Date: Mar 08, 2019
To: "Jalal Nanji" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-172

RE: Manuscript Number ONG-19-172

Impact of a post-cesarean analgesia order-set with split doses of oral opioids

Dear Dr. Nanji:

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 Mar 29, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This paper is globally well written and the topic is in the scope of journal. The statistic analysis is correct and the results are clearly stated.

Reviewer #2: In this retrospective analysis, authors sought to evaluate the impact of introducing split dose opioid prescription on 48-hour in-hospital opioid consumption following cesarean delivery. They reported 56% reduction in opioid consumption with a non-significant increase in mean VAS and a reduction in rates of post-operative nausea and vomiting.

Generally well written and well thought out study of practical impact.

1. Although authors introduced the split doses as a single intervention (coupled with RN education), the pre-intervention trend in use of opioids is not controlled for in their statistical analysis. The most rigorous (and also specifically suited for pharmaceutical interventions) is interrupted time series analysis; as such authors are strongly encouraged to re-run their analysis using this methodology.

2. Authors ought to acknowledge the limitation of not capturing patient satisfaction score, especially given the mildly elevated post intervention VAS score.

3. What exactly were other components of the enhanced recovery after vaginal and CD (lines 103-104)..it seems contradictory to the statement in lines 271-272.

4. This reviewer appreciates the transparency of the discussion on the likely impact of RN education on the results. Rather than a drawback, it actually strengthens the generalizability of the study in informing practices who wish to adopt similar strategies for a more successful program.

* Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. bmj. 2015 Jun 9;350:h2750.

** Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. Journal of clinical pharmacy and therapeutics. 2002 Aug;27(4):299-309.

Reviewer #3: The authors present a retrospective study that evaluates the impact of a new postoperative analgesic order set on reduced post-operative opioid consumption with the hypothesis that the introduction of a default lower split dose of prn oral oxycodone would decrease opioid consumption in the first 48 hours after cesarean delivery without significantly increasing post-operative pain.

The study is well-designed, the paper overall well-written, and the analgesic order set appears to be easily adaptable. As would be expected by reducing default orders for as needed opioids, the total opioid use significantly decreased (by about half), but this did not come at the expense of a clinically significant increase in post-operative pain control.

Following are specific comments and questions:

The abstract and introduction are succinct and well-written. The background information provided is appropriate.

Methods, page 8, lines 141-146: There are comments in the discussion regarding "RNs reported a tendency," "high level of nursing support," and "Nurses also universally like…" (Page 14, lines 277-285). Was this data systematically collected? If so, this should be specified in the methods.

Results:

Page 10, Line 196, Table 1:
-It would be interesting to see if there is a difference in primary versus repeat cesarean deliveries in the "before" and "after" groups as this could impact on pain management if the surgery required increased dissection.
-Similarly, it is stated in the methods that oral gabapentin and/or wound infiltration with bupivacaine CRS were available adjuncts. Did the use of these agents differ between groups?

Figures: This data presented in figure 1 are also presented in the text and in in table 2. This figure is redundant and likely superfluous. The same could be said of figure 2 (data are presented in text and in Table 3) and of figure 3 (data are presented in text and in Table 4).

Discussion:

In addition to the split dosing introduced in the new order set, there was nurse education that was conducted, and breakthrough IV medication was changed from morphine to hydromorphone. The education piece is addressed on page 14, lines 265-270. The potential for impact (or not) of the change in IV medications should be addressed as well.

As noted above, there are multiple comments to nurses' responses to the new order set. If this data was systematically collected, then this should be documented in the methods. If this was not, then nurse statements are anecdotal and to say that they "universally like" something is inappropriate and beyond the scope of the discussion.

Reviewer #4:

1. This is a retrospective electronic chart analysis of the change in dosage of Opioids administered in the first 48 hours following Cesarean delivery. A more precise study would have been a blinded randomized trial of these two therapeutic modalities. Respecfully, I disagree with the authors statement regarding/negating this point (see lines 259-261) stating "a randomized control study is likely impractical in this setting"(?).

2. Clearly the primary goal of decreasing Opioid dosage is avoiding potential addiction in the months/years following exposure/delivery. I note the marked absence of follow up data pertaining to possible Opioid addiction.

3. To my knowledge, dosage thresholds for developing Opioid dependence/addiction have not been well established. Therefore, unless proven that lower rates of subsequent dependence/addition are forwarded, any long-term result of decreasing Opioid dosage remains unproven, insufficient and although possibly correct, speculative in nature.

4. In my assessment, the far preferred clinical approach to decreasing Opioid dependence/addiction, is avoiding the primary exposure to this pain medication - irrespective of dosage.

5. In our inner City teaching Hospital, wide application of intra-operative intrathecal or epidural Cesarean Opioid (Morphine) management is practiced. As a result, approximately 95% of our patients do not require post Cesarean systemic Opioids and will suffice with either Tylenol, Ibuprofen or Gabapentin. In addition, Obstetrical Anesthesiology in our institution utilize ultrasound-guided Quadratous Lumborum Block for post Cesarean delivery pain (see reference and abstract below)

a. Krohg A, Ullensvang K, Rosseland LA, Langesæter E, Sauter AR. The Analgesic Effect of Ultrasound-Guided Quadratus Lumborum Block After Cesarean Delivery: A Randomized Clinical Trial. Anesth Analg. 2018 Feb;126(2):559-565. doi: 10.1213/ANE.0000000000002648.

Abstract
BACKGROUND:
Landmark and ultrasound-guided transversus abdominis plane blocks have demonstrated an opioid-sparing effect postoperatively after cesarean delivery. The more posterior quadratus lumborum (QL) might provide superior local anesthetic spread to the thoracolumbar fascia and paravertebral space. The aim of our study was to evaluate the efficacy of the QL block after cesarean delivery.
METHODS:
A randomized, double-blind, controlled trial was performed. Forty parturients undergoing cesarean delivery received bilateral ultrasound-guided QL blocks with either 2 mg/mL ropivacaine or saline postoperatively. All patients received spinal anesthesia with bupivacaine and sufentanil and a postoperative analgesic regimen of paracetamol, ibuprofen, and ketobemidone administered by a patient-controlled analgesic pump. The ketobemidone consumption and time of each dose administered were recorded. The primary outcome was ketobemidone consumption during the first 24 hours postoperatively. Secondary and exploratory analyses compared repeated measures of pain scores, nausea, and fatigue, and total differences in time until patients were able to stand and able to walk 5 m, and the interaction between the effective analgesic score and time.
RESULTS:
All 40 patients completed the trial, 20 in each group. The cumulative ketobemidone consumption in 24 hours was reduced in the active group compared with the control group (P = .04; ratio of means = 0.60; 95% confidence interval, 0.37-0.97). The effective analgesic scores were significantly better in the treatment group compared with the placebo group both at rest (P < .01) and during coughing (P < .01).
CONCLUSIONS:
QL block with ropivacaine reduces the postoperative ketobemidone consumption and pain intensity as a part of a multimodal analgesic regimen that excludes neuraxial morphine.

