OBSTETRICS & GYNECOLOGY

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- 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: Apr 03, 2020
To: "Philip Haraldson" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-393

RE: Manuscript Number ONG-20-393

Botulinum toxin A as a treatment for provoked vestibulodynia: a randomized controlled trial

Dear Dr. Haraldson:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by May 03, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a well done randomized controlled trial comparing botulinum toxin A and placebo for patients with provoked vestibulodynia.

1. Introduction: Please spell out abbreviations at first mention in the manuscript (PFM, BTA, RCT).

2. Introduction: Please provide more rationale for the dose of botulinum toxin A chosen.

2. Methods: Please add a figure to indicate where the injections were placed in the bulbocavernosus muscles. This will be helpful to readers. What was the role of the EMG device? To confirm the needle was in the muscle?

3. Methods: Please clarify that the tampon test recorded pain with insertion only, not including removal of a dry tampon which can be uncomfortable.

4. Results Table 1: Please clarify that infections means history of past infections I assume?

5. Results: Table 1: Contraceptives seems like a broad category. Why collect this information and report it? What impact would it have on the study?

6. Results: Table 1: Please define primary and secondary PVD. How was the cause of PVD determined in the subjects for secondary PVD?

7. Results: While I appreciate the figures, there also needs to be a Table 2 that clearly reports the pain scores for each group at each time point measured.

8. Results: Figure 3b: It is difficult for the reader to interpret what is going on here. Is this showing the pain score at visit 3 and at visit 5, it doesn't appear that the pain score is declining over time. I think the data need to be represented in a more intuitive way.

9. Discussion: I appreciate the authors' tempered interpretation of the data. Did the authors do any assessment of subject satisfaction with the treatment and/or ability to detect which group they were in? Did the authors measure the pain of injection? Is this a treatment that participants would want to continue?

REVIEWER #2:

Overall, this is a well-designed RT evaluating botulinum toxin A injections in women with PVD and overactive (hypertonic) pelvic floor muscle dysfunction. My comments and queries are for the most part minor.

Introduction:

Add "(PFM)" following "pelvic floor muscles in the 3rd line of the second paragraph of the introduction. Otherwise, "PFM" in the 5th line of that paragraph is not identified.

Add "(BTA)" following "botulinum toxin A" in the 2nd line of the 3rd paragraph of the introduction.

"Only two double blind RCTs have been published…" Please provide a line on why it is postulated there was no effect or a comment on the methodology or limitations of these studies to show why you are presenting your positive effect hypothesis and proceeding with the current study.

Materials and Methods:

Study design:

Why were the bulbocavernosis muscles injected and not the pubococcygeus?

Please specify what substance served as the placebo- saline?

"pain upon touch"- how was this determined? By neurosensory (cotton swab) exam? Please clarify.

How many of the participants were doing pelvic floor physical therapy? Where participants permitted to be doing pelvic floor physical therapy during the course of the study?

Can the authors provide a diagram to show their injections sites? Or at least clarify where in the superior-inferior plane the injections were targeted.

Outcome measures:

Primary outcome: Please add temporality. When was the primary outcome determined, meaning how many weeks after injection?

Secondary outcome: please define "safety aspects" - are you referring to incontinence or adverse events? Needs clarified.

Procedure:
Why was 50 units of BOTOX chosen as the dose? Why was 100 units not chosen?

Results:
Pain ratings:
Line "Within-group comparison in means (Figure 3a)…. from baseline to post treatment…" Please clarify the time course for "post treatment." Is this referring to 3 months after the first set of injections or 6 months after the first two sets of injections? If both of these are analyzed together, then why were they not separated in the analysis?

The reference to the "tampon test" in the second paragraph under the pain rating section is a bit confusing because there is the weekly tampon insertion the patients were recording in their e-diary, and then the tampon tests done at the procedural visits. I recommend adding "tampon test during the study visits" or something to that effect to clarify for the reader.

Discussion:
Please include a few sentences on the role of pelvic floor physical therapy in conjunction with BTA injections.

In the first line, separate "50unitsof" into separate words.
Add a "." after Peterson et al.
6th line of the 4th paragraph: "choose" should be "chose"

Table 1:
50% of these women were on contraceptives, can the authors specify if these were combined oral contraceptives (birth control pills) versus progestin-only contraceptive devices vs. non-hormonal? This may be important in PVD.

