**Effects of Pulsed Low Frequency Magnetic Field Therapy on Patients with Musculoskeletal Chronic Low Back Pain: A Randomized Double Blind Placebo Controlled Trial.**

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**ABSTRACT**

**Introduction:** Chronic low back pain (CLBP) is a major reason for disability world-wide. Available interventions for CLBP are short lived for the majority of the cases. The search for safe, non-invasive and cost-effective approaches is under way. The aim of the present study is to investigate the effectiveness of pulsed low frequency magnetic field (PLFMF) on the management of CLBP.

**Methods and Design:** A randomized double blinded control trial will be conducted, involving two hundred patients with various subtypes of musculoskeletal CLBP. Patients will be recruited from King Fahd Hospital of the University. Participants will be randomized in a 1:1 ratio to receive either active PLFMF (experimental arm) or sham treatment (control arm) using a permuted-block design which will be stratified according to three subtypes of musculoskeletal CLBP (nociceptive, peripheral neuropathic or central sanitization). The study treatment consists of 3 sessions/week for over 6 weeks in both the intervention and the control arms. The primary outcome is defined as the percentage reduction in Numeric Rating Scale (NRS) pain at week-24 after treatment completion with respect to baseline score. Secondary outcomes includes percentage NRS pain during treatment and early after treatment completion, short form 36 of quality of life, disability measurement using the Roland and Morris Disability Questionnaire; Depression Anxiety Stress Scale 21, function measurement using Patient Specific Functional Scale, Global perceived effect of condition change, Pittsburgh Sleep Quality Index and Modified Fatigue Impact scale. Measures will be taken at baseline, 3 and 6 weeks after the beginning of intervention and 6, 12 and 24 weeks after trial completion. Adverse events between arms will be evaluated. Data will be analyzed on an intention-to-treat basis.

**Conclusion**: This randomized trial is powered to assess the effectiveness of PLFMF on the management of CLBP.

**Funding, ethics and dissemination:** The study is funded by the Imam Abdulrahman Bin Faisal University. It has been approved by the IRB of Imam Abdulrahman Bin Faisal University (IRB‐ 2017‐03-129). The study will be conducted at King Fahd Hospital of the University and will be monitored by the Hospital research office. Results obtained will be presented in international conferences and will be published in peer-reviewed journals.

**Trial registration number** >>>>>>>>>>>>>>>>>>>> I am working on it

**Strengths and limitations of this study**

* The present study is a well-designed trial to investigate the long-term efficacy and safety of PLFMF on the management of chronic low back pain.
* Subgroup analysis investigating efficacy of PLFMF on various subtypes of pain based on pain mechanism will be performed. This may help to explain controversial results reported by previous clinical trials.
* Outcome measures include various aspects of low back pain problems (pain intensity as well as disabilities, functional limitations, sleep quality and quality of life).
* All outcome measures used in the present trial are self-report which may potentiate pain and other measured outcome.

**INTRODUCTION**

Chronic low back pain (CLBP) is pain or discomfort localized in the lumbosacral region, with or without leg pain (sciatica) that persists for more than 3 months.1 Eight out of every 10 adults will experience low back pain (LBP) at least once in their life with more than 60% of such cases have a recurrent LBP.2 The causes of LBP are many, they can range from simple spasm or mechanical causes to more serious causes such as herniated disc and different types of cancer.3 Symptoms of LBP may vary from one patient to another. In many patients the symptoms may go beyond pain to lead to severe consequences such as sleep disturbances, psychological and social problems which may affect the quality of life .4 CLBP accounts for about 15% of all cases of LBP, however, it has been reported to be the world-leading source of disability.5 In addition, CLBP is often associated with socioeconomic burden and psychological distress.6 For example, the treatment cost for low back pain in the US is estimated to be more than $90 billion per year7 and $17 billion per year in the UK.8

LBP can be classified based on several criteria. It has been classified to acute and chronic based on how long the pain has persisted. It can also be classified into inflammatory and neuropathic based on the underlying mechanism.9 The main issue is how to differentiate the various subtypes clinically. In many occasions differentiating the various phenotypes clinically is difficult. Smart et al.10-12 proposed a mechanism based classification to differentiate between different types of musculoskeletal LBP (central sensitization, peripheral neuropathic and nociceptive).

