

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Nov 01, 2019
To: "Jennifer Villavicencio" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1859

RE: Manuscript Number ONG-19-1859

Buffered Lidocaine on Pain Scores during Vulvar Biopsy Infiltration: a Randomized Controlled Trial

Dear Dr. Villavicencio:

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 Nov 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a well-written, well-executed randomized controlled trial examining the pain score difference from vulvar biopsies after infiltration with buffered lidocaine or lidocaine alone. The study found no significant difference in pain scores at any point in the trial although there was a trend toward decreased pain in the buffered lidocaine group.

The authors are to be commended for submitting a negative study. That being said, your conclusion is the main flaw of your paper. The entire point of conducting a RCT is to provide good science. If you did not find a difference then your conclusion should reflect your findings: "Given the more complicated nature of mixing buffered lidocaine and in light of shortages, unless further data becomes available, buffered lidocaine should not be used over plain lidocaine to reduce pain in vulvar biopsies."

In addition, I have the following questions or comments:

1. Were there any adverse side effects in either group?
2. Please include any other interventions that were done or standardized to decrease pain. For example, was topical medicine or oral analgesics prohibited? Heat? Ice? Was there a universal script prior to injection of the lidocaine? Post-biopsy instructions and pain relief?
3. Details of the biopsy should be included - were they all punch biopsies? How was hemostasis obtained.
4. Why do you posit that so many patients reported 0 pain during infiltration - wouldn't most people feel a little pain with the needle insertion?
5. Why do you think that you had negative results given the previously demonstrated differences in other gynecologic procedures?
6. There are two sets of figures and tables at the end of the paper.

REVIEWER #2:

The authors submit an RCT comparing buffered lidocaine to non-buffered lidocaine for vulvar biopsy. The primary outcome was pain. There were no significant differences reported in outcomes. The authors attribute this to a smaller difference in the use of the pain scale.

Overall, I like the way this reads. It's straightforward and is one simple project. I would avoid the casual use of the words "significant" or "non-significant" trend: you did point out clearly that there were not significant differences.

My copy includes the vulva diagram twice - I wonder if you can find a better version (less blurry, etc)

REVIEWER #3:

Study is nicely done. Study design is well thought out. Hypothesis is clear. The study addresses a common question around a common procedure: how to make a patient more comfortable during a vulvar biopsy. The abstract was brief and on target. Your introduction was clear and laid out a logical approach to this. Methods and results were clear. Your conclusions however are not as clear. The data from the study does not support your hypothesis. You admit this, but then go on to try to justify ongoing use of buffered lidocaine. I think it would make more sense to recognize your negative results and think about why they are negative and what you would do next to evaluate this further.

STATISTICAL EDITOR'S COMMENTS:

1. lines 154-161: Should state which SD estimate was used to arrive at sample size = 64 per arm (it was the larger SD of 30, the smaller SD would have required only ~ 32 per arm). Also, need to change the final version of the paper to conform to the RCT abstract format.
2. lines 184-187: The first sentences should be reporting the primary outcome, then the secondary ones.
3. lines 193-196: Interesting, but since these were not the primary outcome and were not part of the initial power/sample size calculation, the NS results and the proportions cannot be generalized.
4. lines 204-207: Using the a priori threshold, the differences cited were all NS, therefore there was no trend. The numerical differences cited were simply random variation and no conclusion can be generalized, except that the primary outcome was NS. That is, this RCT, as designed and formatted, had a negative outcome. There is no other conclusion or trend.
5. Table 1: Since this was an RCT, there is no need to statistically compare the baseline characteristics. Any difference is thought to be due to random chance. Need units for age, BMI.
6. All Tables: Given the size of the denominators, the %s should be rounded to nearest integer, there is no basis for citing precision to nearest 0.1%.
7. Table 3: Need to clearly demarcate the primary outcome measure (during infiltration) from the others. The N's reported are actually PP, even though the number excluded were quite small. Should report the ITT (all 129), then the PP (the 125 reported), for completeness.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is

an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

5. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

6. 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 and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.

* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com>

/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

16. The Journal's Production Editor had the following comments about the figures in your manuscript:

"Figure 1: What is the source of this illustration?"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

17. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and

* A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, 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 Nov 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

November 21, 2019

Nancy C. Chescheir MD
Editor-in-Chief
Obstetrics and Gynecology

Dear Dr. Chescheir,

We are pleased to submit our **revised** manuscript entitled “Buffered Lidocaine on Pain Scores during Vulvar Biopsy Infiltration: a Randomized Controlled Trial” for consideration as an Original Research article in *Obstetrics and Gynecology*. **The lead author (author of this cover letter) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects have been omitted; and that any discrepancies from the study as planned and registered have been explained.**

The point by point revisions organized by reviewer and statistical editor are listed below (and tracked in the manuscript itself. The original cover letter is copied below that.

