Reumatismo, 2012; 64 (6): 388-394

Far infrared emitting plaster in knee osteoarthritis: a single blinded, randomised clinical trial

G.L. Bagnato, G. Miceli, M. Atteritano, N. Marino, G.F. Bagnato

Department of Rheumatology, University of Messina, Italy

SUMMARY

Objective. Therapeutic approach of osteoarthritis (OA) still represents a challenge in clinical practice. The aim of the study is to assess the efficacy of far infrared (FIR) emitting plaster in the treatment of knee OA.

Design. This is a randomized, single-blind, placebo-controlled, parallel group with equal randomization (1:1), clinical trial. Patients affected by knee OA were randomly allocated to 1 of 2 treatment groups, either placebo plaster or far infrared emitting plaster. Primary endpoint was to assess pain improvement from baseline to 1 months posttreatment in the visual analogue score (VAS). Secondary end point was to evaluate pain score after 1 week of treatment and to compare ultrasonographic findings after 1 month of treatment.

Results. Each group comprised 30 (in the FIR group) and 30 (in the placebo group) completers. VAS scores of the placebo and the FIR group were significantly lower at 1 week post-treatment (95% confidence interval CI = -1.14 to 0.31; P<0.05) and at the end of the study (95% confidence interval CI = -2.57 to -0.89; P=0.01). Effect size was -0.43 after one week of treatment and -1.38 after one month of treatment. The mean decrease in VAS values was ≥20% in the FIR group. The number of patients from the FIR group with joint effusion was lower (40%) compared to baseline (80%), while no changes were seen among the placebo group.

Conclusions. Far infrared emitting plaster could be considered an effective non-pharmacological choice for the therapeutic management of knee OA.

Key words: *Osteoarthritis, knee, ultrasound, non-pharmacological therapy, pain assessment and management.*

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease characterized by a variety of patterns of joint failure (1). Progressive loss of cartilage, changes in subchondral bone, inactivity related stiffness and chronic pain are the main clinical and histopathological features of the disease (2). Osteoarthritis is the most common joint disorder worldwide and is a major cause of disability (3) and impaired quality of life (4). Knee osteoarthritis is one of the major reasons for seeking medical and physical therapy services and its prevalence has increased with population aging. In people older than 80 years it has been reported that 53% of women and 33% of men had radiographic signs of osteoarthritis of the knee, while the age-standardized and the sex-standardized incidence of knee osteoarthritis is 240 per 100.000 person-years (5). Since there are no curative therapies currently available for OA, non-pharmacological treatment including physiotherapy, occupational therapy, weight loss and exercise is currently the first line of treatment. However in many patients these approaches are not sufficient and pharmacological therapy is required (6-8). Paracetamol is the drug of choice for symptomatic treatment of pain in OA because of its safety and efficacy (9), but frequently patients respond poorly and switch to a different treatment or another drug is added, such as NSAIDs or opioids. The higher rate of adverse events (10) with a frequently small evidence that combination therapies (11) are effective limit the use of other analgesics. Therefore, it is highly desirable to search for effective non-pharmacologic alternatives that can be easily used for the treatment of OA. Infrared radiation is invisible electromagnetic radiation, the wavelength of which is longer than that of

Corresponding author:
Gianluca Bagnato
Department of Rheumatology
University of Messina
A.O.U. "Gaetano Martino"
Via Consolare Valeria, 1
98100 Messina, Italy
E-mail: gianbagnato@gmail.com

visible light. According to differences in wavelength, the International Commission on Illumination (CIE) recommends dividing infrared radiation into the following three bands: near-infrared radiation (IR-A: 0.7, 1.4 mm), middle-infrared radiation (IR-B: 1.4, 3 mm), and far-infrared (FIR) radiation (IR-C: 3,1000 mm). FIR therapy has been widely applied in medicine, including the treatment of chronic fatigue syndrome (12), chronic pain (13), wound healing (14) and primary dysmenorrhea (15) with encouraging results in pain management. Recently, it has been demonstrated that in patients affected by OA of the knee FIR pads can lower the intensity of pain, measured through the numeric rating scale (NRS), and thus reduce the discomfort experienced during the postoperative phase after total knee arthroplasty (16).
In the current study we tested the hypothesis that far infrared (FIR) emitting plaster could represent an effective non- pharmacological treatment of knee OA.