Infections- this must be previous infection, as in history of these infections? Please clarify in the table that this is history of infection.

REVIEWER #3:

1. The approved use of BTX needs to be stated and off label use declared

2. Demographically was there any information collected on the duration of the patient history of vulvodynia diagnosis, prior treatments (ie pelvic floor muscle rehabilitation, surgery, and mental health assessment)?

3. Were all procedures preformed in office without analgesia?

4. Could consider exclusion if they were not having vaginal intercourse for a duration of time for example 1 year of abstinence prior to study enrollment. Did the authors also take in consideration patients who are in lesbian relationships?

5. Why was a standard perineometer not used instead of cystometric catheters?

6. Explain the purpose of EMG leads during injection?

7. Could the authors discuss historical alternative treatment of vestibulectomy in treatment of this group of patients and why botulinum toxin injection is considered?

STATISTICAL EDITOR'S COMMENTS:

Abstract: Should conform to our abstract template for RCTs.

Table 1: The groups are randomized, so there is no need to statistically compare the cohorts for baseline characteristics. Any difference is thought to be due to random chance. Should omit the columns of Chi-square and p-values and simply list the values.

pg 6, para 1: Primary outcome and page 10, section Statistics: "post-treatment period is defined as the average of all visits after visit 1"

Therefore, need to clearly separate the primary from all other outcomes. The sample size calculation is based on discerning a difference of 20 in VAS with an estimated SD = 31. However, the exposition of results show differences in each group vs that group's baseline measurements and at various times, not apparently aggregated into one post treatment mean VAS as outlined in the stats methods. The difference in pre vs post treatment for the placebo group is interesting, but not relevant to the primary outcome. The demonstration of NS difference in VAS scores at baseline for cohorts subsequently treated with placebo vs BTA is not relevant and any difference would be due to random chance.

In summary, various differences are cited with statistical significance, but the proposed primary outcome (difference in follow-up VAS pain scores) are not clearly stated, but appear not to be significant.

Need to clarify and state whether the primary outcome was significantly different or not, thus was this an RCT with negative results or positive conclusions? All other outcomes were secondary, were not part of the power analysis and are of secondary interest.

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. 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).

4. 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.

5. 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.

6. 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).

7. 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.

8. 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.

9. 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.

10. 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.

11. 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%").

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"Figure 1: This is a box, please rename and renumber.
Figures 2-6: Please upload as figure files on Editorial Manager. "

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.

13. 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/ifauth.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.

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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 30 days from the date of this letter. If we have not heard from you by May 03, 2020, 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

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April 29, 2020

Karolinska Institutet
Danderyd Hospital
Department of Clinical Sciences
Division of Obstetric & Gynaecology
Philip Haraldson, MD

To the Editor of Obstetrics & Gynecology

Dear Sir/Madam,

We hereby submit our revised manuscript: **"Botulinum Toxin A as a Treatment for Provoked Vestibulodynia: a Randomized Control Trial".** We thank you and the reviewers for all the valuable comments on the manuscript. Below is a point-by-point list of each question with the corresponding responses.

We have used track changes in the manuscript to highlight changes we have made, except for the abstract and the result section which have been substantially re-written.

The study was pre-registered 16 May 2016 at ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT02773641. After the revision, the study still does not deviate from the protocol registered in 2016.

Manuscript Number ONG-20-393

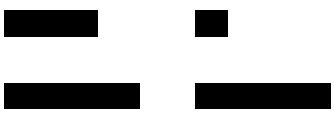
REVIEWER COMMENTS:

REVIEWER #1:

This is a well done randomized controlled trial comparing botulinum toxin A and placebo for patients with provoked vestibulodynia.

1. Introduction: Please spell out abbreviations at first mention in the manuscript (PFM, BTA, RCT).

Response: The abbreviations for Botulinum toxin A = BTA, Pelvic floor muscles = PFM and Randomized controlled trial = RCT are now spelled out in the introduction.



