

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.*

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

obgyn@greenjournal.org.

Date: Jul 18, 2019
To: "Christina A. Penfield" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1084

RE: Manuscript Number ONG-19-1084

A randomized trial of the effect of ibuprofen on postpartum blood pressure in hypertensive disorders of pregnancy

Dear Dr. Penfield:

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 Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors clearly present the findings of a prospective, randomized, intention to treat, blinded trial of postpartum ibuprofen v. acetaminophen for pain relief in patients with hypertensive disorders of pregnancy characterized by mild hypertension only. Their results are consistent with other recent studies that even patients with severe hypertensive disorders or no hypertensive disorders can be treated with NSAIDs postpartum without fear of the medication causing hypertensive morbidity. The ACOG Hypertension in Pregnancy Task Force document clearly needs to be corrected with the addition of recent papers showing that NSAIDs are not contraindicated in patients with hypertensive disorders of pregnancy.

The prospective randomized, blinded, intent to treat method with a clearly defined population and preestablished outcome analyses for blood pressures in the hospital, daily mean blood pressures over time, outpatient blood pressure evaluation, pain control, diuresis and patient satisfaction make this a significant contribution to the literature.

The authors did not include patients with chronic hypertension (increased BP prior to 20 weeks gestation) so this is still a population that needs to be studied but this paper now supports the use of NSAIDs in patients with preeclampsia, with and without severe features.

The fact that blood pressure measurements were standardized by nurse receiving instructions is something that has not been addressed in many of the other papers on this subject. This was great.

A few concerns:

1. The authors included patients with preeclampsia with severe features who did not have BPs over 160 systolic or 105 diastolic. Since there were only 4 patients who met these criteria, I think the outcome would not be any different, but it would have been a more homogeneous population to evaluate only those patients with hypertensive disorders without any severe features.
2. Can the authors explain why they chose to use 105mm Hg diastolic when the definition of severe is 110mmHg diastolic? This certainly doesn't change the results, but it did seem odd.
3. Can the authors comment on the low follow up at 1 week (28%)? With that low follow up the conclusion related to post discharge BPs may not be valid.
4. The low number of CS patients makes one question if the conclusions of the paper related to pain control and patient satisfaction are applicable to patients who have had a CS. Certainly there is no reason why the findings related to BP are in

doubt.

This paper does add to the body of evidence showing the safety of NSAIDs for pain control in patients with any hypertensive disorder of pregnancy and should be cited highly and considered when ACOG comes out with its revision of the next Hypertension in Pregnancy Task Force document. For this reason, it should be published.

Reviewer #2: In this double-blinded randomized trial, authors sought to evaluate the impact of Ibuprofen use on mean arterial blood pressure of women diagnosed with hypertensive disorder of pregnancy (HDP) including those with severe features and mild hypertension. They found no differences between in MAP between those who received Ibuprofen and Acetaminophen.

Good design and well written manuscript.

1. As authors would be aware, 2 recent publications demonstrated the safety and lack of worsening BP in the cohort of patients with HDP with severe features-including those with mild hypertension treated with Ibuprofen. Blue et al. (2018) showed in a randomized trial (similar to the present study) that included 100 patients that use of NSAID (Ibuprofen) did not increase the duration of elevated BO in patients with HDP with severe features, did not increase MAP (as this study found), did not increase the need for use of anti-hypertensive, and did not show any adverse effects at 6 weeks post partum. Similarly, Viteri et al (2017), using a retrospective design that included 399 patients did not show adverse impact on BP with use of Ibuprofen in HDP with severe features. Both studies included patients with mild range BPs and severe HDP features. Therefore, what exactly do authors feel their study add to what is already known?
2. Introduction; lines 118-123; characterizing the inclusion of chronic hypertension as a limitation is misleading; there is value in understanding the effect of Ibuprofen in this population and that is what these studies set out to investigate. Would suggest rephrasing.
3. Methods lines 128-227; It might be interesting to evaluate impact of Ibuprofen on serum creatinine levels and creatinine clearance? Also, are you able to show data on rates of oliguria (urine output <30m/hr X 2 hours) between the groups? These 2 parameters might hint at pharmacologic effects of Ibuprofen that may not show immediate impact. Finally, lack of data at 6 weeks post partum is a study limitation. It is conceivable that Ibuprofen effects may be more evident later in the course of postpartum recovery.
4. Table 1; are you able to show the tests of significance for use of regional anesthesia? It is a possible confounder and rates appear at face value to be different between the 2 groups.
 - a. Blue NR, Murray-Krezan C, Drake-Lavelle S, Weinberg D, Holbrook BD, Katukuri VR, Leeman L, Mozurkewich EL. Effect of ibuprofen vs acetaminophen on postpartum hypertension in preeclampsia with severe features: a double-masked, randomized controlled trial. American journal of obstetrics and gynecology. 2018 Jun 1;218(6):616-e1.
 - b. Viteri OA, England JA, Alrais MA, Lash KA, Villegas MI, Balogun OA, Chauhan SP, Sibai BM. Association of nonsteroidal antiinflammatory drugs and postpartum hypertension in women with preeclampsia with severe features. Obstetrics & Gynecology. 2017 Oct 1;130(4):830-5.

Reviewer #3: Review manuscript ONG-19-1084

General comment. A randomized double blind controlled trial with the primary objective to assess the effect of NSAID ibuprofen (n=31) and non-NSAID acetaminophen (n=30) on postpartum blood pressure and pain relief in patients with a mild transient hypertensive disorder of pregnancy (HDP), including severe preeclampsia and eclampsia. The motive to undertake the study is well explained in the introduction. The paper presents a great number of secondary outcomes (breakthrough pain medication, duration of hospital stay after delivery, diuresis, patient satisfaction after discharge, blood pressure after discharge). It is not reported whether or not those secondary outcomes were defined before the start of the study. Analyses are said to be performed on the basis of "intention-to-treat" but some patients were withdrawn after randomization. The null hypothesis of no significant differences between groups was not disproved, and the authors therefore- incorrectly -conclude that they demonstrated the absence of an effect of NSAID's on blood pressure.

