Author’s response to reviews

Title: Effectiveness of Music Therapy for Alleviating Pain During Haemodialysis Access Cannulation for Patients Undergoing Haemodialysis: A Multi-facility, Single-blind, Randomised Controlled Trial

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Author’s response to reviews:

Response to peer review comments

Thank you very much for reviewing this manuscript. Below are the responses for each comment. The changed points in the manuscript are highlighted in yellow.

Reviewer #1: The authors have designed a novel study looking at the effects of music on pain when inserting needles for hemodialysis. They include an interesting mix of outcomes, including VAS pain score, salivary amylase and others.

1) The major difficulty with this protocol is recruiting participants with sufficient pain for the intervention to be beneficial. In their pilot study, the authors report a mean VAS pain score below the 30mm considered "moderate pain". The enrolment procedure (p8) makes no assessment of the level of pain and is a major weakness of the study. I don't believe using this enrolment questionnaire will be very different from approaching all patients to participate, regardless of pain experience. Is there a particular level of pain that the intervention is meant to alleviate, or is the study open to people with any level of pain (i.e. including VAS pain scores below 20mm or less)?

<Reply> Thank you for your opinion. Yes, this study is open to people with any level of pain (i.e.
including VAS pain scores below 20 mm or less). This is because we think that music therapy is worth being performed even for patients feeling just slight pain, since music therapy is a quite safe and inexpensive treatment. Therefore, the most important purpose of our questionnaire for qualification is to ‘exclude patients who have not experienced any pain (VAS is 0 mm) throughout the week of intervention’. In order to exclude patients who do not experience pain, the VAS format was not necessary. The question method of whether the participant experienced pain, using a categorical scale, is enough to exclude patients who did not qualify for the study. We have clarified this in the text (lines 126-129, page 9).

In addition, there is another reason why we chose not to use the VAS scale but a categorical scale for the enrolment procedure. With VAS, respondents are most commonly asked to report ‘current’ pain intensity or pain intensity ‘in the last 24 hours’ (Arthritis Care & Research 63(S11) (November 2011): S240–S252). Clinically and empirically speaking, haemodialysis patients do not feel constant pain. Instead, they experience occasional pain. From the result of our pilot study, we found that there are many haemodialysis patients who did not experience any pain at the time of cannulation due to effects of topical analgesics and habituation to the cannulation process. To catch these pains using the VAS, the patients would be required to repeatedly respond to the VAS. These types of repeated responses would not be suitable for inclusion considering the feasibility of our study. On the other hand, a Likert scale such as the SHORT FORM 36 is used for acute (1-week) recall. Moreover, there is a linear relationship between the non-visual categorical scale and the VAS (The Clinical Journal of Pain 3(4) (1987): 197-200).

In reality, this study has already been started, and using this questionnaire, we have successfully excluded many patients who do not feel pain during cannulation.

2) How much does the intervention rely on the timing of venepuncture being when the second movement commences? Nurses in dialysis units can be very busy and have competing priorities. I am not confident that they can be relied upon to needle a fistula at precisely the right time. This may be further delayed if the initial venepuncture is unsuccessful. Will the timing of venepuncture in relation to the start of the Sonata be recorded/reported?

<Reply> Thank you for your valuable opinion. There is no study showing a relationship between listening time and the effect of music therapy on reducing cannulation pain. However, of course, we cannot deny the possibility that the effect of music therapy would be affected by the time of music onset or that nurses in dialysis units can be very busy and have competing priorities. We have decided to substitute non-adherence to address your apprehension. In this study, we plan to use ‘A complete or full analysis set (FAS)’ (see lines 366-372, pages 22). In FAS, non-adherence is ignored and subjects are compared based on their assigned treatment category. In the clinical trial, assigned treatment is considered a misclassified measure of received treatment and cannot be expected to produce unbiased estimates of the effect of received treatment. Using FAS will give us a conservative result.

In addition, we will perform the analysis using per protocol set (PPS). To maintain the quality of the study, we are recording the listening times. As a countermeasure to this, we are recording the time of sound onset and the end of the intervention using REDCap. Since the data regarding cannulation failures and the number of cannulations will be recorded, we would like to confirm the relationship between these factors and the effect of reducing cannulation pain in the PPS. We have added this information to the text (lines 170-176, pages 11-12; lines 203-204, page 13).

3) The sample size is based on a 20% reduction in VAS pain score from 25.4 to 20.5mm in a pilot study. Is there any literature on what reduction in VAS pain score is clinically important?
Thank you very much. As you know, placebos have also been found to be effective to some extent in studies whose outcome is pain (Pain 157(12) (2016 Dec): 2766-2772). We think the difference between placebo and music shows the true effect of music therapy. To test this difference, we calculated the sample size using the difference between placebo and music therapy, which is crucial in this study. The difference between the two groups was 4.9 mm in the pilot study, which you mentioned, based on the results of VAS: 25.4 mm in the music therapy group and 20.5 mm in the NEWS group (as a placebo). This is not the reduction, but simply shows the difference.

Music therapy is safer and more inexpensive than analgesic agents. In other clinical studies, a difference of around 5 mm on the VAS has already been recognised as clinically important amounts of pain. For example, the effects of NSAIDs for pain range from 5.9 to 6.9 mm (Cochrane Database of Systematic Reviews (2016 Feb): 10.1002/14651858.CD012087). The effects of mirogabalin for pain was found to be 5.1 mm in a low dose group (Pain 160(5) (2019 May) 1175-1185).

Based on these facts, we considered that a difference of 4.9 mm is clinically important and used it for the sample size design. I have added this to the text (lines 277-279, page 17).