2. Introduction: Please provide more rationale for the dose of botulinum toxin A chosen.

Response: At the point of initiating this study only one RCT was published and had used 20 units of BTA with no difference in pain reduction between BTA and placebo. The rationale for using 50 units in this study has been explained more in detail in the introduction, please see third paragraph, page 4, and further discussed in the second paragraph of the discussion, page 14.

3. Methods: Please add a figure to indicate where the injections were placed in the bulbocavernosus muscles. This will be helpful to readers. What was the role of the EMG device? To confirm the needle was in the muscle?

Response: We could provide an illustration, but it is difficult with short notice. However, both injection sites were in the bulbocavernosus muscle, in the superficial part of the PFM, below the plane of the levator ani even though a diffusion of the toxin to other PFM might have occurred. This information has been added on page 8. The EMG system was used to ensure correct deposition of the drug in the muscle, which is clarified in the second paragraph, page 8.

4. Methods: Please clarify that the tampon test recorded pain with insertion only, not including removal of a dry tampon which can be uncomfortable.

Response: Clarified in the last paragraph, page 6.

5. Results Table 1: Please clarify that infections means history of past infections I assume?

Response: Changed to History of past infections in Table 1.

6. Results: Table 1: Contraceptives seems like a broad category. Why collect this information and report it? What impact would it have on the study?

Response: We agree with this comment, the information on contraceptives does not have any impact on the study, it is just a detail that is commonly reported in clinical studies. The data on contraceptives has been removed from Table 1.

7. Results: Table 1: Please define primary and secondary PVD. How was the cause of PVD determined in the subjects for secondary PVD?

Response: Primary PVD was defined as pain at first tampon insertion or intercourse attempt. Secondary was defined as pain at tampon use or vaginal intercourse, with a prior history of a pain free period. The cause of secondary PVD was based on medical history and questionnaire data. The definition has

been added to Table 1, page 18-19.

8. Results: While I appreciate the figures, there also needs to be a Table 2 that clearly reports the pain scores for each group at each time point measured.

Response: Table 2 and 3 have been added for clarification of the results. Table 3 shows the results of the primary outcome of dyspareunia or pain at tampon use at each visits 1,3 and 5, see page 21.

9. Results: Figure 3b: It is difficult for the reader to interpret what is going on here. Is this showing the pain score at visit 3 and at visit 5, it doesn't appear that the pain score is declining over time. I think the data need to be represented in a more intuitive way.

Response: Figure 3b shows the difference in difference in pain scores between BTA and placebo. It is correct that the pain score does not decline between visit 3 and 5. By also including Table 3, the results will be more clear to the reader.

10. Discussion: I appreciate the authors' tempered interpretation of the data. Did the authors do any assessment of subject satisfaction with the treatment and/or ability to detect which group they were in? Did the authors measure the pain of injection? Is this a treatment that participants would want to continue?

Response: Thank you for that comment. No assessment of subject satisfaction with the treatment was done and we did not measure the pain of injections. It would have been valuable to have done that. The injections are painful, but it is for a very short time and none of the participants dropped out for this reason.

REVIEWER #2:

Overall, this is a well-designed RT evaluating botulinum toxin A injections in women with PVD and overactive (hypertonic) pelvic floor muscle dysfunction. My comments and queries are for the most part minor.

Introduction:

1. Add "(PFM)" following "pelvic floor muscles in the 3rd line of the second paragraph of the introduction. Otherwise, "PFM" in the 5th line of that paragraph is not identified.

Response: The abbreviation PFM has been spelled out in the introduction.

2. Add "(BTA)" following "botulinum toxin A" in the 2nd line of the 3rd paragraph of the introduction. P

Response: The abbreviation BTA has been spelled out in the introduction.

3. "Only two double blind RCTs have been published…" Please provide a line on why it is postulated there was no effect or a comment on the methodology or limitations of these studies to show why you are presenting your positive effect hypothesis and proceeding with the current study.

Response: We have re-written paragraph 3, page 4 in the Introduction to explain the rationale for our study design. We have also expanded paragraph 2, page 14, in the discussion to further discuss the methodological differences of the previous studies.