Specific comments.

1. Line 125-127. Only one of the many objectives of study is mentioned here. Secondary outcomes?
2. Line 137. Why not selection based on MAP? All analyses, including power calculation, are performed with MAP.
3. Line 154. What kind of blocks were patients randomized in? How large were the blocks?

- 4.Lines 176-177. Why the change to manual sphygmomanometry when severe hypertension was detected?
- 5.Lines 179-181. In which groups was oral antihypertensive therapy initiated? Lines 238-239 suggest that they were excluded from analysis.
- 6.Line 224. Did those complications occur?
- 7.Line 226. How were the results included in the analysis?
- 8.Line 235. Statistical power was calculated to be able to reject a hypothesis of an increase of 6 mm in MAP with $\alpha=0.05$ and $\beta=0.80$. However, Line 251 indicates that an $\alpha=0.001$ was used in the analyses. Failure to reject the hypothesis of an effect - as in this experiment - does not mean that the alternative hypothesis of no effect is correct as the authors assume in their discussion and conclusions (see e.g. précis).
- 9.Line 237. Analyses on an "intention-to-treat" basis? That is not in agreement with the exclusion of patients after randomization. (Lines 239-244, line 255).
10. References: adequate.
11. Tables. May be combined and reduced in number.
12. Fig.4 . How was the difference between the two Kaplan-Meier curves tested? The 1-survival on the y-axis may be omitted.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Needs to conform to our template for RCTs.
2. lines 232-236: Since the Authors were evaluating an increase in MAP, the baseline of 107 should be compared to a treatment MAP value of 113, not 101. This does not change the sample size calculation.
3. Table 1: Need units for age, BMI. Since the column sample sizes were $N = 31$ and 30 , the %s should be rounded to nearest integer, not to nearest 0.1%. What were the initial MAPs for the two cohorts and was their anti hypertensive treatment similar?
4. Table 2: Should clearly identify the primary outcome.
5. Table 3,5: With these sample sizes, should round the %s to nearest integer %, not to nearest 0.1%.
6. Table 4: Were the pain scores normally distributed? If not, then should cite as median(IQR or range) and test non-parametrically.
7. Tables 3,4,5: Could consolidate these into one table of secondary outcomes.
8. Fig 2: This plot is based on the method of survival analysis, but no need to label the y-axis as (1-survival), since all women survived in the usual meaning. "Cumulative probability of diuresis" alone is sufficient. Although this was NS, the study was not powered to evaluate a difference in hazard rate of diuresis, nor of any of the other NS secondary findings.

Associate Editor's Comments:

Please report blood pressures and percentages in whole numbers only and percentages

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. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at <http://ong.editorialmanager.com>. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

6. 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.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

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

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

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

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

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

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

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

14. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

15. 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.

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

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

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

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

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter.

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

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by Aug 08, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

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

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

Christina A. Penfield, MD, MPH
Magella Medical Office
2888 Long Beach Blvd. #400
Long Beach, CA 333 90806

August 22, 2019

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

To the Editor-in-Chief,

Please find the electronically submitted revised manuscript “A randomized trial of ibuprofen on postpartum blood pressure in hypertensive disorders of pregnancy” by Christina A. Penfield, Jennifer A. McNulty, Megan C. Oakes, and Michael P. Nageotte. This manuscript is not under consideration elsewhere and will not be submitted elsewhere until a final decision is made by the Editors of *Obstetrics & Gynecology*.

In this letter, we have included a point-by-point response to each of the received comments that was developed in consultation with all co-authors and each author has given approval to the final form of the revision. We agree to publish this point-by-point response letter. We have followed the CONSORT guidelines and included a data sharing statement. I am the lead author and I affirm 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. I have read the Instructions for Authors for Obstetrics and Gynecology manuscript submissions.

Thank you for your consideration,

A handwritten signature in black ink, appearing to read 'Christina Penfield', with a stylized, flowing script.

Christina A. Penfield, M.D., M.P.H.

Reviewer #1: The authors clearly present the findings of a prospective, randomized, intention to treat, blinded trial of postpartum ibuprofen v. acetaminophen for pain relief in patients with hypertensive disorders of pregnancy characterized by mild hypertension only. Their results are consistent with other recent studies that even patients with severe hypertensive disorders or no hypertensive disorders can be treated with NSAIDs postpartum without fear of the medication causing hypertensive morbidity. The ACOG Hypertension in Pregnancy Task Force document clearly needs to be corrected with the addition of recent papers showing that NSAIDs are not contraindicated in patients with hypertensive disorders of pregnancy.

The prospective randomized, blinded, intent to treat method with a clearly defined population and preestablished outcome analyses for blood pressures in the hospital, daily mean blood pressures over time, outpatient blood pressure evaluation, pain control, diuresis and patient satisfaction make this a significant contribution to the literature.

The authors did not include patients with chronic hypertension (increased BP prior to 20 weeks gestation) so this is still a population that needs to be studied but this paper now supports the use of NSAIDs in patients with preeclampsia, with and without severe features.

The fact that blood pressure measurements were standardized by nurse receiving instructions is something that has not been addressed in many of the other papers on this subject. This was great.

A few concerns:

1. The authors included patients with preeclampsia with severe features who did not have BPs over 160 systolic or 105 diastolic. Since there were only 4 patients who met these criteria, I think the outcome would not be any different, but it would have been a more homogeneous population to evaluate only those patients with hypertensive disorders without any severe features.

