Author's response to reviews

Title: Extracorporeal shock wave therapy in the treatment of primary bone marrow edema syndrome of the knee: a pilot study

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Author's response to reviews:

Dear chief editors Mr Umile Giuseppe Longo and Ms Eloisa Nolasco,

Thank you for your kind letter and the reviewers’ concerning our manuscript entitled “Extracorporeal shock wave therapy in the treatment of primary bone marrow edema syndrome of the knee: a pilot study” (9066061081612224). Based on the comments we received, careful modifications have been made to the manuscript. We hope the new manuscript will meet your magazine’s standard. Below you will find our point-by-point responses to the reviewers’ comments/questions:

A. Responses to Comments of Reviewer Thomas Niethammer

This data seems to be very interesting, but I have several concerns about the study. In general, this manuscript is well written.

6. Detailed information for Authors (optional)

Response: Thank you very much for your kind review. Based on the comments we received, careful modifications have been made to the manuscript. We hope the new manuscript will meet your magazine’s standard.

Title:
No comments

Abstract:

Line 41: Conclusion is too strong formulated. There is no supporting data in the current manuscript which provide this strong conclusion. Please rephrase these sentences.

Response: Thank you for your suggest. We have rephrased the original sentences. We hope the new one will meet your magazine’s standard. Thank
Introduction:
Line 78: Why do you give this information about electromagnetic fields in this manuscript? Electromagnetic fields are not part of this paper.
Response: Thank you very much for your valuable suggestions. We appreciate your comments about the sentences. We deleted them. Thank you.
Line 85: There is no information about the chosen control group with Iloprost and bisphosphonate treatment in the introduction section. Please give some information.
Line 85: Please add the hypotheses of this study at the end of the introduction.
Response: Thank you very much for your valuable suggestions. Careful modification has been made to the sentences based on your comments. We added the relevant information. Thank you.

Methods:
Line 98: Why do you take this control group instead of a non-treatment group? Please give some literature to explain why.
Response: According to the previous literature, non-surgical treatments to BMESK that have been reported as being beneficial include reduction in weight-bearing load of the joint, bisphosphonates and prostaglandin inhibitors (e.g. iloprost). We took iloprost and bisphosphonate treatment served as the control group based on some literature as follows. Besides, before purchasing extracorporeal shock wave instrument, we chose these medications as the main method of treatment to BMESK in our hospital. Thank you.
Line 122: Why do you take this ESWT adjustment? Is there a reference?
Response: Thank you very much for your kind review. In this work, we performed a pilot study firstly to evaluate the effectiveness of ESWT in normalizing the symptoms and imaging features of BMES of the knee, so there is no uniform reference in present. Our ESWT orthopedic settings were prepared and used according to the methods described by some literature as follows. Besides, the settings were in accordance with the specifications and operating instructions of the Electromagnetic Shock Wave Emitter. We are very sorry for that. Thank you.


EMSE 140F (Type C) Dornier Compact Delta (with Orthopaedic Option)

Shock wave Data
Principle Electromagnetic Shock Wave Emitter
Type of EMSE 140F (Type C)
Aperture (mm) 140 mm
Penetration Depth 150 mm
Aperture Angle 50
Measuring Device Fiberoptical Hydrophone
Triggering
(shocks / min) 60 –120
ECG
Number of levels 9 (ABC 1-6)
Capacitor

C

650 nF / kV
Charging Voltage P+ Mpa
Focal pressure ED mJ/mm²
Energy Flux Density
E (12 mm)
mJ
Effective Energy Focal Geometry
At –6dB (FWHM)
Lateral Setting
Axial Setting
Orthopaedic

Settings

A 8 kV 6.7 0.03 2.5
B 9 kV 10.5 0.07 3.7
C 10 kV 16.0 0.11 7.0
1 11 kV 21.6 0.15 11.0 9 mm 90 mm
2 12 kV 31.5 0.28 20.0
3 13 kV 42.0 0.44 29.0 4.7 mm 57 mm
4 14 kV 48.0 0.59 39.0
5 15 kV 52.0 0.72 52.0
6 16 kV 55 0.96 70.0 7.5 mm 78 mm

Line 125: Why do you use the t-test instead of a test for non-normally distributed data.
Line 125: Did you perform a power analysis?

