Author's response to reviews

Title: Improved Healing Response in Delayed Unions of the Tibia with Low-Intensity Pulsed Ultrasound: Results of a Randomized Sham-Controlled Trial

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Author's response to reviews: see over
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Professor Rene Verdonk
Editor
*BMC Musculoskeletal Disorders*

RE: MS: 9464881183921728

Dear Prof. Verdonk:

My coauthors and I are delighted that you are favorably inclined to publish our contribution entitled “Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial” based on our response to the reviewers’ comments and recommendations. We noted generally that the reviewers’ comments were minor and we have addressed each, on a point-by-point basis, below.

**Response to Reviewer 1 (Rene Verdonk)**

This reviewer had no suggested modifications aside from the possibility of including some case illustrations to improve the readability of the report. We concur that the text is somewhat dry and weighted heavily on complex statistical analyses. However, we believe these evaluations were necessary to reduce bias. The cases were performed quite some time ago which makes including individual case reports difficult.

**Response to Reviewer 2 (Hendrik Pieter Delport)**

This reviewer had no suggested modifications and thought the article was well written and of importance to the field.

**Response to Reviewer 3 (Peter Reynders)**

1. *Defining the delayed union at a cut-off point of four months from the incident is debatable. Six months, as a time frame would be more realistic.*

The four month time frame to define delayed union was specified in the study protocol *a priori*. Thus, we are disinclined to alter these pre-defined study parameters *post hoc*. Additionally, our definition of nonunion is in line with the standard definition provided by Phieffer and Goulet in their review article on delayed unions of the tibia (ref #13). Finally, inspection of Table I illustrates that most fractures were quite old. In fact, approximately 75% of fractures were older than 24 weeks.

2. *Limiting this study to four months is a serious drawback, which makes conclusions about the study difficult.*
Due to the sham procedure and the blinded nature of this trial, the respective ethics committees would not allow the conduct of this study beyond 16 weeks. Thus, our primary outcome, BMD, as described is a surrogate measure of progression toward healing. The results of this blinded, sham-controlled trial demonstrated a 34% larger increase in BMD after LIPUS treatment compared to no LIPUS treatment, even after adjustment for multiple covariates.

3. I have the impression that because of the missing data, an impressive arsenal of statistical methods was used to compensate for this. Were these missing data at random or not?

The reviewer is correct. We employed a multiple imputation procedure to conduct the ITT analysis in this trial in accordance with ICH E9 guidelines for statistical analysis of a multi-site trial. This procedure adjusts for data randomness and differences in baseline covariates between treatment groups.

Report details of the software used. Report the number of imputed datasets that were created. What variables were included in this imputation procedure? Were there non-normally distributed variables? The statistical interactions included in the final analyses, were they also included in the imputation models?

Regarding the software used, we have added the following wording as the first sentence of the Statistical Methods subsection of Methods:

“All analyses employed Statistical Analysis Software (SAS).”

Regarding the issues raised about the imputation procedure, we indicated in the Statistical Methods subsection of Methods of the original text the following language: “For each of five stochastically completed data sets, analysis of covariance (ANCOVA) was used to estimate a treatment group contrast that controlled for the baseline value of the clinical endpoint as well as clinical site.” We also indicate in the same subsection: “Multiple imputation uses multiple predictions of missing clinical endpoints based on patient characteristics and the baseline value of the clinical outcome variables.” We believe this language adequately addresses the reviewer’s queries. This subsection of Methods is already quite detailed. However, if the Editor would prefer that we expand this subsection with further statistical detail, we would be happy to comply.

4. The chosen endpoints namely in first rank BMD and secondary, change in gap area are not really impressive for the clinicians. Hypertrophic non-unions have also an increase in bone formation around the fracture gap. So the statistical differences seen with this study corroborate this also with a significant clinical difference? For instance the differences in the transformed Hounsfield units, how important is this?
We appreciate the position of the reviewer in regard to this matter. Indeed, this sentiment has been raised by Busse et al in a recently published systematic review of LIPUS (BMJ 2009;338:b351). Lack of corresponding patient reported outcomes is a limitation of the current trial.

However, given the mandated short duration of this trial, an objective quantitative outcome such as CT assessment of BMD may be preferable to subjective patient reported clinical outcomes such as pain or function. It is unlikely that over 16 weeks, notable improvements in functional outcomes would emerge prior to complete fracture healing. Indeed, we noted this shortcoming in the original text of the fourth paragraph of the Discussion section: “It is unlikely that most established delayed unions will heal completely in this time frame or show discernible improvement in patient reported outcomes.”

Editorial Comments

1. **Our associate editor has requested that a statement be added to the statistics section of your manuscript stating that the statistical content of the manuscript had been approved by an expert in medical statistics and epidemiology.**

We have added the following wording as the final sentence of the Statistical Methods subsection of Methods:

   “The statistical content of the manuscript was approved by an expert in medical statistics and epidemiology.”

2. **We note that your study appears to have been sponsored by “Smith & Nephew” a commercial company. This information should be added to the ‘competing interests’ section of your manuscript in accordance with our editorial instructions.**

To comply with this request, we have moved the first sentence of the Acknowledgments section to the first sentence of the Competing Interests section indicating that the study was supported by Smith & Nephew.

We believe that our responses to the issues raised by the reviewers have been adequately addressed herein and that the article is acceptable to the Editor for publication. If additional concerns arise, please do not hesitate to contact my office.

Sincerely,
Jon E. Block, Ph.D.
Corresponding author