MATERIALS AND METHODS

Patients
This randomized, single-blind, placebo-controlled clinical trial, with equal randomization (1:1), parallel group study, was approved by the ethics committee of the Faculty of Medicine at the University of Messina. All patients provided their written informed consent.
Eligibility criteria were:

1. a diagnosis of primary OA of the knee according to the ACR criteria, including radiologic evidence of OA (17);
2. age >40 years;
3. symptomatic disease for at least 6 months prior to enrollment;
4. persistent pain despite receiving the maximum tolerated doses of conventional medical therapy, including acetaminophen (4 gm/day) and/or a nonsteroidal antiinflammatory drug (NSAID), with persistent pain defined as a minimum mean score of 40 mm on the visual analog scales (VAS) for global pain (0-100 mm range for each);
5. daily pain during the month prior to study enrollment;
6. ability to attend follow-up appointments. Patients affected by secondary causes of OA, local or systemic infection, diabetes mellitus, systemic arthritis, allergy to anesthetic agent or contrast material, coagulopathy, anticoagulant therapy and subjects who had previous IA steroid injection, avascular necrosis of bone and who were on specific OA pharmacological therapy (NSAIDS, opioids) for more than 2 weeks prior enrollment were excluded from the study

The study took place at the rheumatology outpatient clinic of AOU "G. Martino" Policlinico Universitario of the University of Messina from November 2011 to February 2012.

Treatment groups
Patients were randomly allocated to 1 of 2 treatment groups, either placebo plaster or far infrared emitting plaster. For allocation of the participants, a computer-generated list of random numbers was used. Patients in the treatment group were administered a plaster emitting far infrared (FIR group). Patients in the placebo group were given a plaster with no far infrared producing properties (placebo group). Plasters were consecutively numbered for each patient according to the randomisation schedule. Each patient was assigned an order number and received the plasters in the corresponding prepacked envelopes. Patients were asked to not use any analgesics drug during the treatment.
The plaster (Fig. 1) is manufactured by Chongqing Kaifeng Medical Instrument Co. Ltd, Shangai, China (tdp.plaster@gmail.com), which provided the FIR emitting and the placebo plasters featured by a plate coated with a proprietary mineral formation consisting of 33 elements designated to generate far infrared through the presence of a radiator. The placebo plaster was matched to the study plaster for color, size and weight, lacking the 33 elements only. The plaster is commercially available.

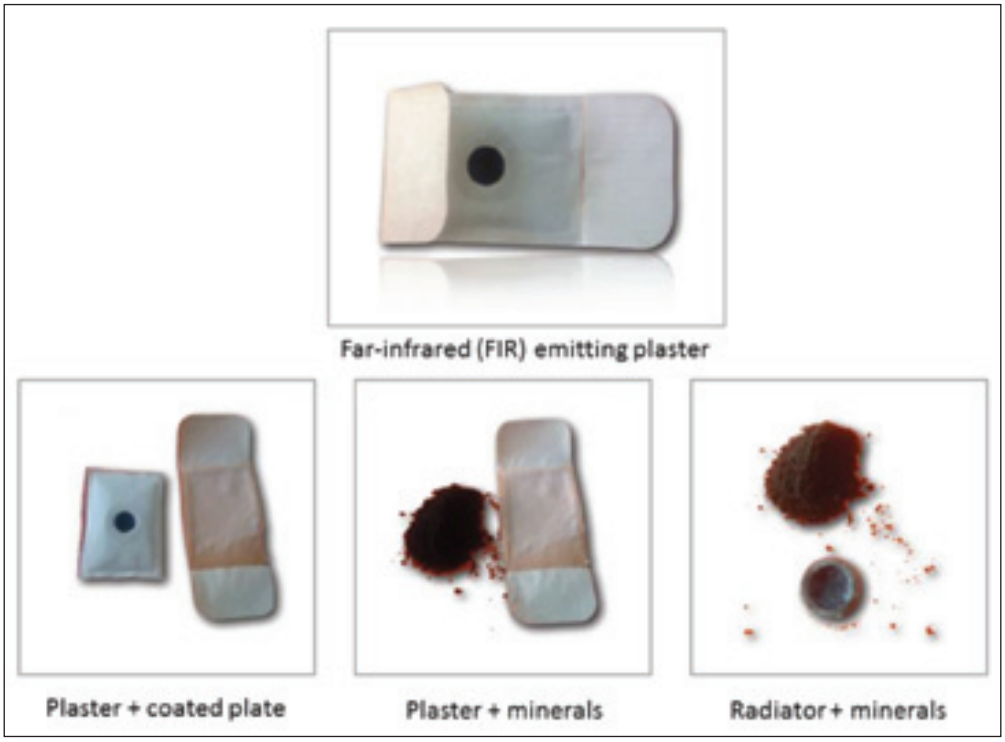

Figure 1 - Far-infrared emitting plaster and its components.