6. Another drawback of the study design of the current submission is that upon implementation of a lower dosage of Opioids, at least potentially, education of staff regarding potential dangers of Opioids may have lead to an observed decrease is utilization of Opioids. Interestingly, the authors themselves have acknowledged this point (see lines # 265 - 273). This point would have been negated in a blinded randomized study.

7. I note the absence of data pertaining to medication prescription upon discharge.

8. The manuscript has not been prepared according to the stipulations of the Journal (see Editorial Manager/Instructions for Authors).

9. I note inclusion of abbreviations not supported by the Journal (QI, RN, PONV, VPS etc).

10. Line # 231: "unsurprising" should be "not surprising".

11. The Precise statement as written is incomplete and should include dosages (and not simply suffice with the statement "split doses"), as the latter could pertain to the same overall dosage given at separate intervals (which does not reflect a decrease in Opioid dosage).

12. The above statement/point also pertains to the Objective in the Abstract (line # 43).

13. The Conclusion statement should center upon results and be devoid of (repetitive) possibly self-complimentary data such as "This study of over 1000 patients".

14. The second sentence of the Abstract Conclusion (lines s# 62 -64), should be omitted, as this is a speculative statement and not a valid/substantiated conclusion.

15. Table 1: I am unfamiliar with the difference between the designations "urgent versus emergent". This should be detailed.

16. In general, I find the list of references lacking/insufficient. For example, I draw the authors attention to a recently published, key peer-reviewed publication by Badreldin et al, which in my assessment must be included in the discussion of Opioid's and Obstetrics (see following);

a. Badreldin N, Grobman WA, Chang KT, Yee LM. Opioid prescribing patterns among postpartum women. Am J Obstet Gynecol. 2018 Jul;219(1):103.e1-103.e8. doi: 10.1016/j.ajog.2018.04.003. Epub 2018 Apr 7.

Abstract
BACKGROUND:
Women commonly receive opioid prescriptions following hospitalization. The rise of the opioid epidemic in the United States

underscores the importance of a better understanding of prescribing patterns. Although delivery is the most frequent reason for hospitalization in the United States, there is inadequate knowledge regarding opioid prescribing at postpartum hospital discharge.
OBJECTIVE:
We sought to describe opioid prescribing patterns at the time of discharge following delivery in a large, diverse cohort, and to describe the relationship of these patterns with objective and subjective measures of pain prior to discharge.
STUDY DESIGN:
This is a retrospective cohort study of all deliveries at a single, high-volume tertiary care center over a 1-year period. Women were excluded from analysis if they had evidence of recent opioid use, or their labor, delivery, or postpartum course was notable for rare, nonroutine events anticipated to increase pain. Medical records were queried for demographic and clinical data, including whether an opioid prescription was provided at discharge, and if so, details of that prescription. The primary outcome was amount of opioid morphine milligram equivalents prescribed at discharge, described separately for women after vaginal and cesarean deliveries. Among women who received a prescription, we additionally assessed associations between prescription quantity and subjective (patient-reported pain score) and objective (inpatient opioid requirement during the final 24 hours of hospitalization) assessments of pain. Descriptive and bivariable analyses were performed.
RESULTS:
Of the total 12,611 women, 12,326 were eligible for inclusion. Of 9038 women postvaginal delivery and 3288 women postcesarean delivery, 30.4% and 86.7% received an opioid prescription at discharge, respectively. Of women receiving discharge opioid prescriptions, median morphine milligram equivalents received was 200 (interquartile range: 120-300) following vaginal and 300 (interquartile range: 200-300) following cesarean delivery. Nearly half (45.7%) of women postvaginal delivery and 18.5% of women postcesarean delivery who received an opioid prescription used 0 morphine milligram equivalent during the final hospital day. Similarly, 26.5% and 18.5% of women after vaginal and cesarean delivery, respectively, reported a pain score of 0 of 10 prior to discharge. Regardless of delivery mode, the amount of opioids prescribed did not differ between those who reported a pain score of 0 of 10 and those who reported a pain score of >0 of 10 immediately prior to discharge. Similarly, for women who underwent cesarean delivery, the morphine milligram equivalents prescribed did not differ between those who used 0 morphine milligram equivalents and those who used >0 in the 24 hours prior to hospital discharge.
CONCLUSION:
Postpartum women are commonly prescribed opioids at the time of postpartum hospital discharge. There is a wide range of morphine milligram equivalents prescribed at hospital discharge following delivery, highlighting a lack of standardization. Furthermore, regardless of objective and subjective measures of pain prior to discharge, women received similar amounts of prescription morphine milligram equivalents following either vaginal or cesarean deliveries.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Table 2: Need to clearly separate the primary outcome (opioid use 0-48 hrs post-op) from the others. Also, need to clarify the difference in non-opioid use in Table 2: 111/542=20.4% (before) and 139/508 =27.4% (after) vs Table 3: 133/540 =24.6% (before) and 152/504=30.1% (after). Some of these could be missing values for pain scores, but that would only account for a handful of the differences. Each of these proportions were significantly different, with more women in the after group requiring no opioids.

Since the protocol (lines 133-140) was not altered from before to after in terms of the VPS threshold, the non-randomized groups had a lower proportion of women who required any opioid, so a further examination of the subsets is needed.

The same proportion of women in each cohort required intravenous opioids, but since the protocol differed in terms of IV drugs used, were the total morphine equivalents for those two groups (n = 72 vs 67) the same per patient, or could that have skewed the total 0-48 dose for one group vs the other?

That is, should include a flow diagram beginning with each group's total "N", then the number requiring no opioid, then the number who needed 5 and the number who needed 10 mg for the first group, then the number who needed 2.5, then the additional 2.5, also the number needing 5, then the additional 5 (that is, according to their VPS stratum). This would offer more comparisons than is conveyed by the total mgms of morphine equivalents. This was not the primary outcome, but since the groups were different in proportion requesting opioids, it would be of interest to the reader to see whether the groups with VPS ≤ 4 or 5-10 were also different in the two groups.

Table 3: Please verify the different in peak pain scores for those requiring opioids: 6.5 vs 6.8 had a p-value of .002. Using the means and SDs provided, I calculate .02.

