OBSTETRICS & GYNECOLOGY

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Date: Apr 12, 2021
To: "Klaira Lerma" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-603

RE: Manuscript Number ONG-21-603

Transcutaneous electrical nerve stimulation for pain management during aspiration abortion up to 83-days gestation

Dear Dr. Lerma:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 03, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a well conducted and written study comparing IV sedation to TENS for people undergoing aspiration abortion. It certainly adds to our understanding of how to manage pain during an aspiration abortion. I do have a few comments that I feel would make the paper stronger.

I had never heard of TENS before reading this paper. I learned that it is over the counter in the discussion. Please consider a more robust discussion of TENS in the intro and help the reader understand what TENS is and why the authors felt this study was needed (I'm so glad it was done, but I didn't arrive at that conclusion until the discussion).

Abstract - clear and concise

Intro
Lines 97-98 "Oral sedation and IV sedation, with paracervical block, are not equivalent, with
98 those having IV sedation reporting clinically significantly less pain." Reads awkwardly. I had to read it twice. Consider rephrasing.
Lines 112-114—I appreciate the context of TENS for hscope. I think a more robust explanation of how it is used for other outpatient procedures is warranted however. Was it just the hscope study that made the authors design this trial? After reading the discussion, I learned that TENS has been used for med ab patients, consider including this information in the intro.

Methods
Lines 154-161: how did the authors develop this protocol for adjusting the TENS? Does it follow standardized guidelines for the device? My expectation is that the audience will have no familiarity with TENS, so some explanation about what standard use of TENS is would be helpful.

Results
Clear and easy to follow.

Discussion
Line 344: here is would be nice to understand what usually happens after a patient gets TENS. Is there any minimal observation time for TENS? Would the only observation needed be for the abortion procedure itself?
Line 352: consider changing to "our study generalizable to a US population"

Reviewer #2:

Introduction:
the authors state previously TENS has not been studied in first trimester abortion, however, the following study did evaluate this question, though intervention was after the procedure: (Platon B, Andréll P, Raner C, Rudolph M, Dvoretsky A, Mannheimer C. High-frequency, high-intensity transcutaneous electrical nerve stimulation as treatment of pain after surgical abortion. Pain. 2010 Jan;148(1):114-119. doi: 10.1016/j.pain.2009.10.023. Epub 2009 Dec 2. PMID: 19959293. RCT, post-op pain relief following first trimester abortion); this study should be included in the introduction/discussion, as it supports this manuscripts assertion

otherwise, the introduction is well written, concise, and supports the need for the current study

Methods:

methodology is generally well written, however, i question that utility of blinding the patients if one of the arms is a sedative, i.e. the patient receiving the sedative would realize either during/after the procedure that they were in fact sedated, vs the patients not in the sedative group would similarly realize that they are not sedated, how do the authors account for this type of bias, i don't think this really diminishes the results, i just think it is not possible to truly blind a patient if one arm is placebo and one arm is a drug that impacts cognition, thus i do not think you can realistically call this a blinded study, since the investigators were also unblinded unless level of sedation was monitored in both groups and were similar; additionally in the results 80% of patients knew which arm they were in, which again, argues against the fact that this was a blinded study, while the intention maybe was to have participants blinded

line 195: has pain at the time of aspiration been reported as the worst pain related to this procedure? if so, please provide citation;

Results:

line 286-287: in the manuscript the authors state the in the intention to treat analysis the TENS VAS scores for block, dilation and aspiration have a statistically significant difference compared to IV sedation, however, the reverse appears to be true, the per protocol table shows TENS patient pain to be significantly higher at multiple instances compared to IV; and ITE analysis reveals that only dilation and baseline pain are significantly different; additionally i am confused about how the TENS group pain scores indeed are higher in the ITE than the per protocol group with IV sedation scores remaining the same, but are no longer statistically significant; this does not seem to make sense

Discussion:

line 330-339: do the authors have an explanation for why pain scores were under-predicted by the providers? even the patient anticipated pain scores were higher. If the study was designed using anticipated or actual pain scores in the study, would the sample size to demonstrate non-inferiority be different?

