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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)*
- Email correspondence between the editorial office and the authors*

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

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Questions about these materials may be directed to the Obstetrics & Gynecology editorial office:

obgyn@greenjournal.org.
RE: Manuscript Number ONG-18-1974

IV Acetaminophen Prior to Pelvic Organ Prolapse Repair, A Randomized Placebo Controlled Trial

Dear Dr. Turner:

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 Dec 10, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a well done randomized controlled trial evaluating preoperative IV acetaminophen for postoperative pain after laparoscopic or vaginal repair of pelvic organ prolapse.

1. Introduction: Reference 6 seems very old to be justifying a claim that we don't give NSAIDs to elderly patients. If this a true recommendation, there must be something more recent on it.

2. Introduction: I don't see any discussion regarding the cost of IV acetaminophen, we are actually not allowed to use it at our institution because it costs more than rectal or oral acetaminophen.

3. Introduction: It seems that the duration of action of IV acetaminophen is 4-6 hours, I would include that in the descriptions on line 81 of the pharmacokinetics.

4. Methods: If the duration of action is 4-6 hours, why is pain at 24 hours the primary outcome? Why not pain at 4 hours postop? What about narcotic use in the first 4-6 hours?

5. Methods: I am concerned about grouping these diverse procedures into "laparoscopic" and "vaginal" It would seem to me that someone having a vaginal obliteratorive procedure would have a different pain experience than someone having a vaginal hysterectomy. Why wasn't the sample limited to people having the most similar surgeries? e.g. all with hysterectomy or all without.

6. Methods: It should be noted that the power for this study is the active agent vs. placebo. Once we get into the subanalyses of laparoscopic active agent vs. laparoscopic placebo, for example, the power is greatly reduced (half the number of subjects).

7. Discussion: Line 293, please clarify that the following two sentences are about abdominal hysterectomy, it is not clear to the reader.

REVIEWER #2:

The design of this clinical trial was thoughtful and well-planned. The intervention was simple which brings valuable information that is highly clinically relevant. The primary outcome was chosen considerately to be both easy to obtain to
minimize missing information but also both applicable to this study as well as generalizable. The reviewer has a few comments for your consideration.

1. The introduction section of the paper flows nicely into the primary aim of the paper. Much of the focus is on pre-emptive use of medications to be given preoperatively for postoperative pain management. There is a thoughtful discussion on the background of intravenous acetaminophen. There is no mention of oral acetaminophen and whether there is previous work utilizing oral acetaminophen for pre-emptive pain control. The reviewer notes the comment on intravenous form having highest postoperative concentrations. Adding any background information known regarding the use of oral acetaminophen for postoperative pain management. This may be useful to highlight other reasons why you chose to study the intravenous route, despite this formulation being more costly.

2. The materials and methods section is quite thorough and the reviewer notes the thoughtful application of the CONSORT guidelines. Inclusion/exclusion criteria, aims, the hypothesis, recruitment, randomization and allocation are all clearly stated. The reviewer appreciates the randomization plan stratified by surgical route as it would account for differences among the two patient populations which would impact pain scores. The allocation concealment methods are adequate with concealment down to the level of container of the medication. It may be informative to the reader when discussing the methods to elaborate that no other preoperative pain medications were given routinely to either group as part of an early recovery after surgery pathway. This was noted later in the discussion but it may be helpful to add earlier in the paper for context.

3. Inclusion criteria state that the intended plan was a 24 hour observational stay; however, some patients appeared to have been discharged early. Pain scores were to be collected q4 hours for 24 hours, including if they were discharged. It is unclear to the reader if these scores were performed independently by the patient while inpatient or if these were proctored by a member of the research team. There may be a difference in scores of those collected inpatient versus those self-collected upon discharge.

4. I would like to comment on the utility of the secondary outcomes also obtained in the study. The APS-POQ-R seems a good choice for a QOL survey regarding pain control. The timeline is appropriate taken at 24 hours postop, when considering in the contest of comparing patients that had a single dose of IV acetaminophen. However, the other survey (PROMIS PI-SF-8a) done at 7 days postop would seem to have little, if any, clinical relevance to a single dose of IV acetaminophen given on postoperative day 0. It would seem unlikely that an impact could be detected 7 days after a single dose of medication with a dosing regimen of every 4-6 hours. If there was a difference the reviewer feels there may be too many other variables that could have impacted this score to be able to attribute the difference to the IV acetaminophen alone.