Most of mechanical low back pain respond to rest and various physical modalities. Different conservative and surgical interventions have been used to manage CLBP; however, the optimal therapy is still debatable.13 Many physical therapy interventions were tried in the management of CLBP such as soft tissue mobilization and neurodynamic techniques,14-15  massage therapy,16 ultrasound, laser therapy and shock wave therapy,17 exercises,18 Pilates practice19 and acupuncture.20 While some of the rehabilitation interventions were effective on the short term, none of such interventions produced long term effectiveness in the management of CLBP.

Many pharmacological interventions have been used to manage CLBP. For example non-steroid anti-inflammatory drugs and trammel were mildly to moderately effective in reducing pain without much effects on function.16 Similarly, opioids, benzodiazepines and duloxetine effects on reducing CLBP were small without inducing any improvement in functions.21 Other drugs were used such as Tricyclic antidepressants, gabapentin, however, their efficacy were not established.22 Since the CLBP persist for long term, pharmacological interventions are not a suitable solution due to many reasons. Such reasons include toxicity due to long term use, side and adverse effects in addition to problems with tolerance and addiction.23 Surgical procedures have been used in some cases of CLBP with mixed outcome,24 however, many patients are reluctant to go through surgery. Add to that the high cost of the surgery to the health care system. Furthermore, the number of what is called “failed back surgery syndrome” are in the rise.25

Since the conservative approaches currently used to manage CLBP do not seem to be effective on the long term, new approaches are needed to be developed. The new approaches should be safe, noninvasive and cost effective.

Several line of evidence indicated that the pulsed low frequency magnetic field (PLFMF) may be an attractive option for the management of CLBP. Magnetic field blocked the sensory neuron action potential in cultured neurons;26 however, it enhanced neuronal growth in the presence of growth factor.27 In rats, magnetic field suppressed the formation of edema.28 Weintraub et al.29 showed that magnetic field has a pronounced anti-nociceptive effect. Robertson et al.30 showed that PLFMF affected pain and thermal signals in normal volunteers. Selvam et al.31 reported that PLFMF restored the calcium ATPase activity of the plasma membrane and produced anti-inflammatory effects. PLFMF also inhibited pain processing in a dose dependent manner .32 Clinically PLFMF has been used for the treatment of different types of pain. Such as planter fasciitis,33lumber radicular pain,34 postoperative pain,35 peripheral neuropathy29 and osteoarthritis.36 Recently we concluded a study which showed that PLFMF was effective in reducing pain, improving sleep and quality of life in patients with carpel tunnel syndrome.37

In the case of CLBP few studies were done and produced conflicting results. While Krammer et al.,13 Oke and Umebese,38 and Harden et al.39 reported that PLFMF was not superior to sham treatment in patients with CLBP other studies reported that PLFMF significantly reduced pain intensity in patients with CLBP.40-42 Most of the six studies which tested the effects of PLFMF on CLBP suffered from methodological problems and flaws. Such problems included failure to perform intention to treat as well as lack of proper blindness of patients and researchers. All these studies failed classify the CLBP into different subgroups since CLBP is heterogeneous. Two of the studies reporting positive findings failed to compare PLFMF with other therapeutic modality.41-42 All the mentioned studies used small number sample sizes (16 – 40 patients). Some of these studies did not do any follow-up after the conclusion of the interventions or a follow-up for short period.43 Finally the six studies used different machine producing different magnetic field intensity and frequency and different treatment protocols. Similarly, various studies reported controversial results regarding the effects of PLFMF on level of disability and quality of life in patients with CLBP. Some studies reported that PLFMF improved level of disability and/or quality of life40-41, 44 while other studies reported no effects for PLFMF on disability and/or quality of life.13, 42, 45 Two systematic reviews investigated the effects of PLFMF on CLBP. Andrade et al.43 concluded that PLFMF treatment is superior to placebo treatment. However, Hug and Roosli46 concluded that available evidence is not sufficient to recommend the use of PLFMF clinically. Both reviews recommended better controlled randomized studies are needed to clarify the effects of PLFMF on CLBP.

In addition PLFMF is known to be safe, non-invasive, low cost, easy to administer and has no known side effects in the management of patients with CLBP.46 Improving the condition of patients with CLBP will spare the patient going through several rounds of pharmacological and non-pharmacological treatment as well as invasive procedures like surgery with the ultimate goal to improve the patient quality of life.