Thank you for your question regarding our inclusion criteria for the study population. The goal of the study was to evaluate the effect of ibuprofen use on blood pressure in a population of women with hypertensive disorders of pregnancy without severe hypertension. We chose to exclude the presence of severe hypertension in particular, rather than all of the other severe features of preeclampsia, because of the high potential for severe hypertension to bias our findings. Women with severe hypertension receive medications to lower blood pressure, and thus any potential influence of NSAIDs on blood pressure would be masked. In contrast, we considered other severe features of preeclampsia (such as thrombocytopenia, renal insufficiency, impaired hepatic function, symptoms of preeclampsia, and pulmonary edema) to be less likely to confound the relationship between ibuprofen and postpartum blood pressure, particularly because all participants had platelets >50,000, AST/ALT<500, and creatinine <1.3 to be eligible for randomization to either ibuprofen or acetaminophen.

We agree that inclusion of the four participants with preeclampsia with severe features without severe hypertension did not likely change our outcomes, nor how the findings should be interpreted.

2. Can the authors explain why they chose to use 105mm Hg diastolic when the definition of severe is 110mmHg diastolic? This certainly doesn't change the results, but it did seem odd.

Thank you for the opportunity to explain this slight deviation in the definition of severe hypertension used in the study. Our hospital follows the guidelines and recommendations in the California Toolkit to Transform Maternity Care called “Improving Health Care Response to Preeclampsia¹,” which was endorsed by the California Maternal Quality Care Collaboration (CMQCC) and reviewed by the California Department of Public Health. In this toolkit, the Preeclampsia Early Recognition Tool (PERT) defines one of the severe warning signs requiring provider notification as a diastolic blood pressure ≥ 105 mmHg. The CMQCC recommends that hospitals choose a diastolic blood pressure of either 105 or 110 mmHg for initiation of standardized treatment and at the time of this study, our hospital-initiated treatment if the diastolic reached 105 mmHg.

As a result, when designing the study protocol, we did not want to include study participants with 105-109 mmHg diastolic blood pressures into the cohort with mild hypertension, as they would be candidates for IV antihypertensive therapy at our hospital.

We agree that this slight deviation in the definition of severe hypertension should be explained more clearly in the text and have added a clarification to the manuscript.

Original manuscript (lines 138-140): By study design, all of these women had mild hypertension and no measurements of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 105 mmHg prior to randomization.

Revised manuscript (lines 138-142): By study design, all of these women had mild hypertension and no blood pressure measurements prior to randomization that would need antihypertensive therapy (i.e. there were no measurements of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 105 mmHg, as defined by the California Maternal Quality Care Collaboration Preeclampsia Toolkit).

¹Druzin ML, Shields LE, Peterson NL, K M, Cape V. Preeclampsia Toolkit: Improving Health Care Response to Preeclampsia. 2013:1-136.

3. Can the authors comment on the low follow up at 1 week (28%)? With that low follow up the conclusion related to post discharge BPs may not be valid.

Thank you for your comment. While we agree that 28% is a low follow-up rate, this follow-up rate is similar to that observed in other published studies of outpatient blood pressure visits up to 10 days following discharge. One center described a 30% average rate of attendance in a high-

risk blood pressure transition clinic over a 2-year period, which did not improve despite text message and phone call reminders as well as expanded visit availability.¹ Even in a research setting where the primary outcome of interest evaluated the rate of return for outpatient blood pressure visit, follow-up rates were as low as 43.7%, and even lower at 33% for Black women.^{2,3}

Additionally, the low rate of return as an outpatient may also be explained by the fact that our hospital is a tertiary care facility that receives transports from other areas, and many women will prefer to follow-up with their local provider for outpatient care after discharge despite having been given an appointment for follow-up with us prior to discharge. Finally, this study evaluated women with mild hypertension only, and participants may not have considered this outpatient evaluation to be critically important.

Nonetheless, we agree with your concern about the validity of this outcome due to the low participation in outpatient blood pressure visits. We want to communicate to the reader that our study is not able to adequately evaluate blood pressure differences between the two study groups. At your suggestion, we will add more emphasis on this limitation in the manuscript.

Original Manuscript (lines 325-327): Though limited by a low rate of follow-up, this provides preliminary evidence suggesting the safe use of NSAIDs as an outpatient analgesic regimen in women with mild hypertension.

Revised Manuscript (lines 331-334): Although there was no evidence of an adverse impact of NSAIDs on blood pressure after discharge, the low rate at which subjects in the study returned for their scheduled outpatient follow-up limits our ability to draw conclusions about this outcome.

¹Scalise LF, Stringer M. Follow-up Text Messages for Patients at High Risk of Postpartum Hypertension. *J Obstet Gynecol Neonatal Nurs* 2015;44(s1):S6

²Hirshberg A, Downes K, Srinivas S. Comparing standard office-based follow-up with text-based remote monitoring in the management of postpartum hypertension: a randomised clinical trial. *BMJ Quality & Safety* 2018;27:871-877.

³Hirshberg A, Sammel MD, Srinivas SK. Text message remote monitoring reduced racial disparities in postpartum blood pressure ascertainment. *Am J Obstet Gynecol*. May 2019.

4. The low number of CS patients makes one question if the conclusions of the paper related to pain control and patient satisfaction are applicable to patients who have had a CS. Certainly there is no reason why the findings related to BP are in doubt.

We agree that the high vaginal delivery rate (85% of the overall study population) likely did not affect the primary outcome of mean MAP during the immediate postpartum period. On the other hand, mode of delivery could have influenced our results for the pain control and patient satisfaction outcomes, and we therefore included it as a limitation in our discussion.

However, we do not think that the high vaginal delivery rate invalidates the findings for these outcomes, since the randomization of acetaminophen versus ibuprofen would have a higher likelihood to influence pain control and satisfaction after vaginal delivery rather than pain control and satisfaction after a cesarean delivery. This is because most women only require a mild analgesic regimen following vaginal delivery, whereas women who undergo cesarean delivery also receive stronger medications, such as opioids, to control pain.