5. In the sample size calculation, the authors note that there is little information on which to base a clinically meaningful change in VAS scores for the surgeries of interest. A single calculation was made and applied to both vaginal surgery group and the laparoscopic surgery group. The reader questions whether it may have been useful to use different known mean/standard deviations of VAS pain scores to make separate calculations for each surgical group. The mean/standard deviations used from prior studies are very different between the two groups. If you chose against doing this, it may be helpful to mention the reasoning.

6. In the results section, the reviewer appreciates the figure 1 denoting any withdrawal or loss to follow-up throughout the study period. It was notable that 32 of the subjects were missing 24 hour VAS pain scores, which was the primary outcome. The author does not disclose which groups (vaginal/laparoscopic) these subjects came from but does disclose if they received medication vs placebo (13 placebo, 19 medication). This is concerning that the study was not powered to detect a clinically significant difference given this loss of data.

7. While reading the tables 1 & 2 we note that midurethral sling or other anti-incontinence procedures were not included in the concomitant procedures. This was not noted to be an exclusion criterion. This may be due to the authors electing to perform only staged procedures. If so, it might be helpful to note this in the methodology of results section.

8. The reader was surprised to note the difference in 24-hour VAS pain scores noted in the present study compared to the study with which the power calculation was based. Particularly that the vaginal scores were higher than the laparoscopic scores in this study. The reviewer postulates whether this is due to the high number of levator myorrhaphies in this group.

9. The discussion highlights many interesting points in the paper and has a thoughtful discussion regarding strengths and limitations of the study. The reviewer disagrees with one statement regarding the generalizability of the study. While technically multi-institutional 90% of the subjects came from one center. Additionally, 96% of these were Caucasian women, which may limit generalizability. I agree with the authors that it may be difficult to detect a significant impact with IV acetaminophen given the pain scores being low immediately after surgery. It is also difficult to decide what a clinically meaningful difference is regardless of historical values. These differences are subjective. It may be interesting to compare any literature of oral acetaminophen here as well, especially given the cost difference. Lastly, the reader agrees that it seems unlikely that the IV acetaminophen had a direct effect bladder function resulting in urinary retention. However, the reader appreciates the many thoughtful comments and work that went into eliciting a potential cause.

Overall this paper is well-written with outstanding methodology. While some of the secondary outcomes appear to be difficult to attribute directly to the IV acetaminophen given the timeframe the data points were collected, it provides
interesting information regarding pain and quality of life during recovery of urogynecologic surgery.

Future directions could be to utilize Toradol instead of acetaminophen?

REVIEWER #3:

To summarize, this was a double-blind placebo-controlled randomized multi-center trial to evaluate whether preemptive IV acetaminophen given prior to pelvic organ prolapse surgery had an impact on postoperative pain scores. Overall narcotic use, patient satisfaction, side effects and quality of life were also evaluated as secondary outcomes.

General comments:
As a fellow FPMRS physician, I read this article with deep interest. I appreciate the efforts of the authors to perform this study. The study appears to conform to the CONSORT guidelines for randomized controlled trials.

The question of whether acetaminophen alone impacts postoperative factors is important, but may not be sufficient to draw conclusions from given the growing data on ERAS pathways. While this hospital system seems to be beginning the process of incorporating the ERAS pathway, there is good data given the growing utilization of minimally invasive surgical routes that LOS and narcotic use is already reduced compared to open surgeries and may not be subject to as dramatic improvement with utilization of these preoperative additions.

The vaginal surgical route is likely the most likely to benefit as there is data that pain scores are increased in this route compared to laparoscopic approach. An indicator in this study to this fact is that the primary outcome for VAS pain score change in the vaginal surgery group did appear to be trending toward a significant finding, however it is unfortunate that the authors were missing 15% of their primary outcome data, and thus not powered to find a difference if one existed.

Prior to publication, I believe the manuscript should comment or address several points below:

Abstract:

1. Line 50-54: Please include p values for these comparisons in the abstract
2. Line 89: Recommend removal of "immensely" as it reads as if the authors have a desire or bias toward which result they desire to find
3. Line 96: These may or not be related; may consider changing "consequently" to "...which may result in..."
4. Line 103: For these surgical patients, it is typically hospital (and insurance) policy to admit for 23 hour observation status. Why was the inclusion criteria of "patients anticipated to stay for >24 hours" selected? Was this a good inclusion criteria statement? May have considered "undergoing an apical reconstructive surgery" instead.
5. Line 110: Would consider making "use in prior studies" as first and foremost reason for using VAS as primary outcome. Although it is also easy and feasible, the best reason should be listed first.
6. Line 110 (and 83, 293 and others): Please standardize punctuation to be placed before the citation
7. Line 173-182: This paragraph could be summarized. All continuous variable comparisons appear to use t-tests; would just say this.
8. Line 230: Is this because of inclusion criteria utilized? A good percentage of patients go home prior to 24 hours postoperative. Though self-report and mail-in option was used, the authors should have included another method to ensure the primary outcome data was complete for analysis as 15% is missing (19% in the vaginal surgery group). This should be addressed in the discussion section, likely limitation section.
9. Line 248: Same as above. Missing 23% of data.
10. Line 253: Given the minimal use of narcotics noted in the first place in this surgical population, may want to include in discussion section with additional sentence around line 318.
11. Line 265: Interesting given more PR in placebo group. Good hypothesis for reason.
12. Line 316-318: This sentence could be better worded to end the paragraph with a better synopsis for the reason of all the references included. Please address.
13. Line 362: Again, could speculate here that the minimally invasive nature of the surgeries performed may influence the findings or the lack thereof.
14. Line 369: As noted above, another limitation that needs to be addressed should include the fact that while the authors
planned for a 5% drop-out, their inclusion criteria and decision to study a parameter at the 24 hour postoperative mark resulted in missing primary outcome data for 15-23% of the outcome data. While no differences were concluded between the groups, the loss of outcome data decreases the power of the study to find a difference if one exists. It should be listed in limitations.

STATISTICAL EDITOR'S COMMENTS:

1. lines 42-44: Should clarify this sentence, since the sample size/power calculation was based on providing 80% power to discern a change in 12 mm VAS score (assuming SD of 20.8) for each surgical group. At present, it may be misinterpreted by the reader to apply to the aggregate comparison, not the subsets by surgical approach.

2. Tables 1, 2: Since this was a randomized trial, no need to statistically test for baseline differences, any difference is thought to be random. I am surprised that EBL, OR time, LOS were normally distributed. They often are skewed. Please verify that these were normally distributed. If not, should cite as median(IQR or range).

3. Table 3: Should clearly separate the primary outcome(s) of VAS scores from the secondary outcomes.

ASSOCIATE EDITOR-GYN:

1 - 200 subjects total should not require stating percentages to a tenth %ile (line 46 should read 96% instead of 95.6%)

2 - Similarly, VAS score should not require reporting out to tenths of a %ile

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, as well as subsequent author queries. 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:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. 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). Examples of statements can be found online at http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf.

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. 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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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 appendices).

Please limit your Introduction to 250 words and your Discussion to 750 words.
6. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

12. 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.

13. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College 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. 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 a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

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

"Figure 1: Please upload as a figure file 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.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (http://cjs.cadmus.com/da/index.asp) for more direction on digital art preparation.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Dec 10, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.
December 1, 2018

Dear Obstetrics & Gynecology Editors,

I am pleased to submit our revised manuscript to be considered for publication in Obstetrics & Gynecology entitled “IV Acetaminophen Prior to Pelvic Organ Prolapse Repair, A Randomized Placebo Controlled Trial.” Thank you once again for your consideration of this manuscript for publication. We appreciate the reviewer comments. Enclosed you will find our responses to these comments.

As stated in our previous letter, this study was approved by the University of Pittsburgh and Allegheny Health Network Institutional Review Boards and was registered on clinicaltrials.gov and is identical to the posted trial (NCT02155738). All authors fulfill the criteria for authorship and have read and approved the revised manuscript. The authors have no conflicts of interest. 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. The manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the Editors of Obstetrics & Gynecology. Additionally, we OPT-IN for publication of our responses for the peer-review process.

If I can provide any additional materials or assistance, please do not hesitate to contact me.

Best wishes,

Lindsay C Turner MD, MSc
Reviewer 1, Comment 1:
Introduction: Reference 6 seems very old to be justifying a claim that we don't give NSAIDs to elderly patients. If this a true recommendation, there must be something more recent on it.
Response: We have adjusted the language of this sentence and have added a more current reference: “Although nonsteroidal anti-inflammatory drugs (NSAIDs) would be ideal for this indication due to their reduction in pain and inflammation, they are used with caution in elderly patients because of interference with platelet and kidney function.(6)"

Reviewer 1, Comment #2:
Introduction: I don't see any discussion regarding the cost of IV acetaminophen, we are actually not allowed to use it at our institution because it costs more than rectal or oral acetaminophen.
Response: Please see response to Reviewer 2, Comment #1