Appendix 1: How many patients were given infusion of bupivacaine and in which groups? How many were given gabapentin and in which groups?

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=.) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

Many of our opioid studies report the MME. Although you apparently only used oxycodone, so that it is easy for people interested in this topic to compare findings in different studies, please report the MME's as well as the mg of oxycodone.

- from what I can find out, an "impact study" is primarily used in business and will be unlikely to be familiar to the majority of readers. In the manuscript, and perhaps in the supplemental digital content, please describe the methods. I'm most familiar with a before/after study for medical interventions How does this differ? This also could be consider a QI project. Why did you not pick either of these types of approaches?

- was the primary outcome any use or did you use MME?

- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- Do not begin a sentence with a numeral. Either reorganize your sentence to not start with a number OR write out the number in words.

- I'm not clear what you are averaging here. Could you please describe that in the methods? How often are patients queried about their pain level?

- Please note that this is not an acceptable abbreviation. Please consult the Instructions for Authors regarding the use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. ghout the manuscript. Please spell out all abbreviations on first use. It is reasonable to not use abbreviations for words that are seldom used in the paper. We try to limit "unique" abbreviations so that readers don't have to frequently refer back to the first notation of the abbreviation to remember its meaning. We realize that this may affect word count but believe it makes it easier in most cases for the reader.

- and divergence of meds to others

- do you have a reference for this?

- Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

- Understanding that this is an "impact" study, it is an idiosyncratic fact that at the Journal we tend to avoid the use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow.

- do you have enough data to break out scheduled vs non scheduled CS to see if there were differences?

- So, I see this is a QI project. It should be presented as such in the methods section. Please read the instructions for authors as we require the SQUIRES publication guideline for QI projects. W/ revision, please submit the check list. Please state if your IRB allows you publish QI projects even if they exempt them prior to performance of them.

- By describing this as novel, you are making a primacy claim: yours is the first, biggest, etc…In order to assert that, you need to provide the search terms used and the data base (s) searched (PubMed, Google Scholar, etc) to substantiate the claim. Otherwise, it needs to be deleted.

- do you mean maintenance dosing?

- Is this for throughout the post op period or only in the immediate post op period?

- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

- to be clear, prior to the change, if a patient gave a verbal pain score of 1, you gave her 5 mg of oxycodone? Why?

- At UNC, the anesthesia service manages post op pain in the OB unit, including post partum Is that true at Stanford?

- Was the patient told she was receiving 1/2 dose?

- please describe the protocol for obtaining verbal pain scores. Since you are reporting an average result, we need to know how often these were collected.

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=.) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

- were there any other changes in the way cesarean deliveries were performed during this time frame or any other anesthetic changes?

- please tell us how many did require IV rescue.

- rather than say "Large" just give the percentage and let the reader just its relative size.

- was this solicited feedback? One of the problems with some of the studies we've seen is that the lack of feedback from the nurses, when not solicited in a proactive manner, is interpreted as the lack of an effect on the nurses. Please comment.

- you should state this in the methods. The methods read as though a pain score <=4 should be treated with a 2.5 mg dose of oxycodone.

2. Your manuscript is a QI study. Please edit your manuscript so that it conforms to the guidelines for the Clinical Practice and Quality manuscript type. Please also submit a completed SQUIRE 2.0 checklist. Please see the Instructions For Authors at https://edmgr.ovid.com/ong/accounts/authors.pdf for the full instructions for this article type.

3. 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.

4. 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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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: Clinical Practice and Quality articles 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. Title: Please do not use the word "impact" in your title or manuscript. Would the substitution of "Association of..." be more appropriate?

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: Clinical Practice and Quality, 300 words. Please provide a word count.

10. 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.

11. 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.

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' (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.

14. Figures - The figures may be resubmitted as-is.

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

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

16. 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 and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 29, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Nancy C. Chescheir, MD
Editor-in-Chief

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

March 26, 2019

Attention:
Dr. Nancy C. Chescheir, MD
Editor-in-Chief, Obstetrics & Gynecology

Re: Manuscript Title: Evaluation of a post-cesarean analgesia order-set with split doses of oral opioids

Dear Dr. Chescheir,

Thank you for reviewing and providing feedback on our study for potential publication in *Obstetrics & Gynecology*. We have responded line-by-line to all the reviewer comments, which can be found attached to this letter. We have corrected the manuscript as requested and have used the Track Changes feature in Microsoft Word to account for the changes as per your instructions. We are happy to make any further changes if needed.

The manuscript has not been submitted for publication nor has it been published in whole or in part elsewhere. We attest to the fact that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to *Obstetrics & Gynecology.* There are no possible conflicts of interest, and sources of financial support, corporate involvement, patent holdings, etc. for each of the authors are outlined in the title page. Copyright transfer and the signatures of all authors will be requested prior to publication of accepted manuscripts.

Yours sincerely,

Jalal A. Nanji
Nan Guo
Edward T. Riley
Bethan Faulkner
Christina Do
Brendan Carvalho

REVIEWER COMMENTS:

Reviewer #1: This paper is globally well written and the topic is in the scope of journal. The statistic analysis is correct and the results are clearly stated.

Thank you for the feedback.

Reviewer #2: In this retrospective analysis, authors sought to evaluate the impact of introducing split dose opioid prescription on 48-hour in-hospital opioid consumption following cesarean delivery. They reported 56% reduction in opioid consumption with a non-significant increase in mean VAS and a reduction in rates of post-operative nausea and vomiting.

Generally well written and well thought out study of practical impact.

1. Although authors introduced the split doses as a single intervention (coupled with RN education), the pre-intervention trend in use of opioids is not controlled for in their statistical analysis. The most rigorous (and also specifically suited for pharmaceutical interventions) is interrupted time series analysis; as such authors are strongly encouraged to re-run their analysis using this methodology.

We agree that interrupted time series analysis is the best way to evaluate the longitudinal effect of intervention. However, we did not perform this analysis for several reasons. First, this type of analysis requires the intervention to occur at a specific point in time, and the outcome is expected to change immediately and abruptly as a result of the intervention. As described in our methods, our intervention occurred over 4 months. We therefore dropped patients who received opioids in the intervening period (August 2017 to November 2017 inclusive) from the analysis.

Second, we did not obtain data with enough time periods before the intervention, and sufficient data collected at multiple time points is required in order to obtain a stable estimate of the underlying trend.

2. Authors ought to acknowledge the limitation of not capturing patient satisfaction score, especially given the mildly elevated post intervention VAS score.

We had actually captured satisfaction scores as part of the data-set and have updated the manuscript to reflect the fact that there was no difference in satisfaction score (out of 100) at 48 hours.