4) The authors have worked hard to try to blind study personnel to the intervention, and this is appropriate. Are the any mechanisms in place to ensure/confirm that either the Mozart sonata or white noise was actually delivered? For example an equipment malfunction/headphones becoming unplugged would result in the intervention not being delivered, but the study personnel may not be aware.

Thank you for your opinion. This point is important in research operation. In this study, the most important feature is the difference between the music therapy period and the white noise period. Therefore, these two interventions are provided in a blinded manner. The no-sound period is not blinded in order to avoid the problems that you pointed out. The specific method is as follows.

When we are obtaining informed consent, we explain to patients that the first and third weeks are no-sound periods. Of course, the operators also know that these periods are no-sound periods. On the other hand, from the point of view of blindness, patients and operators cannot know in advance whether the second week or fourth week is a music period or a white noise period. Using this method, participant can simply recognise whether sound will be heard that day or not. If there are no sounds coming from the headphones due to a mechanical failure or unplugged headphones, participants will be able to realise this fact and notify their operator. In addition, in no-sound periods, operators are informed on the tablet’s screen that a no-sound period is underway. We have added this explanation to the text (lines 292-300, page 18).

5) The references are not formatted correctly and should include the title.

Thank you for your comment. We have corrected it.

6) In the Discussion, the authors link the possibility of lowering the pre-dialysis BP by music therapy with improving prognosis. This is highly speculative, particularly given other studies of the pre-dialysis BP and outcome have had different results to the cited study.

Thank you very much. As you pointed out, there are various discussions about the relationship between blood pressure at the initiation of haemodialysis and the prognosis of haemodialysis patients. Studies reporting that lower pre-dialysis BP is associated with bad prognoses (Medicine (Baltimore)
Minor issues:
1) p5 line 70/71: "approximately 20% of patients experience excruciating pain" - this is somewhat emotive language. In the cited study (ref 4), 19.5% of people in the placebo arm reported VAS pain score above 54mm ("severe pain").

<Reply> Thank you for your suggestion. We have corrected this (line 71, page 6).

2) p10 - the "White noise" section is presumably about the control period. The phrase "During this period . . " suggests we are still talking about what has been happening in the previous paragraph.

<Reply> Thank you for your comment. We have revised this as suggested (line 178, page 12).

3) What is the relevance of the weather? (p12, bottom line)

<Reply> Thank you for your advice. It has been reported that the state of anxiety changes under the influence of the weather (Emotion 11(6) (2011 Dec): 1495-1499. doi: 10.1037/a0024649. Epub 2011 Aug 15; British Journal of Psychology 75(Pt 1) (1984 Feb): 15-23. Therefore, we think that the weather may affect not only the degree of pain but also the anxiety of secondary outcomes. We have added this information to the text (lines 229, page 14).

4) p13 line 222/223 - if pain is only evaluated once per session, how is the highest pain score during a session to be used?

<Reply> Thank you for your valuable comment. In order to avoid any misunderstandings, we changed it to ‘The maximum pain of the cannulations will be scored’ (lines 239-240, page 15).

Reviewer #2: 1. The manuscript needs to be revised with scientific terms rather than using lay terms. For example-
   a. The term 'shunt vessel' should be changed to 'hemodialysis access' as shunts are no longer used in clinical practice.
   b. The term 'puncture' should be changed to 'cannulation'.
   c. Please change the term 'external' analgesics to 'oral or topical' analgesics.

<Reply> Thank you for your comment. All of these items have been corrected as indicated.
2. In the abstract and the main text, please clarify who the operator is. Is the nurse cannulating or the person administering the headphones referred as the operator?

<Reply> Thank you for your advice. The operators are doctors, medical engineers, or nurses who perform the cannulation procedure (including disinfection, puncture, and blood removal). We have changed this to be clear (line 48, page 4).

3. Describe the rationale for measuring salivary amylase activity.

<Reply> Thank you for your valuable comment. Salivary amylase activity is a reliable and objective marker that indicates anxiety. The purpose of adding salivary amylase activity is that we want to evaluate anxiety not only with subjective markers but also with objective markers such as salivary amylase activity, since VAS and STAI are participants’ subjective evaluation scales. We have also added the evidence to the Methods section (lines 254-255, page 16).

4. Describe/define white noise as most readers will not be familiar with this term.

<Reply> Thank you for your valuable comments. We have described the explanation of white noise in more detail and additionally cited another paper (Michael LS. ‘The influence of white noise on sleep in subjects exposed to ICU noise’. Sleep Medicine 6 (2005): 423-428) (lines 179-181, page 12). However, as you pointed out, many readers may not be familiar with white noise and may not be able to understand the explanation. Therefore, we have added an URL of the white noise used in this research. (https://www.youtube.com/watch?v=_CMzWGteDCY)

5. Please describe whether the use of concomitant analgesics will be allowed in the trial.

<Reply> Thank you for your comment. The use of analgesics is permitted. We have stressed that in the revised manuscript (line 136, page 9).

6. How is the volume of the sound regulated?

<Reply> Thank you for your valuable comments. As we have already explained in the reply to major issue 4 from reviewer #1, participants and operators can recognise whether sound is to be heard on a given day or not. When the intervention is started, the participant can adjust the volume on the tablet PC screen if it is too low. We have stated this in the revised text (lines 148-149, page 10).

7. Analysis set: please clarify whether the analyses will be conducted according to the intention-to-treat principle. How missing data will be handled? Please clarify whether missing data will be imputed.

<Reply> Thank you for your advice. The analyses will be conducted according to the intention-to-treat principle. A mixed effect model has been widely used in the analysis of longitudinal data, especially when there are missing data. The model is considered to be a suitable method for handle missing data...
as the model assumes Missing at Random (MAR).