Randomization and blinding

Randomization and blinding of treatment were conducted by the research coordinator, which ensured similarity between preparations. The independent research coordinator maintained the randomization codes in sealed envelopes and dispensed either active or placebo plaster. Patients continue to remain blinded to the original treatment allocation. Outcome assessors and data analysts were kept blinded to the allocation.

Study procedures and assessments

Patients were informed to apply the plaster at the posterior surface of the knee, to keep it for 12 h a day and for 5 days a week for a duration of treatment of 4 weeks by the research coordinator.

Study end points and outcome measures

Each patient was reevaluated at 1 and 4 weeks, to assess the safety and efficacy of treatment, by an assessor who was blinded to the treatment. The primary end point for assessment of efficacy was set at 1 months posttreatment. The primary outcome measure was the pain improvement response to treatment from baseline to 1 months posttreatment in the visual analogue score (VAS). Secondary end point was to evaluate pain score (VAS) after 1 week of treatment and to demonstrate ultrasonographic changes during treatment as expressed by reduction of joint effusion in the suprapatellar pouch or in the medial and lateral aspect of the knee if present.

The above evaluation was conducted by another assessor who was blinded to the treatment. The ultrasound machine used was Logiq book xp, GE medical system with a probe 8L-RS 8 MHz, longitudinal and lateral view of knee have been performed.

Statistical analysis

For comparisons between numeric variables Student *t*-test was used. A P-value <0.05 was regarded as indicating statistical significance together with confidence intervals and effect size. To detect a reduction in VAS (visual analogue scale), set as the primary outcome of the study, with a

two-sided 5% significance level and a power of 80%, a sample size of 30 patients per group was necessary. To recruit this amount of patients a 3-month inclusion period was foreseen.

RESULTS

A total of 64 patients were recruited for this study. Age-eligible participants were recruited from November 2011 to January 2012. Participants attended clinic visits at the time of randomisation (baseline) and at 1-week and 1-month intervals for a full period of 1 month. Two patients withdrew due to failure in the follow-up and transportation problems, while other two patients were excluded because suffering from diabetes mellitus. Thus, each group comprised 30 (in the FIR group) and 30 (in the placebo group) completers (participants flow chart shown on Fig. 2). The two treatment groups were not significantly different in demographic data, *e.g.*, sex, age, weight, height, duration of disease, base-line data, vital signs (Tab. I). During the study, the rates of compliance with the different plasters were similar. As a few patients withdrew from the trial, the results were not substantially affected, whether the statistical method was performed by an ITT analysis or analysis on available completers.

At the first follow-up visit (1 week) of the study, there was a mean of 12.87 mm reduction in pain VAS scores for subjects treated with the FIR emitting plaster and a -6.30 mm pain reduction in those who

Table I - Baseline demographic and clinical characteristics of patients with knee osteoarthritis treated with far-infrared (FIR) emitting or placebo plaster.

	FIR (n=30)	Placebo (n=30)
Age, years	63.8±11.2	62.2±9.7
Sex, % female	70	68
Weight, kg	73.7±12.3	74.8±17.7
Height, cm	166.2±8.5	167.6±9.3
Body mass index, kg/m^2	27.7±3.9	26.8±3.8
Duration of disease, years	4.5±3.2	4.7±3.9
Pain score (100-mm VAS)	80±7.4	79±8.2

Except where indicated otherwise, values are the mean ± SD. OA, osteoarthritis; VAS, visual analogue scale; FIR, far infrared.