3. What exactly were other components of the enhanced recovery after vaginal and CD (lines 103-104)..it seems contradictory to the statement in lines 271-272.

These enhanced recovery components have occurred over a number of years, including the addition of intraoperative dexamethasone during CD as well as fluid warming and forced air warming. Importantly, none of these other changes occurred during the study period for this particular order-set change. For clarity, we have removed the confusing language from lines 103-104.

4. This reviewer appreciates the transparency of the discussion on the likely impact of RN education on the results. Rather than a drawback, it actually strengthens the generalizability of the study in informing practices who wish to adopt similar strategies for a more successful program.

We agree, thank you for the feedback. However, in response to comments from Reviewer #3, we have removed the sections of the discussion that are anecdotal, as these data were not systematically collected.

* Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. bmj. 2015 Jun 9;350:h2750.

** Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. Journal of clinical pharmacy and therapeutics. 2002 Aug;27(4):299-309.

Reviewer #3: The authors present a retrospective study that evaluates the impact of a new postoperative analgesic order set on reduced post-operative opioid consumption with the hypothesis that the introduction of a default lower split dose of prn oral oxycodone would decrease opioid consumption in the first 48 hours after cesarean delivery without significantly increasing post-operative pain.

The study is well-designed, the paper overall well-written, and the analgesic order set appears to be easily adaptable. As would be expected by reducing default orders for as needed opioids, the total opioid use significantly decreased (by about half), but this did not come at the expense of a clinically significant increase in post-operative pain control.

Following are specific comments and questions:

The abstract and introduction are succinct and well-written. The background information provided is appropriate.

Methods, page 8, lines 141-146: There are comments in the discussion regarding "RNs reported a tendency," "high level of nursing support," and "Nurses also universally like…" (Page 14, lines 277-285). Was this data systematically collected? If so, this should be specified in the methods.

These data were not systematically collected, and therefore as per below the discussion has been revised.

Results:

Page 10, Line 196, Table 1:
-It would be interesting to see if there is a difference in primary versus repeat cesarean deliveries in the "before" and "after" groups as this could impact on pain management if the surgery required increased dissection.

Unfortunately our EMR coding and how the data is recorded by unit clerks/charge nurses does not allow for precise determination of primary vs. repeat CD, although we agree that this would be an interesting subgroup analysis.

-Similarly, it is stated in the methods that oral gabapentin and/or wound infiltration with bupivacaine CRS were available adjuncts. Did the use of these agents differ between groups?

We have updated the manuscript to report gabapentin use, which did not differ statistically between groups. With our current data-set we are unable to analyze and include wound infiltration with bupivacaine. However very few women receive would infiltration and our practice of selective utilization did not change during the study period.

Figures: This data presented in figure 1 are also presented in the text and in in table 2. This figure is redundant and likely superfluous. The same could be said of figure 2 (data are presented in text and in Table 3) and of figure 3 (data are presented in text and in Table 4).

We feel the data are important to display in figure form, and in order to ensure completeness of the tables we have added them there as well. As per the Editor's comments/suggestions below, we have chosen to resubmit the figures "as is" for this reason.

Discussion:

In addition to the split dosing introduced in the new order set, there was nurse education that was conducted, and breakthrough IV medication was changed from morphine to hydromorphone. The education piece is addressed on page 14, lines 265-270. The potential for impact (or not) of the change in IV medications should be addressed as well.

Only a very small percentage of women overall required IV opioids, and studies that have compared morphine to hydromorphone have found similar efficacy in terms of postoperative analgesia. It is unlikely that this change impacted our results, however we have updated the discussion to highlight that the change from morphine to hydromorphone as IV rescue on the postpartum ward may have had an impact on our results. Please see further details under our responses to the Statistical Editor.

As noted above, there are multiple comments to nurses' responses to the new order set. If this data was systematically collected, then this should be documented in the methods. If this was not, then nurse statements are anecdotal and to say that they "universally like" something is inappropriate and beyond the scope of the discussion.

We have removed the sections of the discussion that are anecdotal, as these data were not systematically collected.

Reviewer #4:

1. This is a retrospective electronic chart analysis of the change in dosage of Opioids administered in the first 48 hours following Cesarean delivery. A more precise study would have been a blinded randomized trial of these two therapeutic modalities. Respecfully, I disagree with the authors statement regarding/negating this point (see lines 259-261) stating "a randomized control study is likely impractical in this setting"(?).

This sentence has been re-worded to reflect that these two methodologies are likely complementary in nature.

2. Clearly the primary goal of decreasing Opioid dosage is avoiding potential addiction in the

months/years following exposure/delivery. I note the marked absence of follow up data pertaining to possible Opioid addiction.

This study primarily focused on in-hospital use of opioids. We agree that evaluating persistent use is an important outcome and that long-term follow up of these patients is critical, and hope that much work goes into evaluating longer-term clinically-relevant outcomes.

3. To my knowledge, dosage thresholds for developing Opioid dependence/addiction have not been well established. Therefore, unless proven that lower rates of subsequent dependence/addition are forwarded, any long-term result of decreasing Opioid dosage remains unproven, insufficient and although possibly correct, speculative in nature.

We have updated the introduction to reflect that the public health implications of opioid reduction may be significant (although as yet unproven).

4. In my assessment, the far preferred clinical approach to decreasing Opioid dependence/addiction, is avoiding the primary exposure to this pain medication - irrespective of dosage.

5. In our inner City teaching Hospital, wide application of intra-operative intrathecal or epidural Cesarean Opioid (Morphine) management is practiced. As a result, approximately 95% of our patients do not require post Cesarean systemic Opioids and will suffice with either Tylenol, Ibuprofen or Gabapentin. In addition, Obstetrical Anesthesiology in our institution utilize ultrasound-guided Quadratous Lumborum Block for post Cesarean delivery pain (see reference and abstract below)

a. Krohg A, Ullensvang K, Rosseland LA, Langesæter E, Sauter AR. The Analgesic Effect of Ultrasound-Guided Quadratus Lumborum Block After Cesarean Delivery: A Randomized Clinical Trial. Anesth Analg. 2018 Feb;126(2):559-565. doi: 10.1213/ANE.0000000000002648.