Reviewer #1:

- a. Conclusion has been revised to reflect the negative outcome.
- b. Lines 178-179 state no complications/adverse events in either group
- c. Lines 133-134 were added to address questions regarding pre-procedure pain control interventions and use of a universal scripts (we did not use any additional pain control methods aside from the lidocaine and there was no universal script used).
- d. Lines 137-139 addresses details of biopsy and hemostasis.
- e. Discussed author’s theory on why 19 patients reported a score of 0 during infiltration.

Reviewer #2:

- a. Conclusion has been revised to reflect the negative outcome (and causal use of term “significant” has been addressed)

Reviewer #3:

- a. Conclusion has been revised to reflect the negative outcome.

Statistical Editor:

- a. SD estimate inserted into abstract (lines 45-50) and is also located in Methods (lines 142-152)
- b. First sentence now reporting primary outcome
- c. Removed generalization regarding no pain during infiltration but kept the report of result given interesting that both groups had several patients report no pain during infiltration (addressed in discussion).
- d. Word “trend” no longer appears in manuscript and nonsignificant conclusion more clear
- e. Units for age and BMI added to Table 1, p value column removed from Table 1

- f. Table percentages and corresponding percentages in body of manuscript rounded to nearest integer
- g. Abstract revised to reflect above changes and be in compliance with requirements.

Editorial Office:

- a. **OPT IN: Yes, please publish my point by point response letter.**
- b. The data sharing statement has been added as a box under the references in the manuscript.
- c. All tables and figures are original to this project. The vulvar figure was drawn using generic references and then customized to allow researchers to label the area the biopsy had taken place. No permissions or rights are required.
- d. This manuscript utilizes definitions consistent with the Revitalize initiative.
- e. There was no external funding for the research and the authors have no financial disclosures.
- f. Database was created by the authors and information was entered into database by the authors. The information was crosschecked by authors to determine accuracy.
- g. Revised Abstract word count: 297, Revised Manuscript Page/Word Count: 18/3641
- h. All abbreviations used are standard
- i. No virgule symbols are used in the manuscript with exception for data representation
- j. The effect size has been added to p values throughout the manuscript
- k. Figure 1 has been removed from the manuscript and attached separately as a .TIFF as per instructions listed in #16. Figure 2 has been removed from the manuscript and attached separately as a word document (flowchart created in word).

Original Cover Letter:

Vulvar lesions are commonly encountered in the outpatient gynecology setting and often require a vulvar biopsy to aid in diagnosis and treatment. However, the vulva is a particularly sensitive region both in its anatomy and the anxiety associated with procedures in this area. Local anesthetic, commonly a 1% solution of lidocaine, is often injected pre-procedure to dull the sensation and improve patient satisfaction. Yet it is well known that lidocaine injection itself can be painful given its acidity. Multiple studies have looked at the role of pre-procedural buffered lidocaine but few have been in the field of obstetrics and gynecology, and none to date have specifically looked at vulvar procedures.

Thus we designed a double-blinded, randomized controlled trial to investigate the impact on visual analog scale (VAS) pain scores with the use of buffered lidocaine compared to non-buffered lidocaine during vulvar biopsy.

A total of 137 women were approached for participation in the study of which four declined to participate, three did not meet the inclusion criteria, and one whose provider felt she was not emotionally able to participate in the study. One hundred and twenty-nine patients were randomized to either the buffered lidocaine group (intervention) or the non-buffered lidocaine group (control), and 125 were analyzed. There were no significant differences between the two groups and baseline pain scores were similar. While there was no statistically significant difference in the primary outcome of mean pain score during infiltration between the two groups,

there was a trend towards lower pain scores in the buffered lidocaine group ($p=0.3$). Similarly, 16% of patients in the buffered lidocaine group reported a VAS pain score of 0 over the entire procedure, compared to only 6.5% in the non-buffered lidocaine group ($p=0.09$).

We believe our paper will be of much interest to readers of *Obstetrics and Gynecology* because vulvar procedures are commonly performed in the outpatient setting and the use of buffered lidocaine to potentially decrease pain is a feasible intervention that may improve the patient experience.

This manuscript has not been previously published and is not under consideration in any other peer-reviewed media. We presented earlier versions of the manuscript as an oral presentation at the regional New England Association of Gynecologic Oncology 2018 Annual Meeting on June 3, 2018 in Camp Neddick, ME and as a poster presentation at the Society for Gynecologic Oncology 2019 Annual Meeting on March 16-19, 2019 in Honolulu, HI.

All authors listed have contributed sufficiently to the project to be included as authors, and all authors have approved the manuscript and its submission to the journal. To the best of our knowledge, no conflict of interest, financial or other, exists. The study was enrolled in Clinicaltrials.gov (NCT02698527) and was approved by the Women and Infants Institutional Review Board (IRB 792658/14-0130).

Thank you for considering our manuscript for publication. We look forward to hearing of the outcome of our submission.

Please address all correspondence concerning this manuscript to us at
jenvillavicencio@gmail.com

Sincerely,
Jennifer Villavicencio, MD and Amita Kulkarni, MD