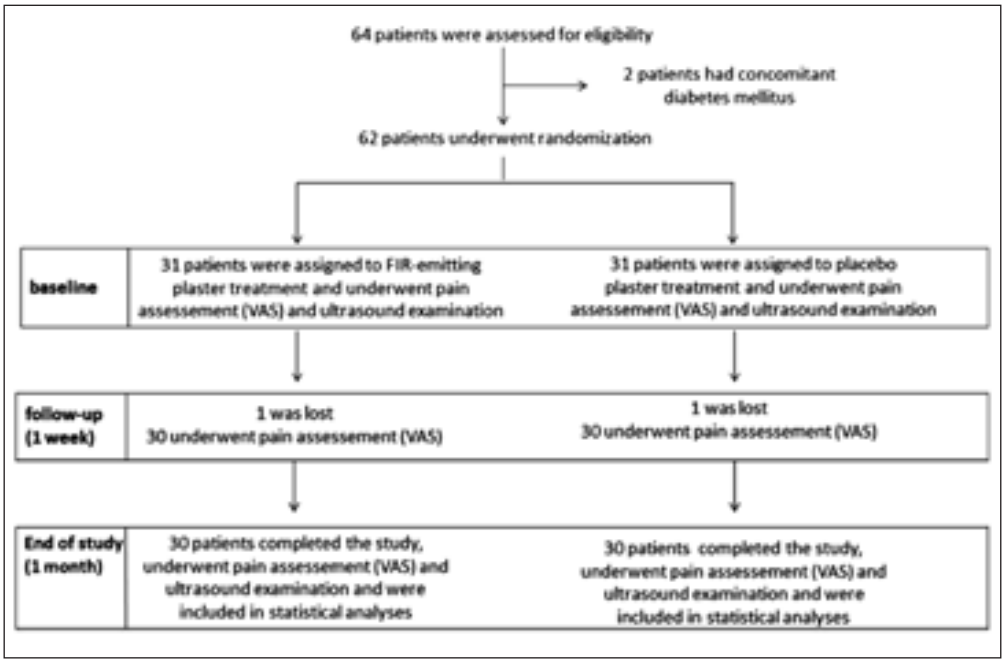

Figure 2 - Flow diagram of FIR emitting vs placebo plast in knee OA clinical trial. FIR, far-infared; VAS, visual analogue scale; OA, osteoarthritis.

received placebo (Fig. 3). Subjects treated with the far infrared emitting plaster had a further 8.02 mm decrease in the pain scale scores between weeks 1 and 4. Those belonging to the placebo group had a further minimal decrease of 0.45 mm in pain scale scores between weeks 1 and 4 (Fig. 3). At the 1-week follow-up visit, the effect size was -0.43 (95% confidence interval CI= -1.14 to 0.31; P<0.05). At 1 month a large standardised effect size (-1.38) was found (95% confidence interval CI= -2.57 to -0.89; P=0.01) (Tab. II). Pain score tended to decrease during treatment significantly in the FIR group (P<0.01), while no significant difference was found in placebo group regarding visual analogue scale. No adverse events were reported during the study.

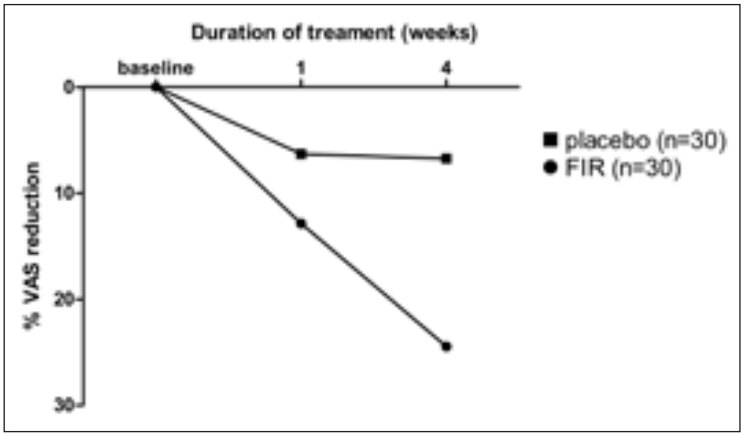

Figure 3 - Changes in pain score, shown as percentage of reduction of Visual Analogue Score (VAS), over time in far infrared (FIR) treated (cirlces) and placebo (square) groups. Pain score significantly decreased in the FIR group at the first week (P<0.05) and at the end of the study (4 weeks) (P<0.01) compared to baseline, while no significant difference was found in the placebo group either at 1 week and at 4 weeks.

Table II - Change in visual analogue scale from baseline after 1 week and 4 weeks of treatment in patients with knee OA treated with far-infrared (FIR) emitting or placebo plaster.

	FIR (n=30)	Placebo (n=30)	CI (95%)
Pain score (100-mm VAS) at baseline	80±7.4	79±8.2	-1.98 to -0.42
Pain score (100-mm VAS) after 1 week	70±5.2	73±8.4	-1.14 to 0.31
Pain score (100-mm VAS) after 4 weeks	60±4.3	73±9.4	-2.57 to -0.89

Values are expressed as the mean ± SD. CI, confidence intervals.