Materials and Methods:

Study design:

4. Why were the bulbocavernosis muscles injected and not the pubococcygeus?

Response: This is an important question. We chose to focus on m bulbocavernosus which is very often tensed in PVD patients. The muscle is easy to palpate and was injected both in the lateral and medial portion. We believe that there might have been an additional diffusion of the toxin also to the superficial part of the levator ani (m pubococcygues/puborectalis), specially during the medial injection close to the midline muscle insertion. This is discussed in the Discussion, second paragraph, page 14, where we also suggest that an additional effect might be achieved if more PFM are injected.

5. Please specify what substance served as the placebo- saline?

Response: The placebo is saline 9 mg/ml, this is added in the first paragraph, page 8.

6. "pain upon touch"- how was this determined? By neurosensory (cotton swab) exam? Please clarify.

Response: In the inclusion criteria, only the patients reported symptoms are included. For confirming the diagnosis of PVD, the cotton-swab test was used, see paragraph 2, page 7.

7. How many of the participants were doing pelvic floor physical therapy? Where participants permitted to be doing pelvic floor physical therapy during the course of the study?

Response: We have no data on what participants were doing pelvic floor physical therapy at the start of the study. However, during the study, no such therapy was allowed. This information has been added to the second paragraph, page 8.

8. Can the authors provide a diagram to show their injections sites? Or at least clarify where in the superior-inferior plane the injections were targeted.

Response: We could provide an illustration, but it is difficult with short notice. However, both injection sites were in the bulbocavernosus muscle, in the superficial part of the PFM, below the plane of the levator ani even though a diffusion of the toxin to other PFM might have occurred. This information has been added on page 8.

Outcome measures:

9. Primary outcome: Please add temporality. When was the primary outcome determined, meaning how many weeks after injection?

Response: The primary outcome was self-reported pain during intercourse or pain at tampon use at insertion the last month using a VAS (0-100) measured at visit 1 (baseline), 3 and 5 (post-treatment). This has been clarified in the last paragraph, page 6.

10. Secondary outcome: please define "safety aspects" - are you referring to incontinence or adverse events? Needs clarified.

Response: “Safety aspects” has been replaced by “monitoring of possible BTA related adverse events” in the paragraph on Outcome measures, page 6.

Procedure:

11. Why was 50 units of BOTOX chosen as the dose? Why was 100 units not chosen?

Response: “At the point of planning this study only one RCT on BTA was published. 20 units of BTA had been used with no difference in pain reduction between BTA and placebo. We therefore considered that 50 U BTA would be a sort of natural next step in dose escalating for PVD. The rationale for using 50 units in our study has been explained more in detail in the introduction, see third paragraph, page 4, and further discussed in the second paragraph of the discussion, page 14.

Results:

Pain ratings:

12. Line "Within-group comparison in means (Figure 3a)…. from baseline to post treatment…" Please clarify the time course for "post treatment." Is this referring to 3 months after the first set of injections or 6 months after the first two sets of injections? If both of these are analyzed together, then why were they not separated in the analysis?

Response: Post-treatment refers to the mean value of the pain score at visits 3 and 5. In Fig. 3b, visits 3 and 5 are analyzed separately. Please also see the new Table 3 where the pain ratings are shown for each visit separately.

13. The reference to the "tampon test" in the second paragraph under the pain rating section is a bit confusing because there is the weekly tampon insertion the patients were recording in their e-diary, and then the tampon tests done at the procedural visits. I recommend adding "tampon test during the study visits" or something to that effect to clarify for the reader.

Response: Thank you for this comment. The tampon test was only done every week at home between visits. No tampon tests were carried out during the visits. The mean value of the weekly tampon tests between visits were used for the statistical analyses and were reported for each visit. We have added this information in the paragraph “Procedure”, page 6-7. By doing that, the results of the tampon test, page 10, is easier to follow and we have also added “weekly” in the results, second paragraph, page 10.

Discussion:

14. Please include a few sentences on the role of pelvic floor physical therapy in conjunction with BTA injections.

Response: We have added the following text in the Discussion, first paragraph, page 14 “In this study, the participants were told not to do any physiotherapy for the PFM to avoid bias. However, in clinical practice, a treatment of appropriate BTA dose in combination with physiotherapy will most probably have an additive effect on the muscle response.”