Response: Thank you very much for your valuable suggestions. We have carefully checked the statistical analysis again. We used the paired difference t-test which met its requirement: a set of paired observations from a normal population. This is appropriate for testing the mean difference between paired observations because the paired differences followed a normal distribution. The means and standard deviations (SD) were calculated for all patients, and 95% confidence intervals (CIs) were determined. And the samples were prepared in pairs. So within-group comparisons, we performed a paired t-test. To perform a power analysis, we asked the members of the Department of Epidemiology and Bio-statistics, School of Public Health, Peking University for help with the statistical analysis, and these have been noted in the acknowledgments section. Thank you.

Results:
No Comments

Discussion:
Line 193: Please start the discussion with your major finding.

Response: Thank you very much for your valuable suggestions. Careful modification has been made to the sentences based on your comments. Thank you.

Line 194: Please discuss the used methods and give literature if it is necessary the show that the used methods are appropriate. Especially the control group is not clear stated.

Response: Thank you very much for your valuable suggestions. Careful modification has been made to the sentences based on your comments. We added the relevant information about the used methods followed by the discussion with your major finding. Thank you.
Response: Thank you very much for your kind suggestions. We added our references updated with recent relevant citations. Thank you.

2. Responses to Comments of Reviewer Thomas Tischer

this is an very interesting study concerning a new indication for extracorporeal shock wave application. however, there are some points, that could be improved and increase the value of the manuscript even further.

Response: Thank you very much for your kind review. Based on the comments we received, careful modifications have been made to the manuscript. We hope the new manuscript will meet your magazine’s standard.

Major Compulsory Revisions:

1. In the introduction, it is stated that the effects of shock waves on bone is not well investigated. however, there are some basic science studies, that could be described, since this is important for understanding this technique. Please delete some references that are not concerning extracorporeal shock wave therapy instead. e.g. Hofmann et al. or Meizer et al., ... about half the listed publications are concerning bone marrow syndrome without shock waves. this publication is about shock wave treatment...

Optimal intensity shock wave promotes the adhesion and migration of rat osteoblasts via integrin #1-mediated expression of phosphorylated focal adhesion kinase.

Xu JK, Chen HJ, Li XD, Huang ZL, Xu H, Yang HL, Hu J.
Dose-dependent new bone formation by extracorporeal shock wave application on the intact femur of rabbits.
Tischer T, Milz S, Weiler C, Pautke C, Hausdorf J, Schmitz C, Maier M.
Response: Thank you very much for your kind suggestions. Based on the comments we received, careful modifications have been made to the reference section. We added the references updated with recent relevant citations. Thank you.