**OBJECTIVES**

The primary objective of this randomized controlled trial is to evaluate the long-term efficacy and safety of PLFMF on the management of CLBP in increasing the percentage reduction in Numeric Rating Scale (NRS) pain at week-24 with respect to baseline score. The percentage reduction in Numeric Rating Scale (NRS) pain at week-24 will also be evaluated according to various musculoskeletal CLBP subtypes based on pain mechanism (nociceptive versus peripheral neuropathic versus central sanitization).

The secondary objectives are to evaluate the effects of PLFMF on: 1) pain intensity during treatment and early after treatment completion, 2) level of disability, 3) functional levels, 4) sleep quality and 5) quality of life in patients with CLBP. The study will also investigate the long term side effect of PLFMF.

This study will also include subgroups exploratory objectives to clarify the role of PLFMF in the management of patients diagnosed with different subtypes of musculoskeletal CLBP. To the best of our knowledge, this trial is the first randomized clinical trial to explore simulaneously the role of PLFMF in the management of peripheral neuropathic, nociceptive and central sensitization musculoskeletal LBP patients together.

**METHODS**

**Study design** This is a two-arm randomized, double blind, placebo controlled clinical trial. The study will be coordinated at the King Fahd Hospital and all participants will be recruited from the Hospital. This study is funded through the Imam Abdulrahman Bin Faisal University project grant (number 2017-308-CAMS). Ethical approval has been obtained from the IRB of the Imam Abdulrahman Bin Faisal University (IRB‐ 2017‐03-129). This study is prospectively registered with the Australian New Zealand clinical Trials Registry (NUMBER**XXXXX**). This trial protocol has been prepared according the CONSORT statement.47

**Sample Size and power calculation**

A total sample size of 200 (100 in each arm) will achieve 90% power to detect a mean difference of percentage reduction in NRS pain of 10% between the two treated arms at week-24. The mean percentage reduction in NRS pain is assumed to be 15% in the control arm (patient treated with SHAM program) and 25% in patients who receive PLFMF therapy. A 25 standard deviation is considered along with a two-sided significance level (alpha) of 5% using a two-sample equal-variance t-test. The sample size allows for 15 percent of patients lost to follow-up at week 24.

Mechanism-based classification will be used to classify patients into different phenotypes of musculoskeletal CLBP. This method discriminative validity was established.10-12 All patients will be analyzed collectively. Subgroup analysis will be performed to assess the effect of PLFMF in subtype of pain.

**Statistical Analysis**

All randomized patients will be analysed on the intent-to-treat basis. Safety analyses will be performed for all patients who received at least one treatment session. Baseline characteristics will be presented by treatment group. Binary and categorical variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator, which will be less than the number of patients assigned to the treatment group will be reported either in the body or a footnote of the summary table. Continuous variables will be summarized by mean and standard deviation as well as by quartiles.

Treatment effect for the primary and continuous secondary outcomes will be assessed through ANCOVA adjusted for the baseline measurement score. Overall treatment effect over time on all continuous outcomes, repeatedly collected over the course of the study, will be estimated using mixed linear models to take into account the correlation within each individual. The mixed linear model will include random intercept adjusted with the baseline score, time as categorical and the interaction between treatment and time.

Categorical binary efficacy measures will be primarily analysed using logistic regression. All tests will be two-sided with P-values less than 0.05 will be considered significant.

**Eligibility criteria:**

Subjects will be recruited from King Fahd University Hospital (an 800 bed teaching hospital located in the Eastern Province of the Kingdom of Saudi Arabia).

Subjects will be included in the study if they fulfil the followings:

* Clinical evidence of musculoskeletal CLBP including subtype classification (nociceptive versus peripheral neuropathic versus central sanitization);
* Age 18-60 years old;
* Primary complaint of pain (at least a score of 5 out of 10 on a 0- 10 numerical rating scale (NRS)) in the area between the 12th rib and buttock crease, with or without leg pain for 3 months or more;

Patient will be excluded if they have any of the followings:

* Pregnant or lactating
* Significant spinal pathology (e.g. spinal fracture, cauda equina syndrome, spinal infective or inflammatory diseases, , metastatic);
* Spinal surgery within the preceding 6 months;
* Recent organ transplants.
* Heart pace maker.
* Cardiac arrhythmia, tachycardia conditions or large aneurysm.
* Heavy psychosis.
* Epileptic episodes.

