, Baraneedharan U, Paul SF, Kaur H, Rangaswami S, Bhaskar E. 2016. Low dose short duration pulsed electromagnetic field effects on cultured human chondrocytes: An experimental study. Indian J Orthop 50:87–93.

Ay S, Evcik D. 2009. The effects of pulsed electromagnetic fields in the treatment of knee osteoarthritis: A randomized, placebo-controlled trial. Rheumatol Int 29:663–666.

Bagnato GL, Miceli G, Marino N, Sciortino D, Bagnato GF. 2016. Pulsed electromagnetic fields in knee osteoarthritis: A double blind, placebo-controlled, randomized clinical trial. Rheumatology (Oxford) 55:755–762.

Bassett CA, Pawluk RJ. 1972. Electrical behavior of cartilage during loading. Science 178:982–983.

Cadossi M, Buda RE, Ramponi L, Sambri A, Natali S, Giannini S. 2014. Bone marrow-derived cells and biophysical stimulation for talar osteochondral lesions: A randomized controlled study. Foot Ankle Int 35:981–987.

Collarile M, Sambri A, Lullini G, Cadossi M, Zorzi C. 2018. Biophysical stimulation improves clinical results of matrix-assisted autologous chondrocyte implantation in the treatment of chondral lesions of the knee. Knee Surg Traumatol Arthrosc 26:1223–1229.

Iannitti T, Fistetto G, Esposito A, Rottigni V, Palmieri B. 2013. Pulsed electromagnetic field therapy for management of osteoarthritis-related pain, stiffness and physical function:

Clinical experience in the elderly. Clin Interv Aging 8:1289–1293.

Jahns ME, Lou E, Durdle NG, Bagnall K, Raso VJ, Cinats D, Barley RD, Cinats J, Jomha NM. 2007. The effect of pulsed electromagnetic fields on chondrocyte morphology. Med Biol Eng Comput 45:917–925.

Kujala UM, Jaakkola LH, Koskinen SK, Taimela S, Hurme M, Nelimarkka O. 1993. Scoring of patellofemoral disorders. Arthroscopy 9:159–163.

Liu H, Abbott J, Bee JA. 1996. Pulsed electromagnetic fields influence hyaline cartilage extracellular matrix composition without affecting molecular structure. Osteoarthritis Cartilage 4:63–76.

Markoll R. 2001. Pulsed signal therapy: A practical guide for clinicians. In: Weiner RS, editor. Pain Management: A Practical Guide for Clinicians. Boca Raton, FL: CRC Press. pp 715–728.

Massari L, Osti R, Lorusso V, Setti S, Caruso G. 2015. Biophysical stimulation and the periprosthetic bone: Is there a rationale in the use of pulsed electromagnetic fields after a hip or knee implant? J Biol Regul Homeost Agents 29:1013–1015.

McCarthy CJ, Callaghan MJ, Oldham JA. 2006. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: A systematic review. BMC Musculoskelet Disord 7:51.

Moretti B, Notarnicola A, Moretti L, Setti S, De Terlizzi F, Pesce V, Patella V. 2012. I-ONE therapy in patients undergoing total knee arthroplasty: A prospective, randomized and controlled study. BMC Musculoskelet Disord 13:88.

Nelson FR, Zvirbulis R, Pilla AA. 2013. Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: A randomized double-blind pilot study. Rheumatol Int 33:2169–2173.

Nunes GS, Stapait EL, Kirsten MH, de Noronha M, Santos GM. 2013. Clinical test for diagnosis of patellofemoral pain syndrome: Systematic review with meta-analysis. Phys Ther Sport 14:54–59.

Ongaro A, Pellati A, Masieri FF, Caruso A, Setti S, Cadossi R, Biscione R, Massari L, Fini M, De Mattei M. 2011. Chondroprotective effects of pulsed electromagnetic fields on human cartilage explants. Bioelectromagnetics 32:543–551.

Ozguclu E, Cetin A, Cetin M, Calp E. 2010. Additional effect of pulsed electromagnetic field therapy on knee osteoarthritis treatment: A randomized, placebo-controlled study. Clin Rheumatol 29:927–931.

Petersen W, Ellermann A, Rembitzki IV, Scheffler S, Herbort M, Brüggemann GP, Best R, Zantop T, Liebau C. 2016. Evaluating the potential synergistic benefit of a realignment brace on patients receiving exercise therapy for patellofemoral pain syndrome: A randomized clinical trial. Arch Orthop Trauma Surg 136:975–982.

Ryang We S, Koog YH, Jeong KI, Wi H. 2013. Effects of pulsed electromagnetic field on knee osteoarthritis: A systematic review. Rheumatology (Oxford) 52:815–824.

Sadoghi P, Leithner A, Dorotka R, Vavken P. 2013. Effect of pulsed electromagnetic fields on the bioactivity of human osteoarthritic chondrocytes. Orthopedics 6:e360–e365.

Servodio Iammarrone C, Cadossi M, Sambri A, Grosso E, Corrado B, Servodio Iammarrone F. 2016. Is there a role of pulsed electromagnetic field in management of patellofemoral pain syndrome? Randomized controlled study at one year follow up. Bioelectromagnetics 37:81–88.

Tan L, Ren Y, van Kooten TG, Grijpma DW, Kuijer R. 2015. Low-intensity pulsed ultrasound (LIPUS) and pulsed electromagnetic field (PEMF) treatments affect degeneration of cultured articular cartilage explants. Int Orthop 39: 549–557.

Thamsborg G, Florescu A, Oturai P, Fallentin E, Tritsaris K, Dissing S. 2005. Treatment of knee osteoarthritis with pulsed electromagnetic fields: A randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 13: 575–581.

Trock DH, Bollet AJ, Dyer RH, Jr., Fielding LP, Miner WK, Markoll R. 1993. A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. J Rheumatol 20:456–460.

Trock DH, Bollet AJ, Markoll R. 1994. The effect of pulsed electromagnetic fields in the treatment of osteoarthritis of the knee and cervical spine. Report of randomized, double blind, placebo controlled trials. J Rheumatol 21: 1903–1911.

Van Der Heijden RA, Lankhorst NE, Van Linschoten R, Bierma-Zeinstra SM, Van Middelkoop M. 2016. Exercise for treating patellofemoral pain syndrome: An abridged version of Cochrane systematic review. Eur J Phys Rehabil Med 52:110–133.

Varani K, De Mattei M, Vincenzi F, Gessi S, Merighi S, Pellati A, Ongaro A, Caruso A, Cadossi R, Borea PA. 2008. Characterization of adenosine receptors in bovine chondrocytes and fibroblast-like synoviocytes exposed to low frequency low energy pulsed electromagnetic fields. Osteoarthritis Cartilage 16:292–304.

Veronesi F, Fini M, Giavaresi G, Ongaro A, De Mattei M, Pellati A, Setti S, Tschon M. 2015. Experimentally induced cartilage degeneration treated by pulsed electromagnetic field stimulation; an in vitro study on bovine cartilage. BMC Musculoskelet Disord 16:308.

Veronesi F, Torricelli P, Giavaresi G, Sartori M, Cavani F, Setti S, Cadossi M, Ongaro A, Fini M. 2014. In vivo effect of two different pulsed electromagnetic field frequencies on osteoarthritis. J Orthop Res 32:677–685.

Wuschech H, von Hehn U, Mikus E, Funk RH. 2015. Effects of PEMF on patients with osteoarthritis: Results of a prospective, placebo-controlled, double-blind study. Bioelectromagnetics 36:576–585.