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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.
RE: Manuscript Number ONG-20-167

Pharmacokinetics and Breast Milk Excretion of Bupivacaine Following Liposomal Bupivacaine Infiltration in Transversus Abdominis Plane in Patients Undergoing Cesarean Delivery

Dear Dr. Mustafa:

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 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Thank you for your work, specific comments:

Abstract: well written.

Introduction:

1. Typos line 66, 67 (shorter, reduced)

2. Lines 77-81: while interesting this does not relate to your study as you are assessing the postoperative period. If you wish to relate this you need a joining idea.

3. Lines 97-99: in my experience most patients do not use PCA, rather duramorph and then oral pain control. This comparison is not as useful, except in general anesthesia patients or those with known OUD.

4. Lines 101-3 this sentence needs to be re-evaluated, it does not read well (too many thoughts in one sentence).

5. Line 103-5: it aims to provide some of the missing data, not all of it.

6. Can you end this section with a discussion of the hypothesis you were testing, or the specific data you were looking for?

Methods:

7. 111: "prospective pharmacokinetics study" is not a sentence.

8. Can you start this section (or end the last) by describing if this is a discrete study done for only this endpoint, or if this is a part of a larger study.

9. Were women with known OUD included in this study?

10. Were patients compensated?
11. Lines 147-8 this is not needed here as there is no sample size calculation and this is adequately explained later.

12. Lines 157-8: detail could be reduced here in text and included as an addendum for those interested

13. Can you describe why AUCs were used?

14. Results: overall well described. Be sure not to overly repeat data between the text and tables

Discussion:

15. You could address in this section how this modality of post op pain control fits into the larger pantheon of options available, including ERAS protocols, rapid mobilization etc... As well as discuss for whom this type of post op pain control might be most useful (ie: OUD mothers, or those on methadone / Subutex during pregnancy and postpartum). As mentioned above comparing this modality cost wise to PCA use is not the most useful, as that is not so commonly used, so how would cost compare to ERAS protocol?

REVIEWER #2:

Pharmacokinetics and breastmilk excretion of bupivacaine.

Abstract:
The objective, methods, results and conclusion are well explained and delineated. All of them concur and the conclusions are supported by the data.

Introduction:
Lines 87-90: Liposomal bupivacaine...or via transversus abdomen plane (TAP) block in various lower abdominal procedures. The references use do not support the information for lines 87-90 as they are for other procedures and not for abdominal procedures. There is only one reference # 27 where the bupivacaine is used for laparotomy. Most of the reference are for orthopedics surgery and laparoscopic/robotic surgery.

Material and Methods:
The study is well design and it may be reproduced.
Sampling schema: Why to divide the participant in 2 groups can this affect the final data. Why not to use the same sampling in all the 30 participants.
Results:
Lines 232-234: Possible selection bias. The participants are 27 patients with a prior C/S vs 3 primary. Is there any data in absorption of bupivacaine in patients with prior surgeries? Could this change your results?
Lines 236-239 and Table 1: Why is transient tachypnea of the newborn considered an AE if the study if is not related to the administration nor the use of the TAP bupivacaine?

Discussion:
Lines 277-280: The references used are not related to a laparotomy are for hemorrhoidectomy mammoplasty and total knee arthroplasty. Is the absorption and plasma concentration of bupivacaine the same irrespective of where it is administered anatomically?
Tables and figures:
Are clear and to support the data from the study.
References:
Some of the references used are not related to a laparotomy. See the above concerns already mentioned.

REVIEWER #3:

This is an excellent prospective pharmacokinetic study evaluating the concentrations of bupivacaine in serum and breast milk following post-cesarean TAP block with liposomal bupivacaine. I applaud the authors in their pursuit to confirm compatibility with lactation of this non-opioid analgesic option given the current opioid crisis in the US.

I have minor requests for revision:

1. Clarification regarding the breast milk samples: Lines 136-137 describe the assigned time points selected for serum and breast milk collection. I would like to know if the patients were instructed to pump/express their breasts to empty, mix the milk, and remove the 1ml sample for research purposes, as is recommended for breast milk pharmacokinetic studies. If this or a different set of instructions was provided to participants, I suggest it be detailed in the manuscript.

2. I would suggest a comment on the infant's metabolism of bupivacaine, and the likely first-pass effect further reducing potential ingestion.
STATISTICAL EDITOR’S COMMENTS:

1. Table 1: The total sample size = 30, so the %s should be rounded to nearest integer %, not to 0.1% precision. Is there any analysis of whether BMI affected maternal concentrations?