Exit criteria:

Participants will be withdrawn from the study if:

* Become pregnant;
* Back pain intensify during the trial to a point which need emergency medical intervention;
* Decided to leave the study voluntarily;
* Added a new medications (was not taken before) which may affect the patients LBP condition.
* Lack compliance.

Patients will be instructed to continue any medication they regularly take before the trial, however, they will be instructed not add any new medications that may affect their back pain during the trial period. All prescription and over the counter medications taken by the participants will be recorded.

**Randomization**

Eligible participants will be randomized in a 1:1 ratio to receive either active PLFMF treatment (experimental arm) or sham treatment (control arm). Randomization list will be centrally generated, in a stratified fashion, using a random permuted block design of size four and six. The stratification factor will be subtypes of musculoskeletal CLBP based on pain mechanism (nociceptive versus peripheral neuropathic versus central sanitization). A researcher who is not part of the study screening, evaluation or treatment will allocate the participants in one of the groups using sealed dense, tamperproof and numbered envelopes, prior to recruitment.

**Tool:**

The BEMER 3000 (BEMER Int. AG) will be used to deliver PLFMF (An average of 14 µT). The signal comprises of a series of half-wave-shaped sinusoidal intensity variations. The signal which starts with low values slowly increases and then decreases but it does not go back to the initial value (i.e. stay above zero). The intensity will gradually get denser with the repetition of the sequence leading to an increase in the ups and downs with repetition. Every second this procedure will be repeated 33.3 times with a reversal of polarity every 2 minutes.48

**Blinding**

The trial product will be provided in a blinded manner. All the magnetic coils are covered by a cloth. When switched on the device does not produce any sound or heat to keep patients blinded. Furthermore, to maintain the blinding of the investigator (and designated staff) an identic mattress (size) and same colour cloth will be used for all patients independent of treatment group assignment. Patients and all healthcare providers (therapists and physicians) who care for the participants during the study will be strictly blinded to randomized interventions. Study medications will be managed using unique vial numbers. Only the treating therapist will know what type of treatment the participant will be given. The assessor and the participants will not have access to such information. The treating therapist will be asked not to mention or talk about the treatment groups to others. Upon the completion of the study each participant will be interviewed to be asked about the group which they think they were at.

**Setting**

The trial will be conducted at the department of physical therapy of King Fahd Hospital of the University. King Fahd Hospital of the University is an 800 beds teaching hospital located at the Eastern Province of the Kingdom of Saudi Arabia. All researchers are clinicians at the departments of physical therapy and orthopedics. The trial is scheduled to begin September 2018.

**Procedure**

All screening, interventions and evaluation will be done by qualified musculoskeletal physical therapists who have 5 or more years of clinical experience. Potential participants will be asked to participate in the study, if agreed they will be screened for inclusion and exclusion criteria then they will be asked to sign a consent form. Subjects will be classified to into peripheral neuropathic, nociceptive or central sensitization musculoskeletal LBP according to Smart et al.10-12 Each participant will be assigned randomly to either the experimental group which will receive PLFMF and the conventional physical therapy program or the control group which will receive sham PLFMF and the conventional physical therapy program. Patients will be asked to lie down on the magnetic mattress for 20 minutes/session, three sessions a week for a total of 18 sessions (6 weeks). In the treatment group, the BEMER mattress will be activated whereas in the control group (placebo), no magnetic field will be generated. The conventional physical therapy program consists of:

* Hot packs for 20 minutes;
* Back, hamstring and calf muscles stretching (performed from long setting position)
* Lumbar erector spinae muscles self-stretching;
* back muscles strengthening (back extension and bridging);
* Abdominal muscles strengthening (posterior pelvic tilt and sit ups);
* Participants will be asked to hold the above positions for 5 seconds. Each exercise will be done 5 times per session with 1 minute rest between any two repetitions.

All patients will be evaluated at baseline, end of the 3rd and the 6th week. To assess for effects persistence, participants will be evaluated at 6 weeks, 12 weeks and 24 weeks after the end of the intervention sessions (Figure 1).