line 347: again, i question whether the patients were truly blinded if the vast majority were aware of what group they were in

the overall conclusion that TENS is non-inferior to IV sedation: while this is true strictly speaking for aspiration in both the ITE and per-protocol analyses patients in the TENS group experienced more pain during parts of the procedure compared to the IV sedation group, and one might argue that overall it is inferior for controlling pain, especially if conclusion is based on the per protocol analysis; i might re-state your conclusion as the following "TENS was found to be non-inferior compared IV sedation for pain experienced with aspiration, but was found to have significantly higher pain scores compared to IV for other portions of the procedure"

Reviewer #3:

General overview

Manuscript # ONG-21-603 reviews a randomized controlled trial that aims to evaluate the effectiveness of TENS for early surgical abortion pain management in comparison to standard intravenous sedation. The investigators demonstrated that TENS might be a useful alternative to IV sedation, when either are combined with paracervical block. After a careful and unbiased analysis of the results, I believe their conclusion that TENS is "non-inferior" to IV sedation is an exaggeration.

The study is randomized appropriately, and both groups apparently begin the study with similar prognoses for achieving the predesigned outcomes. Statistical methods seem appropriate. Clinicians and research personnel were not blinded to group allocation, and 80% of the subjects in both groups were able to accurately determine the group to which they were assigned. What effect this condition may have had on the results is uncertain.

The manuscript is well organized, easy to follow, and mostly well-written. The Discussion section contains sentence fragments, run-on sentences, phrases with vague meaning, and unnecessary adjectives. It requires substantial revision to maintain adherence to acceptable technical writing principles.

Specific questions/comments
I disagree with the conclusion that the study established noninferiority between TENS and IV sedation for the following reasons:
1. 9 of 55 subjects in the TENS group (17%) required rescue treatment with IV sedation, presumably because TENS was not effective for them. These subjects would have had a powerful influence on the results, but they were not counted in the per protocol analysis, and in the Intention to Treat analysis, their response was probably influenced more by IV sedation than TENS.
2. These 9 subjects were completely omitted from the "Likelihood to recommend" analysis because, for some reason, the outcome was measured only by per protocol groups, not intention to treat. Even without their inclusion, the difference nearly reached statistical significance, in favor of IV sedation.
3. Significantly improved pain control was found in the IV sedation group with speculum insertion, tenaculum placement, paracervical block, and cervical dilation. These are important steps of the abortion procedure.

Why were the outcomes in Table 3 analyzed only by per protocol and not intention to treat?

Did the 9 subjects from the TENS group who required crossover treatment continue to receive electrical stimulation in addition to IV sedation? Did they all receive both midazolam and fentanyl? If not, how was the determination made of which drugs to administer?

Overall acceptability of the pain management method should be a primary outcome measure , measured as a categorical variable (acceptable vs. not acceptable), and analyzed based on "Intention to Treat" groups.

In the Discussion, the authors illustrate conditions such as lack of clinician blinding and subject impairment, that may have biased the study in favor of IV sedation, yet no conditions were noted that may have biased the results in the other direction. My impression would be that the lack of blinding would be just as likely to tilt results in either direction, possibly based on the preconceived biases of the clinicians and study personnel. I am also not aware of any good argument that recent receipt of IV opiates or benzodiazepines would make anyone more likely to "over rate" their pain experience.

STATISTICS EDITOR COMMENTS:

General and lines 60-61 and 157-162: How can the participants be blinded to treatment, in that they were were able to feel the effect of the TENS and gave feedback to the staff as to the level required? Does not seem to qualify as a blinded protocol, although the groups were randomized.

Fig 1: Need to analyze results from the ITT groups and then for the PP groups.

Fig 2: The primary outcome should first be shown for the ITT analysis, not the PP analysis

lines 195-198: The primary outcome was pain evaluation at the rime of aspiration, all other times are secondary. Should clearly separate the primary from all secondary outcomes.

Table 1: Since there were from 46 to 55 in each column, the %s should be rounded to nearest integer %, not cited to 0.1% precision.

Table 2: Need to clearly separate the primary from secondary outcomes and the primary outcome should be in format of non-inferiority.

EDITORIAL OFFICE COMMENTS:

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5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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Sincerely,
John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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