2. Table 2: Should include the "n" for each time point and should include the range, rather than 80% CI, since the samples are small and the estimates of %-tiles are imprecise. Are the concentrations precise to nearest 0.01 ng/ml (lines 162-171)? If not, should round to more appropriate precision level.

3. Table 3: The AUC is dependent on both the concentrations and the time points. What precision was the time interval recorded? That will limit the precision of estimation of milk and plasma AUC. Again, should cite the N for each time interval and the mean and range, not 80%-tiles.

4. Table 4: The calculation of infant dosage is based on the assumption of 150 mL/kg/24hr of milk consumption and that the concentration in breast milk is independent of amount of milk produced. So, while a useful exercise, it is not based on actual data. Again, the precision of estimates for dosages seems too precise.

5. Figs 1, 2: As can be seen from these figures, the range of concentrations is wide, complicating precise estimation of population pharmacokinetics.

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. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
   a. Please rewrite lines 306-309 (It is noteworthy...scope of this study). This is taken verbatim from another study. Lines 292-298 should be rewritten or cited (nevertheless, the value...proposed calculation).

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
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; Reviews, 300 words; Case Reports, 125 words; Current Commentary articles, 250 words; Executive Summaries, Consensus Statements, and Guidelines, 250 words; Clinical Practice and Quality, 300 words; Procedures and Instruments, 200 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. 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% ").

13. 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.

14. 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.

15. The Journal’s Production Editor had the following to say about the figures in your manuscript:
"Figures 1–2: Please upload as separate figure files on Editorial Manager."

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

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

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

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

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

16. 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.

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***

If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:
* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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.
March 04, 2020

Re: Resubmission of manuscript “Bupivacaine Pharmacokinetics and Breast Milk Excretion Following Liposomal Bupivacaine use in Cesarean Birth’, # ONG-20-167

The editors
Obstetrics & Gynecology Journal

Dear respectful editors,

Thank you for the opportunity to review our manuscript. We appreciate the conscientious review and constructive suggestions made by the editors and the reviewers. It is our belief that the manuscript is substantially improved after making the suggested edits.

Following this letter are the editor and reviewers comments with our detailed responses, including how and where the text was modified. The revision has been developed in consultation with all coauthors, and each author has given approval to the final form of this revision.

The authors opt-in to publish point-by-point response letter if the manuscript was accepted for publication.

The authors followed STROBE checklist for reporting.

Thank you for your consideration

Sincerely,

Hiba Mustafa

Hiba Mustafa, MD
Department of Obstetrics, Gynecology and Women’s Health
Division of Maternal-Fetal Medicine. University of Minnesota
REVIEWER #1

Abstract: well written.

Introduction

Point 1

Reviewer’s comment: Typos line 66, 67 (shorter, reduced)

Authors’ response: Thank you for your observation. Typos were corrected as seen in line 65.

Point 2

Reviewer’s comment: Lines 77-81: while interesting this does not relate to your study as you are assessing the postoperative period. If you wish to relate this you need a joining idea.

Authors’ response: Thank for your suggestion. Authors agree. These lines were removed from the introduction.

Point 3

Reviewer’s comment: Lines 97-99: in my experience most patients do not use PCA, rather duramorph and then oral pain control. This comparison is not as useful, except in general anesthesia patients or those with known OUD.

Authors’ response: Thank you for your suggestion. Authors agree. These lines were removed from the introduction.

Point 4

Reviewer’s comment: Lines 101-3 this sentence needs to be re-evaluated, it does not read well (too many thoughts in one sentence).

Authors’ response: Thank you for your observation. Authors agree. These lines were removed.
Point 5

Reviewer’s comment: Line 103-5: it aims to provide some of the missing data, not all of it.

Authors’ response: Thank you for your comment. Authors agree. “Some” was added to the sentence as seen in line 104.

“This study aims to provide clinicians the necessary, yet some of the missing clinical data when counseling on liposomal bupivacaine in breast-feeding mothers”.

Point 6

Reviewer’s comment: Can you end this section with a discussion of the hypothesis you were testing, or the specific data you were looking for?

Authors’ response: Thank you for your suggestion. Authors agree. The section was ended with the lines 106-110.

