Author’s response to reviews

Title: Randomized controlled trial of transcutaneous electrical nerve stimulation for pain relief during transvaginal oocyte retrieval using conscious sedation: study protocol for a randomized controlled trial

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Author’s response to reviews:

Dear Editor and Reviewers,

Thank you for consideration of our protocol paper and for the time taken to review it.

Please find attached a point-by-point response, and accompanying changes to the manuscript. We hope that the revised version meets with your approval.

Response to reviewers’ comments

Reviewer #1:

Comment: Please correct some spelling errors.
Line 32, electical
Line 42, satisfaction
Line 100, nocieptive
Line 101, angelsia
Line 115, do you mean "affiliated"?
Line 122, participates

Response: The spelling errors have been corrected. (highlighted in text)

Comment:
Could you please elaborate on side effects: Are there any side effects that you anticipate? If so, please give details about what they are; If an unanticipated effect happens, how will it be considered as a side effect?

Response: The anticipated side-effects include nausea, vomiting, dizziness, drowsiness, skin allergy at the site of TENS pads application, discomfort due to electrical stimulation. (Line: 186 - 187)

The unanticipated effects will be considered as side-effects of TENS if there has been similar side-effects reported.

Comment:
Since post-operative side effects is one of the secondary outcomes, please state how you will define the side-effect outcome variable and what statistical analysis you will use to analyse it.

Response: Each documented side effects will be defined as nominal data (yes or no). Chi-square test will be used for analysis. (Line: 222 - 223)
Comment:

Pain levels prior to oocyte retrieval will be collected. Do you plan to account for pre-procedure pain levels in the main analysis?

Response: Yes, pain levels on venepuncture, intravenous cannula insertion, transvaginal ultrasound and anticipated pain level during oocyte retrieval will be analysis together with pain level during oocyte retrieval.

Reviewer #2: Inclusion/exclusion criteria

Comment:

An exclusion criteria is oocyte retrieval performed on one ovary only. Rarely, egg retrieval from 2 ovaries is planned but the procedure is terminated after retrieval from one ovary. If this happens to a patient during the trial, will the patient then be excluded?

Response: We will exclude the woman from analysis if oocyte retrieval is performed on one ovary.

Comment:

Patients with neurological disorders can possibly have a different response to the treatment. Patients with diabetes mellitus undergoing oocyte retrieval can occasionally have a pre-existing neuropathy. If a patient has a condition such as diabetes or neurological disorders, will they be included?

Response: There is no plan to exclude patients with pre-existing neuropathy which is rare in our population.
Comment:
If a patient undergoing retrieval has a chronic pain disorder such as fibromyalgia or is on chronic treatment with analgesics such as opioids, will they be included in the trial?

Response: Those with chronic pain disorders will not be excluded from the study. History of chronic pelvic pain is collected as baseline information.

Comment:
Randomization sequence
Is there any type of stratification or blocks in the randomization sequence?

Response: The randomization used is simple randomization generated by the computer system without block or stratified randomization. (Line 134-135)

Comment:
Intervention
The intervention is supposed to start 5 min prior and end 5 min after oocyte retrieval. Will the patient be already sedated 5 min prior to retrieval? If so, please explain: who will ensure that intervention is administered?. As patient will likely be sedated 5 minutes after the end of the procedure, who will ensure that intervention stops 5 min after the procedure?

Response: The intervention is started before administration of sedation and sedation is given by the nurse under the surgeon’s supervision just before the procedure. Therefore, the patient will not be sedated at the time of commencement of intervention. A nurse responsible for the study who is unaware of the randomization is responsible for ensuring administration of intervention before oocyte retrieval and withdrawal of intervention after the procedure.
Comment:

It is described that a research nurse will instruct the patients how to titrate the TENS amplitude prior to oocyte retrieval. Will there be any minimum/maximum current amplitudes set to be administered? Will the amplitude of impulses be recorded? If the amplitude is too low it can have less effect and bias the results towards the null.

How was the pulse duration chosen?

Is there a mechanism to verify that the TENS machine worked throughout the oocyte retrieval, to verify that the intervention was indeed administered as planned?

Response:

There will be no lower or upper limit of the amplitude set or recorded. As the patient can alter the amplitude throughout the procedure depending on her pain level, it will be difficult to keep a record. A nurse will be in the theatre to ensure the TENS machine is turned on throughout the oocyte retrieval.

Pulse widths greater than 100 µs are required to evoke serotonin release in the spinal cord for frequencies above 10 Hz. With most TENS devices, pulse duration varies between 50 and 400 µs. A upper limit, 400 µs is chosen as the analgesics effect may increased when it is above 250µs. Increased pulse duration results in increased inhibition of dorsal horn neuron activity.

Comment:

Blinding

If all patients will be instructed how to titrate the TENS machine until feeling paresthesia, in order for them to be blinded this means that all patients would have to do the titration with a working TENS machine, otherwise allocation would be revealed to the patient and the nurse at that time. Please explain: how will the patients be blinded to the intervention? Will the TENS machine be exchanged after titration? And if so, does it mean that the nurse assisting the patient during the titration is not blinded to the allocation?
Response:

The instruction to the patient on how to use the TENS machine is given in the ward before the scheduled oocytes retrieval by a research nurse who is only responsible in that part of the study. The nurse will give the same instructions to patient irrespective of the allocation group. The patients will be told that they might not feel anything after a certain limit of energy is reached. The same machine used during instructions will be used during the procedure. The appearance of the active and placebo TENS are identical. They can only be differentiated by a code at the bottom of the machine.

Comment:

Who will be collecting the primary and secondary outcomes (VAS score)? Will this person be blinded to the intervention?

Response: The research nurse who is blinded to the intervention will be collecting the outcome data. (Line 178-179, 185-189)

Comment:

Outcomes

As per "assessment of pain and sedation levels" section, "the maximum pain level on vaginal puncture and during oocyte recovery will be rated by the women shortly after the operation". Please specify how much time will pass "shortly after the operation", will the patient still be under the effects of sedatives at the time of collection of the primary outcome? Please specify when you expect the patient to be able to record a score on the VAS scale without being under the influence of sedatives

Response:

The patient will be asked to rate the pain immediately after the operation and 4 hours after the operation before they are discharge from hospital. (Line 183-184) The surgeon will comment the sedation level of the patient during the procedure immediately after the oocyte retrieval using Ramsay sedation score. (Line 190 -191) Patients will be only undergone conscious sedation and thus the expected duration that the patient is under the influence of sedation is 1 to 2 hours.
Comment:

Statistics

In the statistics section the stated primary outcome is "pain level during oocyte retrieval" which is to be measured by VAS scale, thus it will be a continuous outcome. The statistical plan is to analyze this data by Mann-Whitney test. Even if the data are skewed, the sample size is large enough to consider a t-test. Please explain why was this test chosen.

Is there a plan for secondary analysis?

Response: Since the sample size if large, despite the pain score will not be normally distributed, t-test will be used for analysis. There is no plan for secondary analysis.

Comment:

Safety monitoring

Is there a plan to record adverse reactions from TENS such as skin rash?

Response: Yes, side-effects/adverse effects of TENS including skin rash will be recorded. (Line 186 – 187)