Manuscript text (lines 355-357): Limitations of the study include the fact that, due to the high vaginal delivery rate in the study, assessment of pain control and satisfaction in women who underwent cesarean delivery was limited.

This paper does add to the body of evidence showing the safety of NSAIDs for pain control in patients with any hypertensive disorder of pregnancy and should be cited highly and considered when ACOG comes out with its revision of the next Hypertension in Pregnancy Task Force document. For this reason, it should be published.

Reviewer #2: In this double-blinded randomized trial, authors sought to evaluate the impact of Ibuprofen use on mean arterial blood pressure of women diagnosed with hypertensive disorder of pregnancy (HDP) including those with severe features and mild hypertension. They found no differences between in MAP between those who received Ibuprofen and Acetaminophen.

Good design and well written manuscript.

1. As authors would be aware, 2 recent publications demonstrated the safety and lack of worsening BP in the cohort of patients with HDP with severe features-including those with mild hypertension treated with Ibuprofen. Blue et al. (2018) showed in a randomized trial (similar to the present study) that included 100 patients that use of NSAID (Ibuprofen) did not increase the duration of elevated BO in patients with HDP with severe features, did not increase MAP (as this study found), did not increase the need for use of anti-hypertensive, and did not show any adverse effects at 6 weeks post partum. Similarly, Viteri et al (2017), using a retrospective design that included 399 patients did not show adverse impact on BP with use of Ibuprofen in HDP with severe features. Both studies included patients with mild range BPs and severe HDP features. Therefore, what exactly do authors feel their study add to what is already known?

We are also very interested in the studies that have recently been published evaluating the effects of ibuprofen on blood pressure in postpartum patients and appreciate your review of their findings. However, we believe that our study provides a significant contribution to our understanding of how NSAIDs affect blood pressure in women with hypertensive disorders of pregnancy. Allow us to discuss in more detail how our study differs from the Blue et al. (2018)¹ and Viteri et al. (2017)² studies you mention.

We would first like to comment on the inclusion criteria for the prior studies. Although they included participants without severe hypertension, both studies required a diagnosis of

preeclampsia *with* severe features to be included. Although this allowed for the recruitment of women with preeclampsia with both mild hypertension and severe features other than severe hypertension, there were very few of these women enrolled in these studies. In Blue et al., 74% of the ibuprofen group and 84% of the acetaminophen group had severe hypertension requiring antihypertensives prior to delivery. In Viteri's study 81% of the NSAID group and 80% of the control group had severe hypertension. Additionally, both studies included women with preexisting chronic hypertension, which made their population more heterogeneous than in our study.

In contrast, our study had no participants with severe hypertension prior to delivery nor preexisting hypertension. In our study population, 90% of the participants in the ibuprofen group and 97% in the control group had diagnoses of gestational hypertension or preeclampsia without severe features, and would have therefore been excluded from the studies by Blue and Viteri. We therefore believe that our study adds to this body of literature by demonstrating the safety of NSAIDs in the population of women 1) with *new-onset* hypertensive disorders of pregnancy and 2) *without* severe hypertension.

Also notable is that the Viteri et al. study was retrospective, and therefore subject to significant selection bias. Ibuprofen was the typical first-line agent for mild analgesia after delivery during the study period, and therefore it was unclear why the 81 women in the control group did not receive NSAIDs for pain control. This made comparisons in outcomes between the NSAID and non-NSAID groups prohibitive.

1. Blue NR, Murray-Krezan C, Drake-Lavelle S, Weinberg D, Holbrook BD, Katukuri VR, Leeman L, Mozurkewich EL. Effect of ibuprofen vs acetaminophen on postpartum hypertension in preeclampsia with severe features: a double-masked, randomized controlled trial. *Am J Obstet Gynecol*. 2018 Jun 1;218(6):616-e1.

2. Viteri OA, England JA, Alrais MA, Lash KA, Villegas MI, Balogun OA, Chauhan SP, Sibai BM. Association of nonsteroidal antiinflammatory drugs and postpartum hypertension in women with preeclampsia with severe features. *Obstet Gynecol*. 2017 Oct 1;130(4):830-5.

2. Introduction; lines 118-123; characterizing the inclusion of chronic hypertension as a limitation is misleading; there is value in understanding the effect of Ibuprofen in this population and that is what these studies set out to investigate. Would suggest rephrasing.

We appreciate your comment. Our concern with including women with both chronic hypertension and hypertensive disorders of pregnancy into the same cohort is that the pathophysiology of hypertension and response to NSAIDs in these two groups could differ in important ways. For example, it has been previously demonstrated that NSAIDs can raise blood pressure in the setting of chronic hypertension.¹ We consider it an advantage that our study cohort had a more homogenous population of women with new-onset hypertensive disorders of pregnancy so that our findings would be directly applicable to this population.

Despite this, we agree that the manuscript text should be altered to describe this heterogeneous study population as a consideration of the study, rather than a limitation.

Original Manuscript (lines 117-119): However, both of these studies were limited by the inclusion of women with preexisting chronic hypertension, rather than focusing on women with exclusively pregnancy-related hypertension.

Revised Manuscript (lines 116-118): Both studies included women with preexisting chronic hypertension as well as women with pregnancy-related hypertension.

¹Frishman WH. Effects of nonsteroidal anti-inflammatory drug therapy on blood pressure and peripheral edema. *Am J Cardiol.* 2002;89(6A):18D–25D.

3. Methods lines 128-227; It might be interesting to evaluate impact of Ibuprofen on serum creatinine levels and creatinine clearance? Also, are you able to show data on rates of oliguria (urine output <30m/hr X 2 hours) between the groups? These 2 parameters might hint at pharmacologic effects of Ibuprofen that may not show immediate impact.