**Figure 1**. Flow chart of participation in the 2-arm randomized double blind trial evaluating the efficacy of PLFMF in CLBP



**Outcome Measures**

1. Numerical rating scale (NRS): Pain severity will be measured by the NRS. It an 11-point numeric scale with one extreme labeled as no pain (0) and the other extreme worst pain imagined (10). It is a valid and reliable scale.49 The patient will be asked to indicate the level of his pain immediately before the session and 5 minutes after the intervention.

The percentage reduction in pain will be calculated at each post-baseline assessment as:

100 x $\frac{(difference between baseline and post-pain NRS scores)}{baseline NRS score}$

1. Short Form 36 (SF-36)**:** An Arabic version of the SF-36 will be used to assess the quality of life of all participants. The validity and reliability of the Arabic versions of the SF-36 was established in a sample of Saudis.50
2. Disability measurement using the Roland and Morris Disability Questionnaire (RMDQ): is a self-reported, condition-speciﬁc questionnaire which consists of 24 questions. It is often used to assess LBP disability. It was translated and adopted into Arabic language.51
3. Depression Anxiety Stress Scale 21 (Dass 21): a 21 questions scale which assess the emotional state of depression, anxiety and stress. Each question is assessed in a four points likert scale. The validity and reliability of an Arabic version of the scale has been established.52
4. Function measurement will be assessed using Patient Specific Functional Scale (PSFS): it is a valid and reliable measure for physical function in musculoskeletal conditions.53-54 It measures 3-5 physical activities which are important to the patient and s/he is unable to do without difficulties. Patients rates the difficulty with which they do the function in an 11 points likert scale from 0 (unable to do) to 10 (not at all affected).
5. Global perceived effect (GPE) of condition change: is an one question scale which ask the patient to rate improvement/deterioration numerically from -5= much worse to 5 much better. It is has been recommended as one of the outcomes in clinical trials which study chronic pain.55 The scale validity and reliability has been established.56
6. Pittsburgh Sleep Quality Index (PSQI). A 19 items questionnaire which assess several aspects of sleep quality (sleep duration, disturbances, quality, efficiency, sleep onset latency, medication, and day-time dysfunction). A global score of sleep quality is the total of the various components of the questionnaire. The higher the score the worse the sleep quality. The questionnaire was translated and validated into Arabic language.57
7. Modified Fatigue impact scale (MFIS): is a 21 items questionnaire which was evaluate the fatigue effects on quality of life in patients with chronic diseases. A likert scale from 0 (no effect of fatigue) to 4 (maximum effect of fatigue) is used to score each item of the questionnaire.

**Safety Measures**

PLFMF has no known side effects, however, long term side effects of PLFMF have not been evaluated. If side effects developed or the symptoms of any participants get worse during the study s/he will be given appropriate medical care till the situation is resolved. Such participants will be withdrawn from the trial, if necessary. Any observed side effects will be recorded and reported to the IRB office at Imam Abdulrahman Bin Faisal University.

**Privacy and confidentiality**

Screening, assessment and treatment will be done in a private area at King Fahd Hospital of the University in the department of physical therapy. Data will coded, only one of the researchers will have the key for the codes. All data will be saved in a secured computer protected with a password. Only researchers will have access to data. Upon report writing and professional publication data will be presented collectively, none of the participants’ identity will be identified.

**Ethics and dissemination**

The trial was approved by the IRB of the Imam Abdulrahman Bin Faisal University (IRB‐ 2017‐03-129). The trial is also registered with XXXXX (in progress). While the trial being conducted the research monitoring office at King Fahd Hospital of the University (where the study will be conducted) will monitor the various milestones of the trial. The study will be explained to all participants by one of the researchers. All participants will sign a consent form before the beginning of any procedures of the study.

The results of the present trial will be presented in international conferences and will be published in peer-reviewed journals.

**Acknowledgments** We would like to thank the deanship of research at Imam Abdulrahman Bin Faisal University for funding this clinical trial.

**Contributors** Study concept, design and drafting of the manuscript: FAA and SA. Critical revision of the manuscript for important intellectual content: MSA, FA, HK. HK refined the protocol. SL contributed to statistical design and data analysis. All authors critically read and approved the final version of the manuscript.

**Funding** This work was supported by by Deanship of Research, Imam Abdulrahman Bin Faisal University grant number 2017-308-CAMS.

**Competing** interest None decleared.

**Patient consent** Obtained.

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