Abstract
BACKGROUND:
Landmark and ultrasound-guided transversus abdominis plane blocks have demonstrated an opioid-sparing effect postoperatively after cesarean delivery. The more posterior quadratus lumborum (QL) might provide superior local anesthetic spread to the thoracolumbar fascia and paravertebral space. The aim of our study was to evaluate the efficacy of the QL block after cesarean delivery.
METHODS:
A randomized, double-blind, controlled trial was performed. Forty parturients undergoing cesarean delivery received bilateral ultrasound-guided QL blocks with either 2 mg/mL ropivacaine or saline postoperatively. All patients received spinal anesthesia with bupivacaine and sufentanil and a postoperative analgesic regimen of paracetamol, ibuprofen, and ketobemidone administered by a patient-controlled analgesic pump. The ketobemidone consumption and time of each dose administered were recorded. The primary outcome was ketobemidone consumption during the first 24 hours postoperatively. Secondary and exploratory analyses compared repeated measures of pain scores, nausea, and fatigue, and total differences in time until patients were able to stand and able to walk 5 m, and the interaction between the effective analgesic score and time.
RESULTS:
All 40 patients completed the trial, 20 in each group. The cumulative ketobemidone consumption in 24 hours was reduced in the active group compared with the control group ($P = .04$; ratio of means = 0.60; 95% confidence interval, 0.37-0.97). The effective analgesic scores were significantly better in the treatment group compared with the placebo group both at rest ($P < .01$) and during coughing ($P < .01$).

CONCLUSIONS:
QL block with ropivacaine reduces the postoperative ketobemidone consumption and pain intensity as a part of a multimodal analgesic regimen that excludes neuraxial morphine.

While we agree that blocks such as TAP and QL likely do have a role in post-cesarean analgesia, given that data to date suggests little benefit when performed in patients who already received neuraxial morphine (including as described in the above abstract), we elected not to discuss them in great detail in this manuscript as all patients received neuraxial morphine in our analysis. Additionally, despite analgesic intervention e.g. TAP/QL blocks, many women still require opioids for breakthrough pain. Our study addresses how to best prescribe for these women and could be applied in any setting including both those in which women receive and do not receive regional blocks.

6. Another drawback of the study design of the current submission is that upon implementation of a lower dosage of Opioids, at least potentially, education of staff regarding potential dangers of Opioids may have lead to an observed decrease is utilization of Opioids. Interestingly, the authors themselves have acknowledged this point (see lines # 265 - 273). This point would have been negated in a blinded randomized study.

Yes, we agree that this is a potential confounder and have attempted to address it transparently in the discussion. Any change in prescribing practice is inherently unblinded, and does require educational effort to get staff familiar with the change. Therefore, these changes are always coupled, and it may be the combination rather than one in isolation that works as we highlight. Reviewer #2 notes that this " actually strengthens the generalizability of the study"

7. I note the absence of data pertaining to medication prescription upon discharge.

We fully acknowledge the importance of practices at discharge and are currently working on individualized opioid prescribing and enhanced patient analgesic education at our institution.

8. The manuscript has not been prepared according to the stipulations of the Journal (see Editorial Manager/Instructions for Authors).

The manuscript has been updated accordingly.

9. I note inclusion of abbreviations not supported by the Journal (QI, RN, PONV, VPS etc).

The manuscript has been updated accordingly to remove specific abbreviations. Per the instructions to authors, we have used only abbreviations found in Dorland's Illustrated Medical Dictionary, 32nd Ed. or those found on the Journal's acceptable list.

10. Line # 231: "unsurprising" should be "not surprising".

The manuscript has been updated accordingly.

11. The Precise statement as written is incomplete and should include dosages (and not simply suffice with the statement "split doses"), as the latter could pertain to the same overall dosage given at separate intervals (which does not reflect a decrease in Opioid dosage).

We have edited the precis to make this clearer given the limitations of the word count.

12. The above statement/point also pertains to the Objective in the Abstract (line # 43).

We have edited the abstract to make this clearer.

13. The Conclusion statement should center upon results and be devoid of (repetitive) possibly self-complimentary data such as "This study of over 1000 patients".

The abstract has been updated accordingly.

14. The second sentence of the Abstract Conclusion (lines s# 62 -64), should be omitted, as this is a speculative statement and not a valid/substantiated conclusion.

The abstract has been updated accordingly.

15. Table 1: I am unfamiliar with the difference between the designations "urgent versus emergent". This should be detailed.

The methods section has been updated to better define these terms for clarity.

16. In general, I find the list of references lacking/insufficient. For example, I draw the authors attention to a recently published, key peer-reviewed publication by Badreldin et al, which in my assessment must be included in the discussion of Opioid's and Obstetrics (see following);

Thank you for drawing our attention to this reference. Our primary focus was on opioid-prescribing in-hospital in the immediate postoperative period, but nonetheless agree that studies on post-discharge prescribing patterns (like that done by Bateman, et al. – already referenced) are vital to a global and holistic understanding of strategies to minimize/eliminate opioid use after CD. We have included this new reference for completeness.

a. Badreldin N, Grobman WA, Chang KT, Yee LM. Opioid prescribing patterns among postpartum women. Am J Obstet Gynecol. 2018 Jul;219(1):103.e1-103.e8. doi: 10.1016/j.ajog.2018.04.003. Epub 2018 Apr 7.

Abstract
BACKGROUND:
Women commonly receive opioid prescriptions following hospitalization. The rise of the opioid epidemic in the United States underscores the importance of a better understanding of prescribing patterns. Although

delivery is the most frequent reason for hospitalization in the United States, there is inadequate knowledge regarding opioid prescribing at postpartum hospital discharge.
OBJECTIVE:
We sought to describe opioid prescribing patterns at the time of discharge following delivery in a large, diverse cohort, and to describe the relationship of these patterns with objective and subjective measures of pain prior to discharge.
STUDY DESIGN:
This is a retrospective cohort study of all deliveries at a single, high-volume tertiary care center over a 1-year period. Women were excluded from analysis if they had evidence of recent opioid use, or their labor, delivery, or postpartum course was notable for rare, nonroutine events anticipated to increase pain. Medical records were queried for demographic and clinical data, including whether an opioid prescription was provided at discharge, and if so, details of that prescription. The primary outcome was amount of opioid morphine milligram equivalents prescribed at discharge, described separately for women after vaginal and cesarean deliveries. Among women who received a prescription, we additionally assessed associations between prescription quantity and subjective (patient-reported pain score) and objective (inpatient opioid requirement during the final 24 hours of hospitalization) assessments of pain. Descriptive and bivariable analyses were performed.
RESULTS:
Of the total 12,611 women, 12,326 were eligible for inclusion. Of 9038 women postvaginal delivery and 3288 women postcesarean delivery, 30.4% and 86.7% received an opioid prescription at discharge, respectively. Of women receiving discharge opioid prescriptions, median morphine milligram equivalents received was 200 (interquartile range: 120-300) following vaginal and 300 (interquartile range: 200-300) following cesarean delivery. Nearly half (45.7%) of women postvaginal delivery and 18.5% of women postcesarean delivery who received an opioid prescription used 0 morphine milligram equivalent during the final hospital day. Similarly, 26.5% and 18.5% of women after vaginal and cesarean delivery, respectively, reported a pain score of 0 of 10 prior to discharge. Regardless of delivery mode, the amount of opioids prescribed did not differ between those who reported a pain score of 0 of 10 and those who reported a pain score of >0 of 10 immediately prior to discharge. Similarly,
for women who underwent cesarean delivery, the morphine milligram equivalents prescribed did not differ between those who used 0 morphine milligram equivalents and those who used >0 in the 24 hours prior to hospital discharge.
CONCLUSION:
Postpartum women are commonly prescribed opioids at the time of postpartum hospital discharge. There is a wide range of morphine milligram equivalents prescribed at hospital discharge following delivery, highlighting a lack of standardization. Furthermore, regardless of objective and subjective measures of pain prior to discharge, women received similar amounts of prescription morphine milligram equivalents following either vaginal or cesarean deliveries.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Table 2: Need to clearly separate the primary outcome (opioid use 0-48 hrs post-op) from the others.

