PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of pulsed low frequency magnetic field therapy on pain intensity in patients with musculoskeletal chronic low back pain: study protocol for a randomized-double blind placebo-controlled trial.
AUTHORS	Abdulla, Fuad; Alsaadi, Saad; Sadat-Ali, MIR; Alkhamis, Fahd; Alkawaja, Hani; Lo, Serigne

VERSION 1 - REVIEW

REVIEWER	Hamada Ahmed Hamada Lecturer of Biomechanics, Faculty of physical Therapy, Cairo University Egypt
REVIEW RETURNED	13-Oct-2018

GENERAL COMMENTS	Thanks for the opportunity to review this clinical trial. The study has some potential for publication due to the good methodological quality. At section of strengths and limitations: you don't mention any limitation and you can't mention any limitation before completion the study. At introduction 1. you should report a range of lifetime prevalence and point prevalence. 2.At line 25, it is better to mention the the treatment cost for low back pain for your country not for US or UK. 3. At page 7/36 you mention "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" need reference for this sentence. 4. you mention that " All the mentioned studies used small number sample sizes (16 – 40 patients). " how you judge that study has small sample size? may be these studies achieve high power? Did you calculate the power and effect size of these studies? 5. I would like more information on the effect of PEMF in other conditions (eg, effect sizes, clinically importance, quality of the evidence). OBJECTIVES : how will you measure the safety of PLFMF? Eligibility criteria: Why Selecting patients' age from 18 to 60. Sample Size and power calculation :

	How did you calculate sample size? What is the software that you used to calculate? Did you obtain to effect size or not? if yes, how. if not, why. Statistical Analysis: 1. you mention that "Treatment effect for the primary and continuous secondary outcomes will be assessed through ANCOVA adjusted for the baseline measurement score" if you used this test while you have different variables, you should perform Bonferroni adjusted for level of significance. or you will have type I error. 2. Normality, homogeneity and assumption of appropriate test should be performed before testing procedures. Procedure: 1. I wouldn't name this intervention as "Conventional physical therapy program" but something like non-guideline approach - this protocol is not recommended by guidelines and shouldn't be called Conventional approach. 2. It would be interesting to add in the method some parameters about pulsed electromagnetic field. Outcome: please add ICC for all outcome measures.

REVIEWER	Santaneel Ghosh, PhD Southeast Missouri State University
REVIEW RETURNED	05-Dec-2018

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.

REVIEWER	Teresa Paolucci Sapienza University of Rome- Rehabilitation Unit Policlinico Umbeto I Hospital (Italy)
REVIEW RETURNED	16-Feb-2019

GENERAL COMMENTS	Please, specify how the differential diagnosis is performed between CLBP subtypes based on pain mechanism (nociceptive versus peripheral neuropathic versus central sanitization)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Introduction

1. You should report a range of lifetime prevalence and point prevalence.

Response:

The following statement was added to the introduction:

“Evidence suggests that LBP has a lifetime prevalence of 40% and a mean point prevalence of 20%.3”

3. Hoy DG, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum 2012; 64(6):2028-37.

2. At line 25, it is better to mention the treatment cost for low back pain for your country not for US or UK.

Response:

Unfortunately, to the best of our knowledge, there is no estimate of low back pain cost in Saudi Arabia, therefore, costs from other parts of the world were used.

The text was amended, the new text reads:

“There is no published evidence of LBP cost in Saudi Arabia, the treatment cost for LBP in the US is estimated to be more than $90 billion per year8 and $17 billion per year in the UK.9”

3. At page 7/36 you mention "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" need reference for this sentence.

Response:

A reference was added to support the statement:

Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet 2017; 6736(16): 30970-9.

4. you mention that " All the mentioned studies used small number sample sizes (16 – 40 patients). " how you judge that study has small sample size? may be these studies achieve high power? Did you calculate the power and effect size of these studies?

Response:

Small-sized randomized trial is a concept used to define randomized trial that involved 100 participants or less. The following reference was added to support the statement.

Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in clinicaltrials.gov, 2007-2010. JAMA 2012; 307(17): 1838-47.

5. I would like more information on the effect of PEMF in other conditions (eg, effect sizes, clinically importance, quality of the evidence).

Response:

Effect size at 24 weeks after treatment completion is expected to be 0.5 (NRS between the two groups at week-24, standard deviation which is 10%-20%). This effect size of 0.5 means that the score of the average person in the active PLFMF (experimental arm) arm is 0.5 the standard deviations above the average person who have had sham treatment (control arm), and hence exceeds the scores of 69% of the control group.