We agree that the effects of ibuprofen on serum creatinine and oliguria is an interesting area to consider. Although the ibuprofen dose and frequency used in the study protocol is considered routine, as a precaution we evaluated any major effects of ibuprofen on serum creatinine in our study patients with our prespecified serum creatinine monitoring study protocol. In our hospital's routine care, every hypertensive obstetric patient receives a measurement of creatinine (along with liver function enzymes and complete blood count) when admitted to the hospital. If serum creatinine measurement was ≥ 1.1 mg/dl during the study, our protocol required repeat monitoring of creatinine levels every 24 hours until the measurement was less than 1.1 mg/dL. If the creatinine increased to 1.4 mg/dl or above, the study medication would be unmasked and if the patient was assigned to ibuprofen, it would be discontinued, and this unanticipated problem would be reported to the IRB. Additionally, our interim analysis evaluated the frequency of elevated serum creatinine between groups; the trial was to be terminated if there were significant differences in numbers of patients in each group with serum creatinine that exceeded >1.4 mg/dl while using the study drug. In the end, we did not have any participants with serum creatinine >1.1 mg/dL while participating in the study, and thus do not suspect that there was any clinically significant adverse influence on renal function as a result of ibuprofen use in this population of women with mild hypertension.

As you suggest, there may also be subtle changes in creatinine over time that may not be clinically significant but could be suggestive of underlying physiologic mechanisms. Unfortunately, we do not have standardized longitudinal data on serum creatinine or creatinine clearances over the course of the study to evaluate these differences between study groups. Similarly, we do not have specific data comparing rates of oliguria between groups. The routine ibuprofen dose used in the study is unlikely to have reduced urine output to such a degree, particularly in our study population who had only mild hypertension and no cases of serum creatinine >1.1 mg/dL. Since our study was unable to demonstrate differences in rates of diuresis (urine output >200 ml/h over 4 hours), and rates of oliguria in this population are usually very low, it would be unlikely to identify differences between groups. This would certainly be an important question to evaluate in detail in a study population of women with preeclampsia with

severe features, many of whom may have impaired kidney function that could be exacerbated by regular ibuprofen use.

3 (continued). Finally, lack of data at 6 weeks post partum is a study limitation. It is conceivable that Ibuprofen effects may be more evident later in the course of postpartum recovery.

Thank you for your inquiry about blood pressure evaluation at 6 weeks postpartum. We considered including these measurements in our analysis but since the randomization of medications in our study was not continued after discharge, we were concerned about significant cross-over between groups as an outpatient. Additionally, most women do not require any analgesic medications the first two weeks postpartum. Since we did not see differences in the inpatient setting, and participants were not likely taking analgesics beyond the first two weeks postpartum, we assume there would be a low probability of finding differences in blood pressure at 6 weeks postpartum in a study of this size.

We did seek to compare other clinically relevant post-discharge outcomes, such as rates of hospital readmissions between groups, although only one participant (in the ibuprofen group) was readmitted for severe hypertension, so comparisons between groups could not be performed. We found the apparently low rate of clinically significant post-discharge adverse outcomes reassuring, but of course acknowledge there were also low rates of follow-up.

4. Table 1; are you able to show the tests of significance for use of regional anesthesia? It is a possible confounder and rates appear at face value to be different between the 2 groups.

Our study was randomized, and we therefore expected the use of regional anesthesia to be similar between groups. However, we also suspected that the use of analgesia could be a confounder and performed an analysis to compare rates between groups. We are including the results of the chi-squared test for use of regional anesthesia below. We did not find any difference in type of delivery anesthesia between groups.

Delivery Anesthesia Type	Control N=30	Ibuprofen N=31	P-value
None	6.7%	12.9%	P=.415
Epidural – vaginal delivery	80.0%	67.7%	
Epidural – cesarean section	3.3%	12.9%	
Spinal anesthesia – cesarean	10.0%	6.5%	

Reviewer #3: Review manuscript ONG-19-1084

General comment. A randomized double blind controlled trial with the primary objective to assess the effect of NSAID ibuprofen (n=31) and non-NSAID acetaminophen(n=30) on

postpartum blood pressure and pain relief in patients with a mild transient hypertensive disorder of pregnancy (HDP),including severe preeclampsia and eclampsia .The motive to undertake the study is well explained in the introduction. The paper presents a great number of secondary outcomes (breakthrough pain medication, duration of hospital stay after delivery, diuresis, patient satisfaction after discharge, blood pressure after discharge). It is not reported whether or not those secondary outcomes were defined before the start of the study. Analyses are said to be performed on the basis of "intention-to-treat" but some patients were withdrawn after randomization. The null hypothesis of no significant differences between groups was not disproved, and the authors therefore- incorrectly - conclude that they demonstrated the absence of an effect of NSAID's on blood pressure.

Thank you for identifying this oversight in the text of our manuscript. Indeed, the secondary outcomes were prespecified in our study protocol prior to the start of the study.

Original manuscript (lines 197-199): Blood pressure trend over time was evaluated by averaging MAP by postpartum day. The first postpartum day spanned the time from medication administration until 24 hours postpartum, the second day from 24-48 hours postpartum, etc.

Revised manuscript (lines 194-197): Several prespecified secondary outcomes were also evaluated. Blood pressure trend over time was evaluated by averaging MAP by postpartum day. The first postpartum day spanned the time from medication administration until 24 hours postpartum, the second day from 24-48 hours postpartum, etc.

Specific comments.

1. Line 125-127. Only one of the many objectives of study is mentioned here. Secondary outcomes?

Thank you for highlighting this opportunity to introduce our secondary outcomes in the introduction. The manuscript text has been revised.