We have rearranged the table for clarity

Also, need to clarify the difference in non-opioid use in Table 2: 111/542=20.4% (before) and 139/508 =27.4% (after) vs Table 3: 133/540 =24.6% (before) and 152/504=30.1% (after). Some of these could be missing values for pain scores, but that would only account for a handful of the differences. Each of these proportions were significantly different, with more women in the after group requiring no opioids.

Table 2 "any opioid" use refers to any opioid use postoperatively until discharge (not just 1st 48 hours). We have updated the table accordingly to clarify this point. Table 3 VPS are only until 48 hours, which explains the difference in the proportion (some patients would have taken their first opioid after the 48 hour mark). Additionally, missing N in each group in Table 3 are due to missing/incomplete VPS data. If you desire we can amend Table 2 to reflect opioid use only up to the 48 hour mark.

Since the protocol (lines 133-140) was not altered from before to after in terms of the VPS threshold, the non-randomized groups had a lower proportion of women who required any opioid, so a further examination of the subsets is needed.

We attempted to discuss this finding in our discussion: "When broken down by opioid users vs. non-users, a small increase in both average and peak VPS is seen in the opioid users. A larger percentage of patients did not use any opioids after implementation of the new order-set and the lack of any clinically significant difference in either average or peak VPS in this cohort suggests that it is unlikely that patients experienced more pain due to lack of access to opioids that would have otherwise been effective after our new order-set was implemented."

If required, we can include these data in the results section.

The same proportion of women in each cohort required intravenous opioids, but since the protocol differed in terms of IV drugs used, were the total morphine equivalents for those two groups (n = 72 vs 67) the same per patient, or could that have skewed the total 0-48 dose for one group vs the other?

In the first 48 hours, in patients who received IV opioids the intravenous morphine equivalents used were 33.5 [24-49] mg before and 19.6 [8.8-34.2] mg after, P<0.001. In patients who didn't receive IV morphine it was 7.5 [0-20] mg before and 2.5 [0-10] mg after, P<0.001. Thus, the reduction in opioid consumption is seen both in those that DID receive IV opioids as well as in those that DID NOT. Furthermore, overall IV opioid use was low as we have discussed and so we do not feel that the switch to hydromorphone or fentanyl from morphine had a marked impact on the overall reduction in opioid consumption.

That is, should include a flow diagram beginning with each group's total "N", then the number requiring no opioid, then the number who needed 5 and the number who needed 10 mg for the first group, then the number who needed 2.5, then the additional 2.5, also the number needing 5, then the additional 5 (that is, according to their VPS stratum). This would offer more comparisons than is conveyed by the total mgms of morphine equivalents. This was not the primary outcome, but since the groups were different in proportion requesting opioids, it would be of interest to the reader to see whether the groups with VPS ≤ 4 or 5-10 were also different in the two groups.

Because pain was assessed as per usual nursing protocol on our unit, the fact that VPS was assessed multiple times for each patient and that the number of individual data points varies between patients, we

find it very difficult to group patients by VPS.

Table 3: Please verify the different in peak pain scores for those requiring opioids: 6.5 vs 6.8 had a p-value of .002. Using the means and SDs provided, I calculate .02.

Below please find the STATA output for this outcome measure showing the T test and p-value.

```
. ttest meas_value if op_dose>0, by(cohort)

Two-sample t test with equal variances
```

Group	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
Before	407	6.464373	.0856158	1.727233	6.296068	6.632679
After	352	6.846591	.0883181	1.656994	6.672892	7.02029
combined	759	6.641634	.0618735	1.704613	6.52017	6.763098
diff		-.3822174	.1233755		-.6244163	-.1400186

```
    diff = mean(Before) - mean(After)                             t =  -3.0980
Ho: diff = 0                                     degrees of freedom =      757

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.0010         Pr(|T| > |t|) = 0.0020          Pr(T > t) = 0.9990
```

Appendix 1: How many patients were given infusion of bupivacaine and in which groups? How many were given gabapentin and in which groups?

We have updated the manuscript to report gabapentin use, which did not differ statistically between groups. With our current data-set we are unable to analyze and include wound infiltration with bupivacaine. However very few women receive would infiltration and our practice to select utilization has not changed during the study period.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect

size= ; 95% CI=.) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

See answer below

Many of our opioid studies report the MME. Although you apparently only used oxycodone, so that it is easy for people interested in this topic to compare findings in different studies, please report the MME's as well as the mg of oxycodone.

Actually, opioid consumption in our study is uniformly reported as IME (intravenous morphine equivalents) and not as mg of oxycodone, as some patients also received intravenous medications for analgesia such as fentanyl, morphine, and hydromorphone postoperatively (as per our Appendix 1). IME is essentially similar to MME except that MME is Oral Milligram Morphine Equivalents and not intravenous.

- from what I can find out, an "impact study" is primarily used in business and will be unlikely to be familiar to
the majority of readers. In the manuscript, and perhaps in the supplemental digital content, please describe
the methods. I'm most familiar with a before/after study for medical interventions How does this differ? This also could be consider a QI project. Why did you not pick either of these types of approaches?

Thank you for the feedback. For clarity, this project was indeed a before/after study associated with a quality improvement initiative that was undertaken at Stanford, and which we retrospectively reviewed. We have removed references to the term “impact” study in the manuscript.

- was the primary outcome any use or did you use MME?