15. In the first line, separate "50unitsof" into separate words. - done
Add a "." after Peterson et al. - done
6th line of the 4th paragraph: "choose" should be "chose" - done

Table 1:
16. 50% of these women were on contraceptives, can the authors specify if these were combined oral contraceptives (birth control pills) versus progestin-only contraceptive devices vs. non-hormonal? This may be important in PVD.

Response: In accordance with another reviewer we have chosen not to include the data on contraceptives in Table 1. If we would have analyzed the various contraceptives used, the groups would have been too small to be able to draw any conclusions on possible impact on PVD.

17. Infections- this must be previous infection, as in history of these infections? Please clarify in the table that this is history of infection.

Response: This has been clarified in Table 1.

REVIEWER #3:

1. The approved use of BTX needs to be stated and off label use declared.

Response: Approval for off-label use of botulinum toxin A (Botox®) was obtained from the Swedish Medical Products Agency. This information has been added in the paragraph "Participants", page 5.

2. Demographically was there any information collected on the duration of the patient history of vulvodynia diagnosis, prior treatments (ie pelvic floor muscle rehabilitation, surgery, and mental health assessment)?

Response: The duration of PVD symptoms was mean 6 years for all participants with no difference between BTA and placebo. Regarding prior treatments, most participants had tried various treatments, most commonly topical lidocaine, pelvic floor physiotherapy and psycho-sexual counseling. Only two participants, one in each group, had previously had PVD surgery. Regarding mental illness, only four patients were on anti-depressive drugs for mild to moderate anxiety/depression disorder. Severe psychiatric disorders were exclusion criteria. This information is added in the results section "Subjects characteristics", page 9.

3. Were all procedures performed in office without analgesia?

Response: No analgesia was used. Using the intra-vaginal approach, avoiding the pain sensitive vestibular mucosa, no analgesia was needed.

4. Could consider exclusion if they were not having vaginal intercourse for a duration of time for example 1 year of abstinence prior to study enrollment. Did the authors also take in consideration patients who are in lesbian relationships?

Response: Thank you for this comment, it is an important aspect. During the planning of the study and defining primary outcome, we discussed the matter. If we only include PVD women with regular vaginal intercourse, there would be a problem recruiting. By using the pain score "Pain during intercourse or pain at

tampon use the last month", we can include most PVD women; those who still are practicing vaginal intercourse, those who have no partner, those who are able to use a tampon and hopefully also lesbian women. In addition, we also have the weekly tampon test as a supplementary pain measure.

5. Why was a standard perineometer not used instead of cystometric catheters?

Response: Much effort was made to find an already existing method for measuring the tone and function of the PFM. We had hoped to be able to use the same method used by Naess et al, ref. 11. However, that method was not commercially available. One advantage of the catheter balloon is that it was placed in the same plane as the injected muscles, which is not quite the same with a perineometer.

6. Explain the purpose of EMG leads during injection?

Response: The EMG system was used to ensure correct deposition of the drug in the muscle, which is clarified in the second paragraph, page 8.

7. Could the authors discuss historical alternative treatment of vestibulectomy in treatment of this group of patients and why botulinum toxin injection is considered?

Response: The best treatment outcome for women with PVD is considered a multimodal approach, including pain management for the vestibular pain sensitivity, physiotherapy for the PFM to restore tone and function and psychosocial adjustments. The rationale for using BTA in clinical practice would be to use it in patients where it is difficult to restore the function of the PFM with PT or exercises. BTA is safe and less invasive compared to surgery, which is generally recommended as last treatment option.

STATISTICAL EDITOR'S COMMENTS:

Abstract: Should conform to our abstract template for RCTs.

Response: The abstract has been re-written using the suggested template for RCTs.

1. Table 1: The groups are randomized, so there is no need to statistically compare the cohorts for baseline characteristics. Any difference is thought to be due to random chance. Should omit the columns of Chi-square and p-values and simply list the values.

Response: We agree with the statistical reviewer that random assignment of treatment status should provide two similar groups at baseline. However, in order to demonstrate that randomization was indeed successful and to exclude potential bias we present chi2 and p-values as test that this is in fact the case.