Reviewer 1, Comment #3
Introduction: It seems that the duration of action of IV acetaminophen is 4-6 hours, I would include that in the descriptions on line 81 of the pharmacokinetics.
Response: Although the medication is dosed at 6 hour intervals, the package insert does not specifically state the duration of action. Therefore we have updated the manuscript to include the dosing instructions and half life.
“The recommended adult dosing is 1000 mg IV administered every 6 hours, with a half-life of 2.4 hours.(9)"

Reviewer 1, Comment #4
Methods: If the duration of action is 4-6 hours, why is pain at 24 hours the primary outcome? Why not pain at 4 hours postop? What about narcotic use in the first 4-6 hours?
Response: Since the goal of preemptive analgesia is to reduce pain amplification by the central nervous system, we chose the 24 hour end point that would better reflect the amplification of pain. Additionally, the 24 hour time point is generally when decisions are made regarding patient readiness for hospital discharge. Although we collected information on narcotic use and VAS scores in the first 4 hours, there were no differences in these values between IV acetaminophen and placebo in either surgical group.

Reviewer 1, Comment #5:
Methods: I am concerned about grouping these diverse procedures into "laparoscopic" and "vaginal" It would seem to me that someone having a vaginal obliteratorive procedure would have a different pain experience than someone having a vaginal hysterectomy. Why wasn't the sample limited to people having the most similar surgeries? e.g. all with hysterectomy or all without.
Response: We agree that each component of vaginal reconstruction may result in a potentially unique pain response; however, in an effort to make this study as generalizable as possible, we wanted to include all women undergoing vaginal prolapse repair. Additionally, since concomitant vaginal hysterectomy was similar between groups (52% acetaminophen and 53% placebo) we do not believe that this would have significantly impacted the results.
Reviewer 1, Comment #6:
Methods: It should be noted that the power for this study is the active agent vs. placebo. Once we get into the subanalyses of laparoscopic active agent vs. laparoscopic placebo, for example, the power is greatly reduced (half the number of subjects).
Response: We apologize that this is not clear. The study was powered to detect differences within each surgical arm (laparoscopic or vaginal). To make this more clear, the last paragraph of the methods section has been amended as follows:
“Assuming a two-sided alpha of 0.05, 48 women in each group (laparoscopic acetaminophen, laparoscopic placebo, vaginal acetaminophen and vaginal placebo) would provide 80% power to detect a clinically significant difference in VAS scores after surgery in those receiving IV acetaminophen compared to placebo.”
“Therefore, this study was separately powered to detect differences within each surgical group (laparoscopic or vaginal).”

Reviewer 1, Comment #7
Discussion: Line 293, please clarify that the following two sentences are about abdominal hysterectomy, it is not clear to the reader.
Response: We appreciate that this is not clear and have clarified these two lines:
“In women undergoing abdominal hysterectomy, a 2009 study reported that preemptive IV acetaminophen significantly lowered 24-hour postoperative pain scores at rest and with movement when compared to placebo.(14) However, in a 2011 study, there was no significant difference in pain scores at rest or with movement between acetaminophen and placebo.(15)"

Reviewer 2, Comment #1
The introduction section of the paper flows nicely into the primary aim of the paper. Much of the focus is on pre-emptive use of medications to be given preoperatively for postoperative pain management. There is a thoughtful discussion on the background of intravenous acetaminophen. There is no mention of oral acetaminophen and whether there is previous work utilizing oral acetaminophen for pre-emptive pain control. The reviewer notes the comment on intravenous form having highest postoperative concentrations. Adding any background information known regarding the use of oral acetaminophen for postoperative pain management. This may be useful to highlight other reasons why you chose to study the intravenous route, despite this formulation being more costly.
Response: We have added a discussion on oral acetaminophen and its associated cost differences with the IV formulation. Two additional references have been added.
The IV formulation of acetaminophen for prevention of pain amplification was selected due to its quick onset of action and high plasma maximum concentration compared with oral and rectal administration; (9,10) however it should be noted that IV acetaminophen is considerably more expensive than oral formulations with an average wholesale cost of $48 per 1000mg dose compared to $0.02-$0.16 per 1000mg tablet. (39) Oral acetaminophen in conjunction with gabapentin, ketamine and dexamethasone has demonstrated a reduction in pain scores and narcotic use in a population of patients undergoing anorectal surgery, (40) but to our knowledge has not been studied as a single agent preemptive analgesic in women undergoing gynecologic surgery. Although oral acetaminophen is a cheaper alternative to IV acetaminophen and a likely
effective component of multi-modal ERAS pathways, we chose to use IV acetaminophen in this study given its quicker onset in a setting where highest tissue concentrations were prudent for prevention of pain amplification.