Clarified. The primary outcome was opioid use (in intravenous milligram morphine equivalents – IME) in the first 48 hours.

- The Journal style doesn’t not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

Done

- Do not begin a sentence with a numeral. Either reorganize your sentence to not start with a number OR write out the number in words.

Done

- I'm not clear what you are averaging here. Could you please describe that in the methods? How often are
patients queried about their pain level?

Methods updated to explain how we arrived at average VPS and peak VPS. As described in methods, VPS assessment was not standardized and occurred per usual nursing protocol. We have acknowledged this limitation in our Discussion also.

- Please note that this is not an acceptable abbreviation. Please consult the Instructions for Authors regarding the
use of abbreviations, and what constitutes an acceptable abbreviation. This is not an acceptable abbreviation. ghout the manuscript. Please spell out all abbreviations on first use. It is reasonable to not use abbreviations for words that are seldom used in the paper. We try to limit “unique” abbreviations so that readers don’t have to frequently refer back to the first notation of the abbreviation to remember its meaning. We realize that this may affect word count but believe it makes it easier in most cases for the reader.

Thank you. As per our response to one of the reviewers above, we have endeavoured to remove all unacceptable abbreviations.

- and divergence of meds to others

Yes, agreed. New reference cited.

- do you have a reference for this?

Unfortunately no. As such, we have removed this sentence.

- Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites.

We have reworded this sentence to not imply causation.

- Understanding that this is an "impact" study, it is an idiosyncratic fact that at the Journal we tend to avoid the
use of the word impact to imply the result of a change, preferring to limit "impact" to mean a physical blow.

As discussed, we have reworded instances of “impact” study to better reflect that this is a before/after analysis of a quality improvement initiative/project

- do you have enough data to break out scheduled vs non scheduled CS to see if there were differences?

Unfortunately our EMR coding and how the data is recorded by unit clerks/charge nurses does not allow for precise determination of primary vs. repeat CD, although we agree that this would be an interesting

subgroup analysis.

- So, I see this is a QI project. It should be presented as such in the methods section. Please read the instructions for authors as we require the SQUIRES publication guideline for QI projects. W/ revision, please
submit the check list. Please state if your IRB allows you publish QI projects even if they exempt them prior to
performance of them.

We will resubmit the SQUIRES publication guideline. We have included a sentence stating that no restriction on publication exists.

- By describing this as novel, you are making a primacy claim: yours is the first, biggest, etc…In order to assert that, you need to provide the search terms used and the data base (s) searched (PubMed, Google Scholar, etc) to
substantiate the claim. Otherwise, it needs to be deleted.

We have recharacterized it as "updated".

- do you mean maintenance dosing?

Yes. Sentence edited for clarity. Our maintenance infusion starts immediately after the bolus, and the starting rate is 7.5 IU/hour (programmed in IV pump).

- Is this for throughout the post op period or only in the immediate post op period?

At any point. Sentence edited for clarity.

- The Journal style doesn't not use the virgule (/) except in numeric expressions. Please edit here and in all instances.

Done

- to be clear, prior to the change, if a patient gave a verbal pain score of 1, you gave her 5 mg of oxycodone?
Why?

They were offered pain relief. This was one of the motivations to change our order set. The old order-set was written this way and provided some of the impetus for the creation of the new one. It said for VPS ≤4, 5 mg of oxycodone should be given. Nurses were unsure if that meant that a VPS of 0 should still receive 5 mg. The new order-set clarifies this by saying VPS 1-4 should receive oxycodone and ONLY if the patient desires additional pain relief.

- At UNC, the anesthesia service manages post op pain in the OB unit, including post partum Is that true

at
Stanford?

At Stanford both OB Anesthesia and OB/Gyn help manage pain. The order-set is initially completed by Anesthesia, and the orders stipulate that the nurse should call Anesthesia first to assess pain and modify analgesia. The OB is also contacted if pain is believed to be surgical in origin or if there appears to be another cause of pain. In reality, we have a well-integrated service in which both specialities help manage and care for women and their pain needs after cesarean.

- Was the patient told she was receiving 1/2 dose?

Yes, in general patients are made aware that the remainder of the dose will be available if the pain is not controlled initially.

- please describe the protocol for obtaining verbal pain scores. Since you are reporting an average result, we
need to know how often these were collected.

Methods updated to explain how we arrived at average VPS and peak VPS. As described in methods, VPS assessment was not standardized and occurred per usual nursing protocol, which can be variable. We have acknowledged this limitation in our Discussion also.

- In both the abstract and the paper, please provide absolute numbers as well as which ever effect size you are reporting (if appropriate) + Confidence intervals. P values may be omitted for space concerns. We strongly prefer CI's as they give more information about strength of association than do P values. By absolute values, I mean something like xx (outcome in exposed)/yy(outcome in unexposed) (zz%) (Effect size= ; 95% CI=.) An example might be: Outcome 1 was more common in the exposed than the unexposed 60%/20% (Effect size=3;95% CI 2.6-3.4).

We updated 95% CI for differences in mean and Odds Ratios. We did not report 95% CI for Wilcoxon Rank-Sum test since the effect size is not intuitive in this scenario, and an exact 95% CI cannot be obtained due to the nonparametric nature of this test. Where appropriate, we have updated the tables as well to report 95% CI instead of P-values as you have requested.

- were there any other changes in the way cesarean deliveries were performed during this time frame or any
other anesthetic changes?

None to our knowledge.

- please tell us how many did require IV rescue.

Done

- rather than say "Large" just give the percentage and let the reader just its relative size.

Done

- was this solicited feedback? One of the problems with some of the studies we've seen is that the lack of feedback from the nurses, when not solicited in a proactive manner, is interpreted as the lack of an effect on
the nurses. Please comment.

This was solicited feedback by authors BC and JN, although unfortunately not collected systematically. We have removed this feedback from the manuscript.

- you should state this in the methods. The methods read as though a pain score <=4 should be treated with a
2.5 mg dose of oxycodone.

We have added this into the methods section for clarity.

2. Your manuscript is a QI study. Please edit your manuscript so that it conforms to the guidelines for the Clinical Practice and Quality manuscript type. Please also submit a completed SQUIRE 2.0 checklist. Please see the Instructions For Authors at https://edmgr.ovid.com/ong/accounts/authors.pdf for the full instructions for this article type.

We will resubmit the SQUIRES publication guideline.

3. 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.

4. 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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can

remove them for you after submission.

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: Clinical Practice and Quality articles 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. Title: Please do not use the word "impact" in your title or manuscript. Would the substitution of "Association of..." be more appropriate?