Original Manuscript (lines 125-127): Therefore, the objective of this study was to directly evaluate the effect of ibuprofen on postpartum blood pressure in women with HDP without severe hypertension. Our hypothesis was that NSAID use would increase blood pressure in postpartum women with HDP.

Revised Manuscript (lines 123-127): Therefore, the objective of this study was to directly evaluate the effect of ibuprofen on postpartum blood pressure in women with HDP without severe hypertension. Our hypothesis was that NSAID use would increase blood pressure in postpartum women with HDP. We also aimed to evaluate the effects of ibuprofen use on diuresis, analgesic efficacy, and patient satisfaction in postpartum patients with HDP.

2.Line 137. Why not selection based on MAP? All analyses, including power calculation, are performed with MAP.

Thank you for your comment. We considered the option of using MAP as an inclusion criteria but decided against it. Our goal was for our study's findings to be easily applicable for providers taking care of postpartum women with hypertensive disorders of pregnancy without severe hypertension. We therefore wanted to use standard ACOG definitions for mild hypertension rather than a certain MAP threshold. Furthermore, we felt MAP calculations would be too cumbersome to perform in a real-life labor and delivery scenario.

3.Line 154. What kind of blocks were patients randomized in? How large were the blocks?

Participants were randomized by computer-generated random assignments of group "A" and "B" in blocks of 30. The research pharmacist involved with the study generated the randomization scheme and all providers were blinded to the randomization sequence and block size throughout the study.

Original manuscript (lines 154-155): Randomization group was assigned by computer-generated block randomization.

Revised manuscript (lines 156-157): Randomization group was assigned by computer-generated block randomization with a block size of 30.

4.Lines 176-177. Why the change to manual sphygmomanometry when severe hypertension was detected?

Thank you for the opportunity to explain our blood pressure measurement protocol. Our hospital follows the guidelines and resources recommendations in the California Toolkit to Transform Maternity Care called "Improving Health Care Response to Preeclampsia¹" which was endorsed by the California Maternal Quality Care Collaboration (CMQCC) and reviewed by the California Department of Public Health. In this toolkit, it is noted that although the automated blood pressure machine is the most commonly used tool for blood pressure measurement in the hospital setting, its margin of error can be as high as 10mmHg. It is therefore recommended to switch to manual sphygmomanometer to confirm automated cuff readings of systolic ≥ 160 mmHg or diastolic ≥ 105 mmHg, so that antihypertensive medications can be initiated if severe hypertension persists after 15 minutes.

¹Druzin ML, Shields LE, Peterson NL, K M, Cape V. Preeclampsia Toolkit: Improving Health Care Response to Preeclampsia. 2013:1-136.

5.Lines 179-181. In which groups was oral antihypertensive therapy initiated? Lines 238-239 suggest that they were excluded from analysis.

Our protocol instructed providers to start oral antihypertensive therapy for non-severe hypertension to keep blood pressure $<150/100$ mmHg, which is in accordance with the recommendations in ACOG's Hypertension Task Force Guidelines 2014.¹ The primary outcome analysis of mean postpartum blood pressure included all participants, regardless of antihypertensive therapy. There was also a planned subgroup analysis of postpartum MAP in women who did not receive antihypertensive therapy.

In our study, four participants developed severe hypertension for the first time postpartum after randomization. One participant in the ibuprofen group had severe blood pressure in the postpartum period that required IV antihypertensive treatment; she was subsequently started on an oral antihypertensive medication. Three participants (1 in the ibuprofen group, 2 in the control group) met criteria for oral antihypertensive medications in the postpartum period. In the planned subgroup analysis of the primary outcome which excluded subjects who received any antihypertensive medication we found that even after excluding these four participants, there continued to be no difference between groups in mean MAP (91.7 in ibuprofen group versus 92.3 in the control group, $p=0.74$), average MAP by postpartum day, or blood pressure trend over time.

Manuscript text (lines 237-239): We planned one subgroup analysis of the primary outcome which excluded subjects who received any antihypertensive medication.

¹American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy. November 2013:1-100.

6.Line 224. Did those complications occur?

Thank you for inquiring about our rate of severe maternal morbidities such as cerebrovascular accidents, pulmonary embolism, ICU admission and readmission. None of the participants experienced severe maternal morbidity during the study. One participant in the ibuprofen group was readmitted for severe hypertension.

Manuscript text (lines 301-302): None of the participants experienced severe maternal morbidity during the study. One participant in the ibuprofen group was readmitted for severe hypertension.

7.Line 226. How were the results included in the analysis?

Thank you for this opportunity to clarify how we performed the analysis of outpatient blood pressure measurements. We have revised the manuscript to explain this in more detail.

The primary outcome of mean MAP only included inpatient postpartum blood pressure measurements, and the analysis of outpatient blood pressure mean MAP was performed separately. For the outpatient analysis, we included the first outpatient blood pressure reading from each participant within 10 days of discharge. Seventeen participants completed this follow-up, and we found that postpartum outpatient blood pressure did not differ between groups, with mean MAP in the ibuprofen group 99.0 (95% CI [89.3-108.8]) versus control group 94.5 (95% CI [84.5-104.5], $p=0.46$).

Original manuscript (lines 225-227): Outpatient blood pressure measurements were recommended for all patients and included in the analysis if performed within 10 days of discharge.

Revised manuscript (lines 226-228): Outpatient blood pressure measurement were recommended for all patients and a separate analysis to compare outpatient MAP between study groups was performed. We included the first outpatient blood pressure reading from each participant within 10 days of discharge into the analysis.

8.Line 235. Statistical power was calculated to be able to reject a hypothesis of an increase of 6 mm in MAP with $\alpha=0.05$ and $\beta=0.80$. However, Line 251 indicates that an $\alpha=0.001$ was used in the analyses. Failure to reject the hypothesis of an effect - as in this experiment - does not mean that the alternative hypothesis of no effect is correct as the authors assume in their discussion and conclusions (see e.g. précis).