2. pg 6, para 1: Primary outcome and page 10, section Statistics: "post-treatment period is defined as the average of all visits after visit 1"

Therefore, need to clearly separate the primary from all other outcomes. The sample size calculation is based on discerning a difference of 20 in VAS with an estimated SD = 31. However, the exposition of results show differences in each group vs that group's baseline measurements and at various times, not apparently aggregated into one post treatment mean VAS as outlined in the stats methods.

Response: Thank you for this comment. We have presented the differences in outcomes between the BTA and placebo group post-treatment i.e. visit 3 and 5 (the between group comparison) in the result section. We have now more clearly separated the primary outcome in the result section, page 10. We have added Table 2- 3 where the all results are presented.

3. The difference in pre vs post treatment for the placebo group is interesting, but not relevant to the primary outcome.

Response: We agree that the within-group comparisons are not the main outcome. We have therefore removed the within-groups comparisons in the text not to confuse readers about the main results which are the between-group comparisons. If other researchers are interesting in a possible placebo effect, this results can be seen in Table 3.

4. The demonstration of NS difference in VAS scores at baseline for cohorts subsequently treated with placebo vs BTA is not relevant and any difference would be due to random chance.

Response: To ensure that randomization was successful we want to examine differences in outcomes at baseline. And even if an outcome is different due to random chance, the effect of any treatment would be difficult to interpret due to already existing differences in that particular outcome. This is exactly the case for resting pelvic pressure (which statistically significantly lower in the BTA group). In order to overcome this issue, we control for pre-existing differences at baseline, we employ a difference-in-difference model to estimate the impact of BTA. That is, in this model we not only compare BTA to placebo post-treatment but we also control for any differences at baseline (e.g Wilke RA A Review of Econometric Analysis of Cross Section and Panel Data (2nd ed.) by Wooldridge).

5. In summary, various differences are cited with statistical significance, but the proposed primary outcome (difference in follow-up VAS pain scores) are not clearly stated, but appear not to be significant.

Need to clarify and state whether the primary outcome was significantly different or not, thus was this an RCT with negative results or positive conclusions? All other outcomes were secondary, were not part of the power analysis and are of secondary interest.

Response: We thank you for your comments and agree that the results of primary outcome should be more clear to the reader. We have done several improvements on this matter. First, we have made major changes in the result section, in which we start with reporting the between-groups comparison of the primary outcome = dyspareunia or pain at tampon used the last month. We highlight the result of the primary outcome in the first paragraph of the discussion where we summarize our main findings. We have also chosen to remove the within-groups comparisons in the text not to confuse readers about the main results which are the between-group comparisons. The conclusion has been re-written with a stronger focus on the primary outcome. In addition, we have re-written the abstract clarifying our primary results.

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.

Response: A. OPT-IN: Yes, please 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.

Response: This has been done.

3. 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).

Response: A statement is written at the end of the article.

4. 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.

Response: There is no problem using these definitions.

5. 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.

Response: The manuscript is within the above stated limits.

6. 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).

Response: All guidelines stated above is adhered to.

7. 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.

Response: The abstract has been checked for consistency in regards to the rest of the manuscript. The word count for the abstract is 300 words including the headings.

8. 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.

Response: The abstract has been edited in alignment to the sample abstract.

9. 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.

Response: Abbreviations and acronyms has been used according to guidelines.

10. 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.

Response: The virgule symbol has been cleared in sentences with words.

11. 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%").

Response: We have chosen to express our results according to your suggestion. P-values have been removed in the text throughout the manuscript, except in the Tables. The new Table 2 includes the results of all the between-groups comparisons with differences in means and 95% CI. In Table 3 the Numbers expressed in percentages have no decimals in the manuscript.

12. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 1: This is a box, please rename and renumber.
Figures 2-6: Please upload as figure files on Editorial Manager.

Response: Figure 1 has been renamed Box 1 and all figures are uploaded separately and removed from the manuscript. A “Figure legend” has been added.

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.

Response: “Figure 1” has been renamed “Box 1”. All other figures have been renumbered accordingly. Figures will be uploaded as requested upon resubmission.

13. 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/ifauth.htm.

Response: At this point the authors choose not to pay for open access.

Signed by: 

Philip Haraldson, MD
Corresponding author
[redacted]