Author's response to reviews

Title: Immediate and Short-term Pain Relief by Acute Sciatic Nerve Press: A Randomized Controlled Trial

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Author’s response to reviews: see over
Dear Sir/Madam:
Thank you for the communication of the comments for this manuscript. Enclosed are our revisions for MS:1406065618123477. We have revised the entire manuscript according to the comments, and included a point-by-point response to the concerns listed.

We have also included the full names of the ethics committee members who approved this study in the first paragraph of the methods section.

We hope that you will be pleased with this revision. We wish to thank you for your patience and thank the reviewers for their kind and thoughtful commentary.

Sincerely

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Methods

Comment 1  Was a prospective power analysis performed?  2X33 patients, or even 2X21 + 2X12 are certainly not enough to detect a definite in VAS scale.  But the study may be considered as an exploratory investigation.  Please discuss this point!

We did a series of tests in pilot studies to establish different optimal parameters (press time, force and location of pressure) before these two clinical studies.  Based on the pilot studies, we did a prospective power analysis for dental diseases which gave a minimum sample size of 2X12.  We didn’t use the sample size as a strict control for these two studies; because, pain relief differed greatly between different diseases indicating a need to separately analyze each.  Unlike acupuncture, the sciatic nerve press gave much more distinct pain relief in pilot studies and the clinical studies reported here.  Thus, the number of participants needed to achieve significance was lower.  This was confirmed by subsequent tests enrolling 253 patients in 6 clinical centers (soon to be submitted).

To clarify this point, we have added in paragraph 5 of the discussion section the following:

This manipulation gave very distinct pain relief results in pilot studies and the clinical studies reported here.  Based on the pilot studies, we did a prospective power analysis for dental diseases which gave a minimum sample size of 2X12 for the 10 min test.  We didn’t use the sample size as a strict limit for these two studies; because, pain relief with this method differed greatly between different diseases.  The minimum sample size increased when the test period was lengthened.  This study confirmed that the minimum sample size to achieve significance could be smaller for this method with some diseases for the 10 minutes observation period.

Comment 2  Did patients know which one was the treatment and which one the placebo “treatment”?  Do they know about Chengfu point in general?  Did you tell them? – Please discuss about this!

Patients did not know which one was the active or placebo treatment; nor what the Chengfu pressure point was in general.  We did not give them this information.

To clarify these questions, we have added an explanation in the first paragraph of the discussion section as below:

The “Chengfu” point, located on the back of thigh just below the juncture of the hip (Figure 1), is recognized by practitioners of the discipline as related to urinary function (such as clarity of urine, frequency, etc) [17], but not to pain relief.  There are five acupuncture points on the front, and five on the back of the thigh according to Chinese Traditional Medicine [17,18].  Usually only specialized doctors would know the specific functions for a given thigh point in China.  To our
knowledge, the pressure stimulation of any anterior or posterior thigh point for
pain relief has not been reported. The exclusion criteria for this study specified
that all patients in the study not have any previous exposure to the method. At
entry to the randomization step, it was confirmed that all patients had no prior
knowledge of, nor exposure to the method. Therefore, we believe that the
blinding of patients was secure and unbroken under our tested protocol.

Comment 3   In the method section you only mention the 10 min testing
period after leg pressure, but later on you tell that pain reduction
sometimes lasted longer than 30 min. please precise, how long you tested
VAS scores in all patients. If you tested 10 (or 30) minutes only, why not
longer?
In this study, we counted only the 10 min period designated as the test period,
but, casually observed some patients for longer times. Subsequently, in further
studies enrolling 253 patients, the testing design included longer observation
periods. We mentioned the observation of a longer effect in this manuscript for
discussion of the mechanism only.