Reviewer 2, Comment #2
The materials and methods section is quite thorough and the reviewer notes the thoughtful application of the CONSORT guidelines. Inclusion/exclusion criteria, aims, the hypothesis, recruitment, randomization and allocation are all clearly stated. The reviewer appreciates the randomization plan stratified by surgical route as it would account for differences among the two patient populations which would impact pain scores. The allocation concealment methods are adequate with concealment down to the level of container of the medication. It may be informative to the reader when discussing the methods to elaborate that no other preoperative pain medications were given routinely to either group as part of an early recovery after surgery pathway. This was noted later in the discussion but it may be helpful to add earlier in the paper for context.

Response: This has been updated in the second paragraph of the methods section as follows: “No other preoperative pain medications were given routinely to either group as part of early recovery after surgery (ERAS) pathways.”

Reviewer 2, Comment #3
Inclusion criteria state that the intended plan was a 24 hour observational stay; however, some patients appeared to have been discharged early. Pain scores were to be collected q4 hours for 24 hours, including if they were discharged. It is unclear to the reader if these scores were performed independently by the patient while inpatient or if these were proctored by a member of the research team. There may be a difference in scores of those collected inpatient versus those self-collected upon discharge.

Response: Pain scores were performed independently by the patient. The patients had previously been instructed on how to complete these during collection of the preop VAS score which was proctored by the research team. The patient was reminded to complete their pain scores when possible by members of the research team or on call residents. If they had been discharged home prior to completion, they were called by a member of the study team to remind them to complete the score. Postoperative pain scores were not proctored. This has been clarified in the 3rd paragraph of the methods:
“Pain scores were independently performed by the patient.”

Reviewer 2, Comment #4
I would like to comment on the utility of the secondary outcomes also obtained in the study. The APS-POQ-R seems a good choice for a QOL survey regarding pain control. The timeline is appropriate taken at 24 hours postop, when considering in the contest of comparing patients that
had a single dose of IV acetaminophen. However, the other survey (PROMIS PI-SF-8a) done at 7 days postop would seem to have little, if any, clinical relevance to a single dose of IV acetaminophen given on postoperative day 0. It would seem unlikely that an impact could be detected 7 days after a single dose of medication with a dosing regimen of every 4-6 hours. If there was a difference the reviewer feels there may be too many other variables that could have impacted this score to be able to attribute the difference to the IV acetaminophen alone.

Response: Since there is limited data on preemptive IV acetaminophen, it is not known how long the potential benefits of reduced pain amplification may last. We agree that 24 hours would seem a more reasonable time frame but wanted to include a slightly longer assessment of pain satisfaction through the first 7 days. Ultimately there were no differences in the results of the PROMIS survey between groups.

Reviewer 2, Comment #5
In the sample size calculation, the authors note that there is little information on which to base a clinically meaningful change in VAS scores for the surgeries of interest. A single calculation was made and applied to both vaginal surgery group and the laparoscopic surgery group. The reader questions whether it may have been useful to use different known mean/standard deviations of VAS pain scores to make separate calculations for each surgical group. The mean/standard deviations used from prior studies are very different between the two groups. If you chose against doing this, it may be helpful to mention the reasoning.

Response: We agree that the published VAS pain scores for vaginal and laparoscopic surgery are quite different. For this reason, we chose the larger of the two standard deviations to ensure that we would be appropriately powered for each group. We have revised the wording of the last paragraph of the methods to make this clearer:
“We performed separate sample size analyses using the larger of the two standard deviations (20.8mm) from previously published studies of robotic and vaginal surgery to assure that there would be appropriate power to detect a difference in pain scores within each surgical route.”

Reviewer 2, Comment #6
In the results section, the reviewer appreciates the figure 1 denoting any withdrawal or loss to follow-up throughout the study period. It was notable that 32 of the subjects were missing 24 hour VAS pain scores, which was the primary outcome. The author does not disclose which groups (vaginal/laparoscopic) these subjects came from but does disclose if they received medication vs placebo (13 placebo, 19 medication). This is concerning that the study was not powered to detect a clinically significant difference given this loss of data.