2. Please be more specific in the materials and methods section:
How long were the patients mobilized with weight-bearing aids? were they partial weight bearing or full weight bearing? where there differences between the groups?
Response: All patients were mobilized with partial weight-bearing and walking aids for 6 weeks. there were no differences between the groups. Thank you.
How was the area of edema in the MRI calculated. On one slide or 3D? where all the MRI with the same fluid sensitive sequence?
Response: We are very sorry for our vague description. We have clarified the sentence. In this study, the experienced radiologist evaluated the area of edema on one slide with the most obvious edema of the resulting MRI films with the same fluid sensitive sequence using the PACS software (Kodak version 11.0, MA, USA) to verify whether the edema lesion showed unchanged, reduced or regressed completely. Thank you.
Shock waves were applied in 2 series of 3 treatments? how is this meant? Were there 6 sessions? or 2?
Energy flux density was greater than 0.5mJ/mm2. How much was it? it makes a great difference between 0.5 or 1.0 for example...
Response: According to the operating instructions of the Electromagnetic Shock Wave Emitter, there are nine levels to be chosen (including LEVEL A,B,C,1,2,3,4,5,6). However, more than or equal to level 3 can meet the standard of shock wave treatment for the bone tissue lesion. The parameters in this study are prepared and used as follows: number of levels, 3–4; at an energy flux density (EFD) of >0.44 mJ/mm2 (level 3); 3000-4000 impulses at a frequency of 2-3 Hz. Each patient underwent two therapy sessions (the time interval between successive procedures was one week). The number of the frequency selected depends on the patient's condition. The frequency in the range of 2-3 Hz means that the shockwave tube can generate a shock wave at 120-180bpm.
We are very sorry for our clerical error in energy flux density. We are very sorry to bring you so much trouble. We really appreciate your magnanimity. We believe that these mistakes will not affect the review of this manuscript. Thank you.
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Principle Electromagnetic Shock Wave Emitter
Type of EMSE 140F (Type C)
Aperture (mm) 140 mm
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5 15 kV 52.0 0.72 52.0
6 16 kV 55.0 0.96 70.0 7.5 mm 78 mm
3. Results
Where are the quantitative data of the MRI investigations? At least semiquantitative data reporting with more than two groups would be recommended to better see the differences between the groups.

Response: We are very sorry for our vague description and poor language. We conducted a qualitative analysis of MRI investigations. In this study, the experienced radiologist evaluated the area of edema on one slide with the most obvious edema of the resulting MRI films with the same fluid sensitive sequence using the PACS software (Kodak version 11.0, MA, USA) to verify whether the edema lesion showed unchanged, reduced or regressed completely. We are very sorry to bring you so much trouble. We really appreciate your magnanimity. We believe that these will not affect the review of this manuscript. Thank you.

4. Discussion: please add a discussion of initiation treatment of BMSK after just two weeks? why not start conservative therapy with partial weight bearing? How many patients do well with this conservative therapy?

Response: Thank you very much for your kind review. We performed a pilot study to evaluate the effectiveness of ESWT in normalizing the symptoms and imaging features of BMESK. The conservative treatment approaches take too long time or are unable to relieve symptoms in some cases. We compared 2 therapies, topical ESWT chosen as the observation group versus iloprost and bisphosphonate treatment served as the control group. We hypothesized that topical ESWT would result in rapid pain relief and functional improvement without substantial complications. Using computer-generated random assignment concealment with sealed envelopes, patients were allocated to receive ESWT (Group A) (n = 20) or alendronate sodium tablets (70 mg po qw; Merck & Co., Inc.; Peking) and alprostadil (10 µg ivgtt qd; Peking Tide Pharmaceutical Co., Ltd.; Peking) (Group B) (n = 20). All patients were mobilized with partial weight-bearing and walking aids for 6 weeks and analgesics on demand with restrictions for impact sports such as sprinting or jumping.

These patients with ESWT had not gotten any iloprost and bisphosphonate. However, we will consider combining topical ESWT with iloprost and bisphosphonate in future studies. We added this issue in the limitation part of our manuscript. Thank you for your kind suggest.

L235: there can also be side effects of shock wave application.

Response: Thank you very much for your kind review. ESWT is a simple, non-invasive treatment that does not require the administration of pharmacological drugs, thus avoiding the reported potential side-effects of these drugs. However, only minor complications occurred after ESWT, such as transient soft tissue swelling or minor bruising.

L238: Please be more specific about the effects and mechanisms of shock wave therapy on bone tissue.

Response: Thank you very much for your kind review. Based on the comments we received, careful modifications have been made to the section. Thank you.
Minor Essential Revisions
References: please think about removing unnecessary references like Ahlbäck, Bellamy, McHorney, ...
Response: Thank you very much for your kind suggestions. We modified our references updated with recent relevant citations. Thank you.

Discretionary Revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests
Response: Thank you very much for your kind review.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper.
We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions. If this article needs further revision, please do not hesitate to contact us.
Sincerely yours,

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