Comment 4   How did you know, how many kilograms were applied to the
nerve? Please indicate!
To clarify this question, we have added the information in the method section as:
Doctors, using the gesture shown in the manuscript, pressed repeatedly on a
balance to experience and learn how much force to use with each fist. The
trained doctors determined how much force to apply based on the patients’ body
type. The heavily muscled and large body patients receiving greater pressure,
(18-20 kg with each fist). Similarly, thin patients received less pressure (11-13 kg
each fist). The ranges that were effective were determined in pilot studies.

Results
Comment 5   What about the results of the other time periods (30 min or
longer)?
Our subsequent study showed the pain relief (VAS in the treatment group versus
VAS in the placebo group) is highest from 10 min to 20 min, and diminished
thereafter, becoming 47% less at 60 min.

Comment 6   Please discuss what kind of renal disease the patients had
who did not benefit of the treatment. Did they suffer a certain kind of
underlying disease, for example renal colic, or was it only the amount of
pain that was the cause of a treatment failure? It is very important to
discuss this extensively!
We have added the information and made the changes in the third paragraph of
discussion section as below:
Near 40% of renal patients did not report any pain relief after the “sciatic press”,
these were all patients with the intense pain of kidney colic before the treatment.
Similarly the tests in dental patients showed excellent relief of pain for dental
caries and periodontal diseases, but poor relief for dental trauma. However, limited by the small number of patients in this study, we can not assert whether the method works less effectively in intense pain states, or, if the loss of effect is related to the diseases' origin, or, to some other factor. To clarify this question…”

**Comment 7**  It would be extremely interesting to demonstrate the median duration of pain relieve, and visualize these results.
It is really interesting and important. To do that, a large numbers of patients and longer time periods will be needed. We will consider this point in organizing future studies. Thank you very much!

**Discussion**

**Comment 8**  This part of the discussion (line 20 of the discussion onwards) gives the impression that force was applied until pain was relieved. Was force in some cases not applied 2 min as described in the methods section, but for a shorter period of time, if pain was relieved earlier? And sometimes even longer than two minutes in case of failure? Those variations were tested in pilot studies (not published). The force was applied for 2 minutes in all patients in this study. We introduced the information in the discussion just to give a clear idea of the method’s effect and, the time frame of pain relief. To avoid misleading readers, we have changed the previous sentence in the discussion section from: “Pressure application was two minutes”, to a new sentence: “Pressure application was two minutes for all patients in this study.”

**Comment 9**  Why was the force only 11 kg in some cases? And again, how was this measured, and was the amount of force measured in ALL cases? What is meant by “insufficient force”? Please describe and discuss these questions in detail, and also insert your answers in the methods section of your work.

The 11kg pressure is used only for thin patients. In pilot studies, some thin patients were uncomfortable when greater force was applied. Our pilot study results demonstrated that the force of 11 kg with each fist can work for pain relief in these thin patients.

For the question “how was this measured”, please see answers to Comment 4.

We did not measure the amount of force received in all cases.

“Insufficient force” meant that the amount of force applied was not enough for any measurable effect. For example, the force applied to thin patients should not be lower than 11kg with each fist. We believe that the answer and manuscript changes for Comment 4 correct this issue.
We have added the information in method section. Please see answers for Comment 4.

Comment 10 Please mention the limitation of your results because of the small number of patients.

We have added the information in the third paragraph of the discussion section. Please see the answer to and changes made for Comment 6.

Abstract
Comment 11 Delete: The “s” in the word Abstracts.
We have made the deletion.

Comment 12 Insert: ……, versus relief of 14% for the placebo press, in median.
We have made the insertion.

Comment 13 Change: Forty percent of renal patients did not report any pain relief after the treatment.
We have made the change.

Background
Comment 14 Delete:….Corticosteroids lead to hypertension and psychosis.
We have made the deletion.

Comment 15 Change: NSAIDS can cause ulcers, gastrointestinal bleeding and renal impairment.
We have made the change.

Comment 16 Change:…Opioids can cause among other things constipation, nausea and vomiting and sedation.
We have made the change, also added a few words according other reviewer’s comment.