Thank you for this opportunity to clarify how our statistical analysis was performed and interpreted. The traditional $\alpha=0.05$ and $\beta=0.80$ was used for the analysis of all study outcomes. The $\alpha=0.001$ was used only in the interim analysis, which was conducted using the validated Peto approach on the primary endpoint when 50% of patients were randomized. This approach specified that the trial would be ended if a significant difference in the primary outcome was found between the two study groups using symmetric stopping boundaries at $p<0.001$. We also specified that the study would be halted if there were significant differences in numbers of patients in each group with serum creatinine that exceeds $>1.4\text{mg/dl}$ while using the study drug using symmetric stopping boundaries at $p<0.001$.

We agree that this trial should not be interpreted as proof that there was no difference in blood pressure between the two study groups. The trial was designed as a superiority trial, and our power analysis assumed that ibuprofen would lead to an increase in mean arterial blood pressure of 6mmHg compared to women who were not exposed to NSAIDs. Our findings did not support this hypothesis. To further clarify this in the manuscript, we are changing the language in the manuscript discussion to more clearly state that we did not find evidence that ibuprofen increased postpartum blood pressure compared to women without NSAID exposure.

Original Manuscript (lines 308-310): In this double-blind, randomized control trial of women with HDP without severe hypertension, ibuprofen did not increase postpartum blood pressure compared to women without NSAID exposure.

Revised Manuscript (lines 313-315): In this double-blind, randomized control trial of women with HDP without severe hypertension, we did not find evidence that ibuprofen increased postpartum blood pressure compared to women without NSAID exposure.

9.Line 237. Analyses on an "intention-to-treat" basis? That is not in agreement with the exclusion of patients after randomization. (Lines 239-244, line 255).

Thank you for allowing us to explain our rationale for having this criterion for exclusion after randomization. First, we would like to agree that intention-to-treat analysis is a comparison of the treatment groups which includes all patients as originally allocated after randomization. This is the recommended method in superiority trials to avoid any bias. As a comparison, per-protocol analysis is a comparison of treatment groups that includes only those patients who completed the treatment originally allocated (in this study, it would have excluded any participant who skipped or had a delayed dose of study medication).

While our intent was to adhere to an intention-to-treat analysis in this study, we were concerned that the hemodynamic changes involved in a serious hemorrhage requiring transfusion would invalidate the participant's blood pressure measurements and potentially skew the study group's average blood pressure result. We therefore included this particular scenario as withdrawal criterion, which we acknowledge is a slight deviation from a strict intention-to-treat approach. However, we also felt that our analysis could continue to be described as intention to treat because it differed so substantially from a per-protocol approach.

Ultimately, there was only one participant excluded from the analysis for this indication, and the study groups remained balanced at the end of the study (N=31 in ibuprofen group versus N=30 in control group). Therefore, we do not suspect that excluding the outlier blood pressure data from the participant with postpartum hemorrhage requiring transfusion significantly impacted our findings.

10. References: adequate.

11. Tables. May be combined and reduced in number.

Thank you for this suggestion—we have omitted Table 3 and incorporated the data into the manuscript.

Original Manuscript (lines 278-280): There was no difference in the proportion of participants who requested additional breakthrough medications for women undergoing vaginal delivery (24% in the ibuprofen group versus 30% in the control group, $p=0.62$).

Revised Manuscript (lines 283-286): There was no difference in the proportion of participants who requested additional breakthrough medications for women undergoing vaginal delivery (24% in the ibuprofen group versus 30% in the control group, $p=0.62$) or cesarean delivery (60% in the ibuprofen group versus 25% in the control group, $p=0.36$).

12. Fig.4 . How was the difference between the two Kaplan-Meier curves tested? The 1-survival on the y-axis may be omitted.

Thank you for your suggestion—the 1-survival on the y-axis has been omitted. The hazard ratio for diuresis was determined using Cox regression analysis and significance based on Wald test statistic. Median hours to diuresis was determined using Kaplan-Meier analysis.

Original manuscript (lines 246-248): Cox regression was used to calculate hazard ratio of diuresis at multiple time points, while Mann-Whitney U Test was used to calculate difference in median length of stay and time to diuresis.

Revised manuscript (lines 250-253): The hazard ratio for diuresis was determined using Cox regression analysis and significance based on Wald test statistic. Median hours to diuresis was determined using Kaplan-Meier analysis. Mann-Whitney U Test was used to calculate difference in median length of stay.

STATISTICAL EDITOR'S COMMENTS:

1. Abstract: Needs to conform to our template for RCTs.

Thank you for your recommendation. We have reviewed the template for RCTs and have ensured that the Methods section includes the primary outcome and sample size justification. The Results section begins with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis.

2. lines 232-236: Since the Authors were evaluating an increase in MAP, the baseline of 107 should be compared to a treatment MAP value of 113, not 101. This does not change the sample size calculation.

Thank you for your suggestion. We have modified the MAP value of the treatment group to 113.

Original Manuscript (lines 230-234): To maximize clinical significance we powered our study to detect a difference in MAP of 6mmHg between the study groups, from a MAP of 107mmHg (which is equivalent to 140/90, the minimum blood pressure requirement for inclusion into the study) to a MAP of 101 mmHg, with a standard deviation for average MAP during postpartum stay of 7.9mmHg.

Revised Manuscript (lines 232-236): To maximize clinical significance we powered our study to detect a difference in MAP of 6mmHg between the study groups, from a MAP of 107mmHg (which is equivalent to 140/90, the minimum blood pressure requirement for inclusion into the study) to a MAP of 113 mmHg, with a standard deviation for average MAP during postpartum stay of 7.9mmHg.