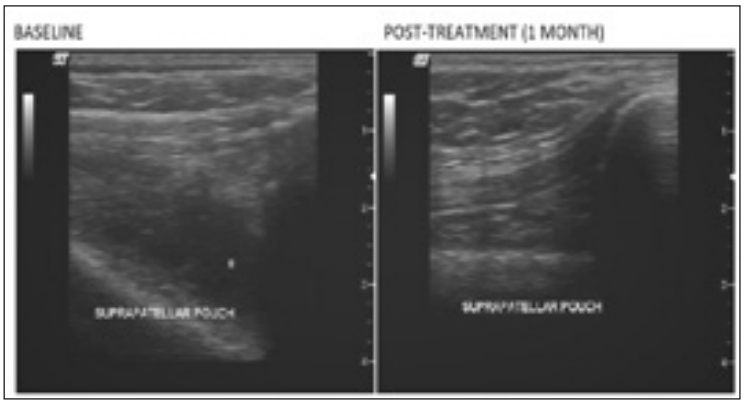

Figure 4 - Longitudinal view ultrasound scan of the anterior compartment of the knee. Ultrasonography shows changes in the suprapatellar pouch effusion before and after treatment in a patient treated with far-infrared emitting plaster. *Effusion.

At the beginning of the study joint effusion was evidenced in 24 patients (80%) from the FIR group while 20 patients (66%) belonging to the placebo group had similar findings. At the end of the study the number of patients from the FIR group with ultrasonographic evidence of effusion was lower (12 patients, 40%), while no changes were seen among the placebo group.

Figure 4 shows ultrasound longitudinal view of the anterior compartment of the knee at baseline and after 1 month of treatment with the FIR emitting plaster.

DISCUSSION

In our study, we show that pain, measured as the percentage of VAS reduction, is significantly lower in patients treated with the FIR emitting plaster compared to controls. Recent findings showed that FIR might play a role in the long-term protective effect on vascular function, probably due to the nuclear traslocation of promyelocytic leukemia zinc finger protein (PLZF) and inhibition of vascular endothelial growth factor (VEGF) (18). VEGF is a key factor in the articular cartilage in human OA and animal OA models (19), as it has been demonstrated that the stain intensity of VEGF immunoreactivity increased simultaneously with the degree of cartilage destruction and reparation in three different OA models (20, 21). In another study, forty-six patients who were hospitalized for chronic

pain (of at least six-month duration) were divided into two groups. Twenty-four subjects participated in a multidisciplinary protocol (cognitive behavioral therapy, rehabilitation, and exercise therapy) without additional saunas, while 22 subjects were enrolled in the same program but also had 15 minutes of 60°C FIR sauna therapy five days weekly for four weeks At the end of the treatment program on discharge, the sauna group exhibited diminished pain behaviors and had statistically lower anger scores (22). Another important factor in cartilage regulation are the reactive species of oxygen (ROS) (23): a reduction in SOD2 is associated with the earliest stages of OA and a decrease in SOD2 was found to be associated with an increase in ROS (24), extracellular superoxide dismutase (EC-SOD), the major scavenger of ROS in extracellular spaces and fluids, is decreased in late stage OA joint fluid compared to fluid from injured/painful joints with intact cartilage (25). Far-infrared therapy has shown antioxidative effects (26). Beside the pain relief effect obtained through hyperthermia, which can be considered the placebo effect seen in our placebo cohort and has been already previously described (27, 28), our study describes for the first time a significant improvement in pain perception with the use of far-infrared therapy, which can be considered a valid alternative for its safety and efficacy in those patients whose therapeutical management is limited.
Limitations of the study are the sample size, despite the result of the effect size, and the poor scientific knowledge of the mechanism of action of far-infrared in osteoarthritis. More studies are needed to further elucidate the biologic effect of FIR in OA symptoms and clinical course.

Authors' contribution
GLB, research design and paper writing; GM, research perform; NM, bibliographic research contribution and paper writing; MA, research perform and data analysis; GFB, research design and data analysis.

Conflict of interests
the authors declare no conflict of interests.

Acknowledgments
the authors acknowledge Company M.F. & Trading Srl for providing the plasters.

Key message
Far-infrared emitting plaster can be considered for its safety and efficacy profile an effective approach in management of pain of patients affected by knee osteoarthritis.

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