Comment 17 Delete: respiratory depression (this is no problem if administered correctly!)
We have made the change.

Methods
Comment 18 Delete the point after “study design and procedure”.
We have made the change.

Results
Comment 19 Correct: two separate hospitals…
We have made the change.
Comment 20  Delete the whole paragraph “After controlling for baseline pain, sex and age…”
We have made the change.

Comment 21  Correct: … and 10th minute dropped
We have made the change.

Comment 22  Delete the whole paragraph “After controlling of baseline pain, sex and age…” This information is redundant with the paragraph before. Or describe exactly what is meant with this correction and how it was performed. It makes no sense to make any correction.
We have deleted the paragraph.

Discussion
Comment 23  Insert: … these were all patients with intense pain before the treatment.
We have made the change. Please see Comment 6.

Comment 24  Correct: … works less effectively in intense pain states, or...
We have made the correction.

Comment 25  Correct: In our pilot study...
We have made the correction.

Comment 26  Please delete the whole last paragraph: “However, pain is intended to tell us when something is wrong…: until the end of the discussion section.
We have made the deletion.

Conclusion
Comment 27  Delete “some” (renal diseases), because it implicates that the kind of underlying renal disease is the cause for a better or less good therapeutic success of nerve pressure. However, if you have an idea whether sciatic nerve press works better with a certain type of renal diseases, specify also in the conclusion section.
We have deleted “some”.
Although, our results have shown that the sciatic nerve press does work less well on certain renal diseases like renal colic, we did not have sufficient numbers of patients to state the difference as significant.

Comment 28  Figure 1+2: Delete the big grey column.
We have made the change.
Quality of written English: Needs some language corrections before being published
We have completed several rounds of language and spelling corrections, and hopefully, caught all the most egregious errors. Thank you.

ABSTRACT
Comment 1  The authors state Abstracts in the plural. I believe there is only 1 abstract for this article.
We have made the correction.

Background
Comment 2  Page 1, second sentence. This study describes a novel manipulation. This sounds like an advertisement rather than a scientific paper.
We have corrected the sentence to “This study describes a new manipulation:.”

Comment 3  The same sentence says “for immediately relieving clinical pain seen in dental and rental patients for short term purposes.”
We have corrected the sentence to “…for rapid short-term relief of pain brought on by various dental and renal diseases.”

Comment 4  The word rental should be changed to renal.
The correction has been made.

Methods
Comment 5  The section should reveal patient recruitment and the type of patients recruited. It may also be worthwhile to define renal patients.
We have added the information in the methods section: Patients were recruited sequentially, by specific participating physicians at their clinic visits to three independent hospitals. The diseases in enrolled dental patients included dental caries, periodontal diseases and dental trauma. Renal diseases in recruits included kidney infections, stones and some other conditions.

Results
Comment 6  Please see the comments in Methods.
We have added accordingly in the results section: The method worked excellently for dental caries and periodontal diseases, but poorly for dental trauma. Forty percent of renal patients with renal colic did not report any pain relief after the treatment.
Comment 7   The authors state that “the time necessary to acquire appropriate pharmaceuticals...means hours or days of sustained pain before relief.” This may be accurate with regards to initial pain but not so if it is chronic, persistent or recurrent pain. In the modern era of over the counter drugs for almost anything, this is not an issue. We have made the correction as: For patients with acute initial pain, the time necessary to acquire appropriate pharmaceuticals...mean hours or days of sustained pain before relief.”

Comment 8    “For example, corticosteroids lead to hypertension and psychosis...” the authors may be best served to describe simple drugs first. Why would somebody take corticosteroids directly? The other reviewer made a similar comment about this issue, and suggested deletion of the words “corticosteroids lead to hypertension and psychosis”. We have made the deletion.