3. Table 1: Need units for age, BMI. Since the column sample sizes were N = 31 and 30, the %s should be rounded to nearest integer, not to nearest 0.1%. What were the initial MAPs for the two cohorts and was their anti hypertensive treatment similar?

The antepartum MAP was not used to compare blood pressures between study groups. Instead, we used our selection criteria to create a homogenous study population of women who had mild range blood pressures. Inclusion criteria for the study specified that the participant had at least two blood pressure measurements of systolic blood pressure of 140mmHg or greater, or a diastolic blood pressure of 90mmHg or greater, at least 4 hours apart. Additionally, participants were excluded if they had any severe hypertension before delivery, defined as at least one systolic blood pressure of 160 mmHg or greater, or one diastolic blood pressure measurement of 105 mmHg or greater. The randomization process was expected to further balance any differences between groups. No participants received antihypertensive medications prior to randomization by design.

4. Table 2: Should clearly identify the primary outcome.

Thank you for this suggestion. We have revised Table 2 to better communicate the primary outcome.

Revised Manuscript (lines 434-435):

Table 2. Comparison of average postpartum mean arterial pressure by treatment group

	Ibuprofen N=31	Control N=30	P value
Postpartum mean arterial pressure (MAP), mean \pm SD	93 \pm 7.5	93 \pm 7.2	P=0.93
Mean arterial pressure trends by postpartum day, mean \pm SD:			
Day 1	92 \pm 8.2	93 \pm 7.7	P=0.64
Day 2	93 \pm 7.4	93 \pm 8.0	P=0.81

5. Table 3,5: With these sample sizes, should round the %s to nearest integer %, not to nearest 0.1%.

Thank you for this suggestion. The tables have been revised to round to the nearest integer percent.

6. Table 4: Were the pain scores normally distributed? If not, then should cite as median(IQR or range) and test non-parametrically.

Thank you for highlighting this issue. The primary area of interest for the secondary pain outcome “pain difference” was normally distributed and therefore the table presented values for means and standard deviations. However, the distribution for another variable (“at rest” pain scores) showed potential departures from normality, as the standard deviation was similar to the mean in both groups. Non-parametric equivalent tests were run and yielded similar findings, as shown below. Wilcoxon signed rank test verified the median pain scores were significantly lower at rest in both groups ($p < .001$) and that the distribution of the differential ([acceptable]- [at rest]) did not significantly differ between groups, Mann-Whitney U test, $p = 1.00$.

We have modified the table to present median and interquartile ranges for each category of pain score.

Change to text in Materials and Methods section

Original Manuscript (lines 243-246): The outcome data were first assessed for normality, and then compared between groups with independent t-test (for continuous variables) and chi-squared test (categorical variables). Differences between groups in MAP trend by day and average pain scores were estimated using repeated measures analysis.

Revised Manuscript (lines 246-250): The outcome data were first assessed for normality, and then compared between groups with independent t-test (for continuous variables) and chi-squared test (categorical variables). Mann-Whitney U test was used to determine whether the distribution of the pain difference score differed significantly between groups. Differences between groups in MAP trend by day and were estimated using repeated measures analysis.

Change to text in Results section:

Original manuscript (lines 280-282): Participants in both study groups had good overall pain control, with average pain scores 4.3 points below their self-reported acceptable level (Table 4).

Revised manuscript (lines 286-288): Participants in both study groups had good overall pain control, with average pain scores 4.5 points below their self-reported acceptable level (Table 3).

Table 3. Participant-reported postpartum pain scores by treatment group*

	Ibuprofen N=31	Control N=30	<i>P</i> value
Pain scores, median [IQR]			
Acceptable	6.4 [5.0, 8.0]	6.0 [5.0, 7.0]	
At rest	1.1 [0.0, 4.3]	1.6 [0.1, 2.5]	
Pain difference, median [IQR]	4.5 [1.6, 6.7]	4.5 [2.7, 6.5]	1.0

*Excludes 4 subjects who had postpartum tubal ligation

7. Tables 3,4,5: Could consolidate these into one table of secondary outcomes.

Thank you for your suggestion. We have omitted Table 3 and incorporated the results into the manuscript text.

Original Manuscript (lines 278-280): There was no difference in the proportion of participants who requested additional breakthrough medications for women undergoing vaginal delivery (24% in the ibuprofen group versus 30% in the control group, $p=0.62$).

Revised Manuscript (lines 283-286): There was no difference in the proportion of participants who requested additional breakthrough medications for women undergoing vaginal delivery (24% in the ibuprofen group versus 30% in the control group, $p=0.62$) or cesarean delivery (60% in the ibuprofen group versus 25% in the control group, $p=0.36$).

8. Fig 2: This plot is based on the method of survival analysis, but no need to label the y-axis as (1-survival), since all women survived in the usual meaning. "Cumulative probability of diuresis" alone is sufficient. Although this was NS, the study was not powered to evaluate a difference in hazard rate of diuresis, nor of any of the other NS secondary findings.

Thank you for your suggestion. We have revised the figure to omit “1-survival” in the label on the y-axis.

We agree the study was only powered to evaluate differences in the primary outcome (mean of postpartum mean arterial pressure) and was not powered to detect differences in any secondary outcomes, including diuresis. The findings of no difference, therefore, could be due to a Type II error. This limitation of the secondary outcome analysis is included in the discussion section of the manuscript.

Manuscript text (lines 339-341): We found no statistically significant differences in rates of achieving diuresis between subjects in the ibuprofen group compared to the control group. However, it is possible that we were not powered to detect differences in this outcome, and therefore the association between NSAIDs and postpartum diuresis should be evaluated further in future studies.

Associate Editor's Comments:

Please report blood pressures and percentages in whole numbers only and percentages

Thank you for this comment. We have revised the manuscript so that the mean MAP blood pressure measurements and percentages are reported in whole numbers. Please let us know if you would also prefer the standard deviations to be presented in whole numbers.