“To achieve this, we aimed to determine bupivacaine concentrations in plasma and milk samples and to model transfer to breastmilk following liposomal bupivacaine TAP infiltration in low risk pregnant patients undergoing scheduled term cesarean birth. This was a discrete study done to address this endpoint, and was not part of a larger study”.

Methods

Point 7

Reviewer’s comment: "prospective pharmacokinetics study" is not a sentence.

Authors’ response: Thank you for your comment. Authors agree. Sentence was changed to “prospective cohort study” as seen in lines 36, and 116.

Point 8

Reviewer’s comment: Can you start this section (or end the last) by describing if this is a discrete study done for only this endpoint, or if this is a part of a larger study.

Authors’ response: Thank you for your suggestion. It was added at the end of the introduction section as seen in lines 109, and 110.
“This was a discrete study done to address this endpoint, and was not part of a larger study”.

**Point 9**

**Reviewer’s comment:** Were women with known OUD included in this study?

**Authors’ response:** Thank you for your question. No, women with known OUD were not included.

**Point 10**

**Reviewer’s comment:** Were patients compensated?

**Authors’ response:** Thank you for your question. Yes, participants were compensated a total of 50$ each.

**Point 11**

**Reviewer’s comment:** Lines 147-148 this is not needed here as there is no sample size calculation and this is adequately explained later.

**Authors’ response:** Thank you for your suggestion. Authors agree. These lines were removed.

**Point 12**

**Reviewer’s comment:** Lines 157-82: detail could be reduced here in text and included as an addendum for those interested

**Authors’ response:** Thank you for your suggestion. Authors agree. These lines were removed.

**Point 13**

**Reviewer’s comment:** Can you describe why AUCs were used?

**Authors’ response:** Thank you for your comment. Milk/plasma (M/P) ratio may be misleading because it is subject to variability. Single paired milk and plasma concentration measurements have often been used to calculate the M/P ratio. However, this assumes that milk and plasma concentrations change in parallel, which is not necessarily the case. The problem of variation can be avoided by measuring the M/P ratio using
measurements of the areas under the maternal plasma- and milk-concentration time curves (AUCs) after a single dose or over a dose interval.

Results

Point 14: overall well described

Discussion

Point 15

Reviewer’s comment: You could address in this section how this modality of post op pain control fits into the larger pantheon of options available, including ERAS protocols, rapid mobilization etc… As well as discuss for whom this type of post op pain control might be most useful (ie: OUD mothers, or those on methadone/Subutex during pregnancy and postpartum). As mentioned above comparing this modality cost wise to PCA use is not the most useful, as that is not so commonly used, so how would cost compare to ERAS protocol?

Authors’ response: Thank you for your suggestion. Authors agree. This discussion was added as can be seen in lines 319-334.

“Pain after cesarean birth can result from two sources, somatic from the skin and the anterior abdominal wall incisions via T10-L1 dermatomes, and visceral from the uterus transmitted by hypogastric nerve that enters spinal cord via T10-L1 dermatomes as well.\(^\text{49}\) Given that, many studies evaluated post-operative pain management through analgesic or local anesthetic infiltration targeting these dermatomes. TAP block which involves local aesthetic infiltration in the neurovascular plane between the transversus abdominis and internal oblique muscles has been evaluated in few gynecologic studies including laparoscopic surgery and total abdominal hysterectomy in which it has been shown to be effective in reducing post-operative pain and opioid use.\(^\text{50,51}\) However, other trials did not show similar results.\(^\text{52}\) This discrepancy in effectiveness between trials could have been related to the difference in studied surgical procedures, TAP block techniques, local anesthetic type and volume, and measured results. The use of liposomal bupivacaine in TAP block after cesarean birth provides a promising alternative in controlling pain, and reducing opioid use which will further reduce nausea, vomiting, delayed mobilization, and bowel malfunction, all of which can improve enhanced recovery after surgery.\(^\text{53}\) However, more data is needed on the benefit of its clinical use”.
REVIEWER #2

Abstract
The objective, methods, results and conclusion are well explained and delineated. All of them concur and the conclusions are supported by the data.