Response: When the data was rerun to clarify the specific breakdown of missing data by group, the authors realized that the number of subjects missing 24 hour VAS pain scores presented in the paper should actually be labeled as change from baseline in 24 hour VAS pain score for the primary outcome. Because there were a few subjects missing preoperative VAS pain scores, the number of subjects missing primary outcome data is actually 40. This has been clarified in Figure 1, table 3, as well as in the results section:
“The change from baseline in VAS pain score at 24-hours was available for 162 subjects [laparoscopic acetaminophen (n=36), placebo (n=41), vaginal acetaminophen (n= 41), placebo n=44)] (missing in 15 subjects receiving placebo (vaginal n=5, laparoscopic n=10) and 25 receiving IV acetaminophen (vaginal n=11, laparoscopic n=14)).”
Additionally, the abstract results section has been amended to clearly reflect the missing primary outcome data:

“Between 2014-2017, 204 women were enrolled, and primary-outcome data from 162 subjects analyzed.”

**Reviewer 2, Comment #7.** While reading the tables 1 & 2 we note that midurethral sling or other anti-incontinence procedures were not included in the concomitant procedures. This was not noted to be an exclusion criterion. This may be due to the authors electing to perform only staged procedures. If so, it might be helpful to note this in the methodology of results section.

**Response:** Midurethral slings were included in the concomitant procedures and can be found under the section of “concomitant procedures” in Tables 1 and 2.

**Reviewer 2, Comment #8.** The reader was surprised to note the difference in 24-hour VAS pain scores noted in the present study compared to the study with which the power calculation was based. Particularly that the vaginal scores were higher than the laparoscopic scores in this study. The reviewer postulates whether this is due to the high number of levator myorrhaphies in this group.

**Response:** We agree that the pain scores in the vaginal arm were slightly higher in this study (Acetaminophen 29.2±28.3, placebo 20.5±23.1) compared to that by Roovers (19.3±14.8mm). Although 85% of those in the Roovers study underwent posterior colporrhaphy it is unclear if any underwent levator myorrhaphy. Additionally, it is unclear from the Roovers study at what time point during the hospitalization VAS pain scores were obtained.

**Reviewer 2, Comment #9**

The discussion highlights many interesting points in the paper and has a thoughtful discussion regarding strengths and limitations of the study. The reviewer disagrees with one statement regarding the generalizability of the study. While technically multi-institutional 90% of the subjects came from one center. Additionally, 96% of these were Caucasian women, which may limit generalizability. I agree with the authors that it may be difficult to detect a significant impact with IV acetaminophen given the pain scores being low immediately after surgery. It is also difficult to decide what a clinically meaningful difference is regardless of historical values. These differences are subjective. It may be interesting to compare any literature of oral acetaminophen here as well, especially given the cost difference. Lastly, the reader agrees that it seems unlikely that the IV acetaminophen had a direct effect bladder function resulting in urinary retention. However, the reader appreciates the many thoughtful comments and work that went into eliciting a potential cause.

**Response:** Please see response to Reviewer #2, Comment #1 above for discussion of cost. We agree that the generalizability of the study is limited by the homogenous population and that the majority of subjects came from one institution. This has been modified in the 3rd to last paragraph of the discussion.

“It should be noted; however, that the majority of subjects were recruited from one institution and that the population was quite homogenous with 96% of subjects being Caucasian and postmenopausal.”

**Reviewer 2, Comment #10**
Overall this paper is well-written with outstanding methodology. While some of the secondary outcomes appear to be difficult to attribute directly to the IV acetaminophen given the timeframe the data points were collected, it provides interesting information regarding pain and quality of life during recovery of urogynecologic surgery.

Future directions could be to utilize Toradol instead of acetaminophen?

**Response:** We agree that Toradol would also make for an interesting future study.

**Reviewer 3**

The question of whether acetaminophen alone impacts postoperative factors is important, but may not be sufficient to draw conclusions from given the growing data on ERAS pathways. While this hospital system seems to be beginning the process of incorporating the ERAS pathway, there is good data given the growing utilization of minimally invasive surgical routes that LOS and narcotic use is already reduced compared to open surgeries and may not be subject to as dramatic improvement with utilization of these preoperative additions.

The vaginal surgical route is likely the most likely to benefit as there is data that pain scores are increased in this route compared to laparoscopic approach. An indicator in this study to this fact is that the primary outcome for VAS pain score change in the vaginal surgery group did appear to be trending toward a significant finding, however it is unfortunate that the authors were missing 15% of their primary outcome data, and thus not powered to find a difference if one existed.

Prior to publication, I believe the manuscript should comment or address several points below:

**Reviewer 3, Comment #1** Line 50-54: Please include p values for these comparisons in the abstract

**Response:** Unfortunately, we are limited by character counts in the abstract which is why p values were not included here.