Comment 9    The most common issue with regards to opioids is the dependency and addiction, consequently, withdrawal, etc. That is not mentioned. We have made the correction combining the other reviewer’s comment: Opioids can cause among other things constipation, nausea, vomiting, sedation, dependency, and addiction.

Methods
Comment 10   The comment with regards to the study design and procedure obviously relates to the blinding. The provider is not blinded but it appears that patients are. It would be surprising to know that most Chinese don’t know the acupuncture points while at the same time almost everyone knows where the sciatic nerve is located. In our test, patients were blinded, but the doctors were not. That is correct. To clarify these questions, we have added an explanation in the first paragraph of the discussion section as below:

The “Chengfu” point, located on the back of thigh just below the juncture of the hip (Figure 1), is recognized by practitioners of the discipline as related to urinary function (such as clarity of urine, frequency, etc) [17], but not to pain relief. There are five acupuncture points on the front, and five on the back of the thigh according to Chinese Traditional Medicine [17,18]. Usually only specialized doctors would know the specific functions for a given thigh point in China. To our knowledge, the pressure stimulation of any anterior or posterior thigh point for pain relief has not been reported. The exclusion criteria for this study specified that all patients in the study not have any previous exposure to the method. At entry to the randomization step, it was confirmed that all patients had no prior knowledge of, nor exposure to the method. Therefore, we believe that the blinding of patients was secure and unbroken under our tested protocol.
Comment 11  People receiving the pressure in the anterior part of the thigh would know that they are in the placebo group. Please see the answer to Comment 10.

Comment 12  The authors should explain how this was avoided of if there was a mechanism that they tested prior to enrolling them. Please see the answer to Comment 10.

Comment 13  The authors also need to explain the mechanism of pain relief in dental and renal patients with a sciatic press. To clarify the mechanism discussion (paragraphs 6-9 of the Discussion section), we have added a sentence to paragraph 8 summarizing the discussion in paragraphs 6 & 7: “The Gate Control Theory of Pain can explain the rapid relief of pain by our method.” Then the mechanism discussion becomes more integrated with the further explanation in paragraph 8. “Another mechanism possibly involved is activation of the endogenous opioid system.”

Participants
Comment 14  The authors should describe the participants in more detail, what kind of renal pain they were suffering with and why would they had sciatic pain.
We have added the information in more detail in the Methods section; please refer to the answers to Comments 5.
In this study, the renal patients did not have sciatic pain. Stimulation of the sciatic was used to relieve the pain brought on by various dental and renal diseases.

Comment 15  It appears that the inclusion was only slightly more than 50%. This appears to be an extremely low enrollment proportion considering that this is a non-invasive technique.
The inclusion rate for this study was low considering it is a non-invasive technique. Our further study of 253 enrolled patients using this technique gave a similar low inclusion percentage to this report for new clinic attendees. One of the most frequent reasons offered by patients for declining to join was skepticism of the method’s simplicity with regard to belief in possible efficacy, as mentioned in the discussion section. Even some doctors participating in this study were skeptical of the efficacy before participating in the test.

Discussion
Comment 16  The authors should clarify various points raised in other sections.
We have made the clarifications in other sections, as listed below:

1: The results showed rapid relief of pain after the press for dental caries and periodontal diseases, but not for dental trauma. ---This point has been added to the first paragraph of results section.
2: …and the pain of kidney colic. -----This point has been added to the second paragraph of results section.

3: “…. This novel method worked excellently on clinical pain from dental diseases…” in the second paragraph of Discussion section has been changed to “….This method worked excellently on clinical pain from dental diseases…”

4: “…immediately significant …” in Conclusion section has been changed to “…rapid significant

Comment 17   The authors should describe what type of effect this will have on various other types of pain problems.
Our further study involving 253 patients with other diseases will be submitted soon.  So, we added a short statement to this effect in the first paragraph of the discussion section as follows:
The rapid pain relief in other diseases by the sciatic nerve press has been demonstrated in our further studies (manuscript soon to be submitted).