We have renamed the title of the manuscript ***Evaluation of a post-cesarean analgesia order-set with split doses of oral opioids***

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.
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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: Clinical Practice and Quality, 300 words. Please provide a word count.

The word count for our abstract is 300.

10. 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.

11. 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.

Done

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' (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.

14. Figures - The figures may be resubmitted as-is.

Thank you

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

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

16. 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.

From: [redacted]
To: Randi Zung
Subject: Re: Your Revised Manuscript 19-172R1 - Author Queries
Date: Friday, April 5, 2019 1:22:28 PM
Attachments: 19-172R1 ms (4-4-19v3) JN Edits.docx

Dear Ms. Zung,

Thank you. I have attached the manuscript with all changes tracked. Additionally, below please find the responses to author queries.

1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.

Thank you

2. Title: Please note the Editors' requested change. They want you to emphasize the outcome (opioid use).

Yes, we are fine with the requested change emphasizing the outcome.

3. Author Information: I don't see any explanation of the superscripts here. Please list your institutional affiliations for each author on the title page.

Have added institutional affiliations to the title page

4. Line 43-44: Please let us know if your presentation is accepted.

It was just accepted. I have updated this disclosure.

5. Line 55: Still a bit confusing. This was a QI study, which should be stated in the methods. In QI studies, the typical approach is to assess status at Time A, introduce a change, and then sometime later at Time B assess outcomes after the intervention. This is typically structured as a prospective study. Did you instead make a clinical practice change, then decide to go back to see whether there were any differences? In other words, is this an afterthought or was this preplanned?

Thank you. I have reviewed the terminology and instructions to authors pertaining to manuscript type. This study is best described as a clinical practice change study as the study itself was not planned prior to implementation of the new order-set. I have updated the abstract and methods accordingly.

6. Line 57-58: Is this correct? It is consistent with what you said in your response to reviewers.

The specification that the patient desired additional pain relief was not present on the old order-set, only on the new one. I have clarified this in the abstract, methods, and discussion.

7. Abstract-Conclusion: Please note the Editors' suggested rewording.

Noted, thank you.

8. Line 84: Be bold. Perhaps "are significant"?

Updated per your request.

9. Methods Section: Please note the question from the Abstract-Methods. Please make sure your abstract and body text as consistent.

See reply to comment in abstract

10. Line 140: Please clarify, as you do in your explanation notes and as I suggest above that the patient had to also want pain relief?

I have noted that our **old** order-set made no mention of whether or not a pt wanted analgesia. The new order-set does (line 225-229 and discussion lines 377-385). Also see Table 1.

11. Line 224-226 (sentence in yellow): Can this fit into the abstract somehow?

I have managed to add this result into the abstract as requested.

12. Line 275: If your study was not preplanned as a study, please list as a limitation that you were not able to collect data on type of caesarean or potentially other factors that may have been important, nor any systematic collection of nursing satisfaction with the change. Even if the analysis was preplanned, it's a limitation that you didn't collet that information.

Agree. I have added two sentences to reflect this point.

Please let me know if there is anything else you require.

Many thanks!

--

[redacted]

On Thu, Apr 4, 2019 at 1:49 PM Randi Zung <RZung@greenjournal.org> wrote:

> Dear Dr. Nanji:
>
> Your revised manuscript has been reviewed by the Editors. We need you to address the following queries. Please make the requested changes to the latest version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.
>
> 1. General: The Manuscript Editor and Dr. Chescheir have made edits to the manuscript using track changes. Please review them to make sure they are correct.
>
> 2. Title: Please note the Editors' requested change. They want you to emphasize the outcome (opioid use).

3. Author Information: I don’t see any explanation of the superscripts here. Please list your institutional affiliations for each author on the title page.

4. Line 43-44: Please let us know if your presentation is accepted.

5. Line 55: Still a bit confusing. This was a QI study, which should be stated in the methods. In QI studies, the typical approach is to assess status at Time A, introduce a change, and then sometime later at Time B assess outcomes after the intervention. This is typically structured as a prospective study. Did you instead make a clinical practice change, then decide to go back to see whether there were any differences? In other words, is this an afterthought or was this preplanned?

6. Line 57-58: Is this correct? It is consistent with what you said in your response to reviewers.

7. Abstract-Conclusion: Please note the Editors’ suggested rewording.

8. Line 84: Be bold. Perhaps “are significant”?

9. Methods Section: Please note the question from the Abstract-Methods. Please make sure your abstract and body text as consistent.

10. Line 140: Please clarify, as you do in your explanation notes and as I suggest above that the patient had to also want pain relief?

11. Line 224-226 (sentence in yellow): Can this fit into the abstract somehow?

12. Line 275: If your study was not preplanned as a study, please list as a limitation that you were not able to collect data on type of caesarean or potentially other factors that may have been important, nor any systematic collection of nursing satisfaction with the change. Even if the analysis was preplanned, it’s a limitation that you didn’t collet that information.

To facilitate the review process, we would appreciate receiving a response by April 9.

Best,

Randi Zung

– –

Randi Zung (Ms.)

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American College of Obstetricians and Gynecologists

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From: Jalal Nanji [redacted]
Sent: Thursday, April 4, 2019 3:43 PM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 19-172R1

I received an email re Figures on Apr 1...but nothing on Apr 2.

On Thu., Apr. 4, 2019, 13:39 Randi Zung, <RZung@greenjournal.org> wrote:

> Dear Dr. Nanji:
>
> I am writing to confirm whether you have received your author queries regarding your submission 19-172R1 (Evaluation of a post-cesarean analgesia order-set with split doses of oral opioids), submitted to Obstetrics & Gynecology.
>
> I have been experiencing technical issues with my email account. The message would have been sent to you on April 2. If you do not see anything from me, please let me know and I will resend your file.

Thank you,

Randi Zung

– –

Randi Zung (Ms.)

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From: Jalal Nanji
To: Denise Shields
Subject: Re: figures in your Green Journal manuscript (19-172)
Date: Wednesday, April 3, 2019 10:17:35 AM

Hi Ms. Shields,

The figures and legend look good. I don't see any mistakes.

Thank you!

Jalal Nanji

On Wed., Apr. 3, 2019, 08:04 Denise Shields, <DShields@greenjournal.org> wrote:

> Re: “Evaluation of a Post–Cesarean Delivery Analgesia Order Set With Split Doses of Oral Opioids”
>
> Dear Dr. Nanji,
>
> Your figures and legend have been edited and they are attached for your review. Please review the attachments 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 appreciate a reply no later than Friday, 4/5. Thank you for your help.
>
> Best,
>
> Denise
>
> Denise Shields
>
> Senior Manuscript Editor

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