**Reviewer 3, Comment #2** Line 89: Recommend removal of "immensely" as it reads as if the authors have a desire or bias toward which result they desire to find

**Response:** This has been removed.

**Reviewer 3, Comment #3** Line 96: These may or not be related; may consider changing "consequently" to "…which may result in…"

**Response:** This has been changed.

**Reviewer 3, Comment #4** Line 103: For these surgical patients, it is typically hospital (and insurance) policy to admit for 23 hour observation status. Why was the inclusion criteria of "patients anticipated to stay for >24 hours" selected? Was this a good inclusion criteria statement? May have considered "undergoing an apical reconstructive surgery" instead.

**Response:** We agree that this inclusion criteria was not ideal; however, we wanted to ensure that the majority of patients were present in the hospital to complete the primary outcome (24 hour VAS pain score) and APS questionnaire. The observation vs admission status was dependent upon the specific procedure.
Reviewer 3, Comment #5 Line 110: Would consider making "use in prior studies" as first and foremost reason for using VAS as primary outcome. Although it is also easy and feasible, the best reason should be listed first.
Response: This has been modified.

Reviewer 3, Comment #6 Line 110 (and 83, 293 and others): Please standardize punctuation to be placed before the citation
Response: This has been modified.

Reviewer 3, Comment #7 Line 173-182: This paragraph could be summarized. All continuous variable comparisons appear to use t-tests; would just say this.
Response: This has been shortened as follows:
“Continuous variables including VAS pain scores and narcotic requirements measured in MME were compared by t-tests.”

Reviewer 3, Comment #8 Line 230: Is this because of inclusion criteria utilized? A good percentage of patients go home prior to 24 hours postoperative. Though self-report and mail-in option was used, the authors should have included another method to ensure the primary outcome data was complete for analysis as 15% is missing (19% in the vaginal surgery group). This should be addressed in the discussion section, likely limitation section.
Response: We agree that there was a high number of subjects missing primary outcome data. Members of the research team made their best effort to remind the patient to complete the pain scores at the appropriate time, but often the missing data was due to subjects forgetting to complete the pain score or sleeping during this time point. We have updated the limitations section to reflect this:
“Limitations of the study include missing primary outcome data for 40 subjects and the lack of consistency in patient completion of postoperative bowel and pain diaries.”

Reviewer 3, Comment #9 Line 248: Same as above. Missing 23% of data.
Response: This missing data had previously been discussed in the limitations section (see comment 8 above).

Reviewer 3, Comment #10 Line 253: Given the minimal use of narcotics noted in the first place in this surgical population, may want to include in discussion section with additional sentence around line 318.
Response: This has been added to the end of the 3rd paragraph of the discussion section as recommended.
“Narcotic consumption is difficult to compare with prior studies in female pelvic reconstructive surgery due to the variability in morphine equivalent conversion factors and time points at which this was assessed\(^{28-30}\) and in general, narcotic use was relatively low in this study.”

Reviewer 3, Comment #11 Line 265: Interesting given more PR in placebo group. Good hypothesis for reason.
Response: Thank you.
Reviewer 3, Comment #12 Line 316-318: This sentence could be better worded to end the paragraph with a better synopsis for the reason of all the references included. Please address.  
Response: We have added a conclusion sentence to the end of this 3rd paragraph in the discussion section: “Ultimately, comparison of our primary and secondary outcomes to other studies is limited by the lack of available data on single dose IV acetaminophen in a urogynecology population.”

Reviewer 3, Comment #13 Line 362: Again, could speculate here that the minimally invasive nature of the surgeries performed may influence the findings or the lack thereof.  
Response: This has been modified in the 6th paragraph of the discussion “However, similar to our study, no significant differences in POD 1 pain scores, side effects, or length of stay were demonstrated, which may be related to the minimally invasive nature of procedures performed in these studies.”

Reviewer 3, Comment #14 Line 369: As noted above, another limitation that needs to be addressed should include the fact that while the authors planned for a 5% drop-out, their inclusion criteria and decision to study a parameter at the 24 hour postoperative mark resulted in missing primary outcome data for 15-23% of the outcome data. While no differences were concluded between the groups, the loss of outcome data decreases the power of the study to find a difference if one exists. It should be listed in limitations.  
Response: The limitations paragraph has been amended as follows: “Our initial power calculation accounted for a 5% loss to follow-up. Since the actual loss to follow-up exceeded this, the lack of primary outcome data decreases the power of the study to detect a difference between IV acetaminophen and placebo. However, when the vaginal and laparoscopic surgery groups were combined (Table 3), statistical power was met and there continued to be no difference between IV acetaminophen and placebo groups.”