The following statement was added to the manuscript:

“The sample size allows for 15 percent of patients lost to follow-up at week 24. A 10% absolute reduction in Numerical rating scale (NRS) pain of at week-24 will translate into an expected effect size of 0.5. This means the NRS score of the average person in the active PLFMF arm is 0.5 the standard deviations above the average person who have had sham treatment, and hence exceed the scores of 69% of the control group.”

Objectives:

how will you measure the safety of PLFMF?

Response:

As indicated in the manuscript under safety measures “Any observed side effects will be recorded and reported to the IRB office at Imam Abdulrahman Bin Faisal University. This will be documented during the trial and the follow-up period after the conclusion of the trial.

Eligibility criteria:

Why Selecting patients' age from 18 to 60.

Response:

Patients over the age of 60 were excluded from the present study for two reasons:

a. Evidence indicates that rehabilitation program may impact people over the age of 60 differently from the way it impacts people who are younger (Song and Qu, 2014).

b. Age-related comorbidities often exist independently of pain which may impact many of the outcome measures in the present study and act as confounding factors (Rudy et al., 2007).

Song J, Qu X. Effects of age and its interaction with task parameters on lifting biomechanics. Ergonomics 2014; 57(5):653-68.

Rudy TE, Weiner DK, Lieber SJ, Slaboda J, Boston JR. The impact of chronic low back pain on older adults: a comparative study of patients and controls. Pain 2007; 131(3):293-301.

Sample Size and power calculation:

How did you calculate sample size? What is the software that you used to calculate? Did you obtain to effect size or not? if yes, how. if not, why.

Response:

We have updated the Sample size and power section accordingly to make this clear and

replicable. The following statement was added

“Sample size calculation was based on two sample t-tests. We used R function power.t.test via R version 3.4.1 (https://cran.r-project.org).”

Statistical Analysis:

1. you mention that "Treatment effect for the primary and continuous secondary outcomes will be assessed through ANCOVA adjusted for the baseline measurement score" if you used this test while you have different variables, you should perform Bonferroni adjusted for level of significance. or you will have type I error.

Response:

We do not need to adjust for multiplicity because outcomes are ranked by level of importance. We have added the following paragraph in the manuscript to clarify why multiplicity adjustment will not be undertaken.

“P-values will not be adjusted for multiplicity. However, the outcomes are clearly categorized by degree of importance (primary, main secondary and other secondary) and a limited number of subgroup analyses are pre-specified.”

2. Normality, homogeneity and assumption of appropriate test should be performed before testing procedures

Response:

The following statements were added to the manuscript

“Before summarizing continuous outcomes, a test of normality will be performed. If the outcome is normally distributed, it will be summarized by mean (standard deviation) in each arm and the difference between arms will be tested using t-test. However, if no evidence of normality, data will be summarized using the median (interquartile range). In such case, the Wilcoxon rank sum test will be used to test the difference between arms.”

Procedure:

1. I wouldn't name this intervention as "Conventional physical therapy program" but something like non-guideline approach - this protocol is not recommended by guidelines and shouldn't be called Conventional approach.

Response

Conventional physical therapy program was replaced with “typical physical therapy program used in our department”.

2. It would be interesting to add in the method some parameters about pulsed electromagnetic field.

Response:

Upon the reviewer suggestion, we added the pulse frequency and duration of the pulsed electromagnetic field.

The text was amended to read as follow:

“The BEMER 3000 (BEMER Int. AG) will be pre-programmed to deliver PLFMF (an average of 14 µT), a pulse-frequency of 30 Hz and a pulse duration of 30 ms.”

Outcome:

please add ICC for all outcome measures.

Response:

We did not find Intra-cluster correlation (ICC) estimates that match the longitudinal outcomes as defined in this study. This study, when completed, will be the first of its kind to provide ICC estimates in patients with musculoskeletal chronic low back pain.

Reviewer: 2

NA

Reviewer: 3

Please, specify how the differential diagnosis is performed between CLBP subtypes based on pain mechanism (nociceptive versus peripheral neuropathic versus central sanitization).

Response

The text was amended to clarify this issue, the new statement reads as follow:

“The 38-item clinical criteria checklist developed by Smart et al.11-13 will be used to classify patients into different phenotypes of musculoskeletal CLBP.”

VERSION 2 – REVIEW

REVIEWER	Hamada Ahmed Hamada Cairo University, Egypt
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	Good effort