STATISTICAL EDITOR’S COMMENTS:

Statistical Editor, Comment #1 lines 42-44: Should clarify this sentence, since the sample size/power calculation was based on providing 80% power to discern a change in 12 mm VAS score (assuming SD of 20.8) for each surgical group. At present, it may be misinterpreted by the reader to apply to the aggregate comparison, not the subsets by surgical approach.  
Response: This has been modified as follows: “Assuming a two-sided alpha of 0.05, and adjusting for 5% loss to follow-up, 102 women in each surgical group (laparoscopic and vaginal) were needed to provide 80% power to detect a clinically significant change in VAS scores for each surgical approach.”

Statistical Editor, Comment #2 Tables 1, 2: Since this was a randomized trial, no need to statistically test for baseline differences, any difference is thought to be random. I am surprised that EBL, OR time, LOS were normally distributed. They often are skewed. Please verify that these were normally distributed. If not, should cite as median(IQR or range).  
Response: The authors would like to clarify if the Statistical Editor is requesting removal of the p values from Tables 1 and 2? If so we agree with removal. Since there were significant differences in baseline POPQ scores and posterior repairs, we would like to clarify how to
represent this in the table? The distribution of EBL, OR time and LOS were rechecked and were found to be normally distributed; therefore, the data were not converted to median.

Statistical Editor, Comment #3 Table 3: Should clearly separate the primary outcome(s) of VAS scores from the secondary outcomes.
Response: This has been modified.

ASSOCIATE EDITOR-GYN:

Associate Editor-Gyn, Comment #1 200 subjects total should not require stating percentages to a tenth %ile (line 46 should read 96% instead of 95.6%)
Response: The abstract has been updated

Associate Editor-Gyn, Comment #2 Similarly, VAS score should not require reporting out to tenths of a %ile
Response: The abstract has been updated

EDITORIAL OFFICE COMMENTS:

Editorial Office Comment #1 Figure 1: Please upload as a figure file on Editorial Manager.
Response: This has been uploaded as a figure
Thank you for your suggestions. I have made all of the necessary changes and agree with the minor edits/deletions throughout. I think I must have provided an incorrect email address for Dr. Shepherd. It is Please let me know if you need anything further.

Sincerely,
Lindsay Turner

On Wed, Dec 5, 2018 at 10:16 AM Daniel Mosier <dmosier@greenjournal.org> wrote:

Dear Dr. Turner,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
2. LINE 3:
   a. Please edit your byline so each author’s name appears as first name, middle initial (or full middle name), last name, academic degrees.
   b. Please ask Dr. Shepherd to respond the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed Dr. Shepherd at – is this the correct address?
3. LINE 20: Please add the exact dates of the meeting.
4. LINE 26: What sort of tasks did she perform – can you be specific?
5. LINE 49: Please be sure this is stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.
6. LINE 50: Please be sure this is stated in the body of your paper. Statements and data that appear in the Abstract must also appear in the body text for consistency.
7. LINE 69: It would be helpful to insert a sentence here about the use of pre-emptive meds in ERAS pathways and their success in reducing postop opioid use, etc
8. LINE 71: With insertion of the above ERAS comment, these 2 sentences are less necessary & the Intro could be shortened somewhat
9. LINE 84: Yet included in ERAS?
10. LINE 100: Please revise "and/or" to mean either "and" or "or." Be sure this is done throughout your paper.
11. LINE 203: For articles submitted to O&G after July 1, 2018, we require a data sharing statement indicating what we’ve listed here. Your answers may be different from what I’ve listed here. If so, please edit the responses accordingly.

12. LINE 309: Note the change in wording. Please provide search terms, names of the databases you searched, and dates searched, including years.

13. TABLE 1: As requested by Stat Editor, please remove p-value columns from Tables 1 and 2; the diff in post colporr (Table 1) and POPQ (Table 2) could be included in Results near line 239 as single sentence or two.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on Friday, December 7th.

Sincerely,

-Daniel Mosier

Daniel Mosier
Editorial Assistant

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This looks accurate. I have no changes.

On Wed, Dec 5, 2018 at 8:13 AM Stephanie Casway <SCasway@greenjournal.org> wrote:

Good Morning Dr. Turner,

Your figure has been edited, and a PDF of the figure is attached for your review. Please review the figure CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article’s publication.

To avoid a delay, I would be grateful to receive a reply no later than Friday, 12/7. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor

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