Introduction
Reviewer’s comment: Lines 87-90: Liposomal bupivacaine…or via transversus abdomen plane (TAP) block in various lower abdominal procedures.
The references use do not support the information for lines 87-90 as they are for other procedures and not for abdominal procedures. There is only one reference # 27 where the bupivacaine is used for laparotomy. Most of the reference are for orthopedics surgery and laparoscopic/robotic surgery.
Authors’ response: Thank you for your observation. Authors agree. The sentence and the references were rearranged as can be seen in lines 87-91.
“Liposomal bupivacaine infiltration has been shown to significantly reduce postsurgical pain and opioid consumption for up to 72 to 96 hours when administered via either local wound infiltration or via transversus abdominis plane (TAP) block in various procedures 21–25 including lower abdominal ones. 26–29 “.

Material and Methods
Reviewer’s comment: The study is well design and it may be reproduced.
Sampling schema: Why to divide the participant in 2 groups can this affect the final data. Why not to use the same sampling in all the 30 participants.
Authors’ response: Thank you for your question. It is very challenging to obtain all the time-points samples from the participants given that the study was done in the immediate postpartum period which is a very challenging stressful time for new mothers, in addition to the fact that the collected milk was during the immature milk period “colostrum” which is “liquid gold”. All together would make recruitment very hard to almost impossible if all time-points were to be obtained from each participant.

Results
Reviewer’s comment: Lines 232-234: Possible selection bias. The participants are 27 patients with a prior C/S
vs 3 primary. Is there any data in absorption of bupivacaine in patients with prior surgeries? Could this change your results?

Authors’ response: Thank you for your observation. There is no data on the difference of local anesthetic absorption after TAP block between primary and repeat cesarean births. TAP block is done under ultrasound guidance by injecting the local anesthetic agent in the neurovascular plane between the transversus abdominis and internal oblique muscles. This anatomical location is not typically involved in cesarean births. It is noteworthy, that none of the participants underwent current or prior vertical midline incisions, for which by clinical experience, authors do not believe there should be any difference in absorption related to the participants’ prior cesarean births.

Reviewer’s comment: Lines 236-239 and Table 1: Why is transient tachypnea of the newborn considered an AE if the study is not related to the administration nor the use of the TAP bupivacaine?

Authors’ response: Thank you for your observation. We changed the sentence to “Reported AEs (related and/or unrelated) were..” in the results section line 246, and to “infants with related or unrelated AEs” in the table.

Discussion

Reviewer’s comment: Lines 277-280: The references used are not related to a laparotomy are for hemorrhoidectomy mammoplasty and total knee arthroplasty. Is the absorption and plasma concentration of bupivacaine the same irrespective of where it is administered anatomically?

Authors’ response: Thank you for your observation. References were updated to include the prior mentioned procedures as well as lower abdominal ones.

Tables and figures

Reviewer’s comment: Are clear and to support the data from the study.

References

Reviewer’s comment: Some of the references used are not related to a laparotomy. See the above concerns already mentioned.

Authors’ response: Thank you for your observation. The above concerns were all addressed.
Reviewer's comment: This is an excellent prospective pharmacokinetic study evaluating the concentrations of bupivicaine in serum and breast milk following post-cesarean TAP block with liposomal bupivicaine. I applaud the authors in their pursuit to confirm compatibility with lactation of this non-opioid analgesic option given the current opioid crisis in the US.

Authors' response: Thank you for your positive comment. Authors highly appreciate it.

Point 1

Reviewer's comment: Clarification regarding the breast milk samples: Lines 136-137 describe the assigned time points selected for serum and breast milk collection. I would like to know if the patients were instructed to pump/express their breasts to empty, mix the milk, and remove the 1ml sample for research purposes, as is recommended for breast milk pharmacokinetic studies. If this or a different set of instructions was provided to participants, I suggest it be detailed in the manuscript.

Authors’ response: Thank you for your suggestion. The participants were given these instructions. Further clarification was added to the methods section as seen in lines 145-146.

“Participants were instructed to express the milk via pumping or hand expression, to mix the collected milk, and to remove 1 ml for the research study after expression”.

Point 2

Reviewer's comment: I would suggest a comment on the infant's metabolism of bupivicaine, and the likely first-pass effect further reducing potential ingestion.

Authors’ response: Thank you for your suggestion. Authors agree. The comment was added to the discussion section as seen in lines 316-318.

“It is noteworthy, since bupivacaine is metabolized primarily in the liver, infant’s absorption will likely be even lower given the first pass effect”.
STATISTICAL EDITOR’S COMMENTS

Point 1

Editor’s comment: Table 1: The total sample size = 30, so the %s should be rounded to nearest integer %, not to 0.1% precision. Is there any analysis of whether BMI affected maternal concentrations?

Authors’ response: Thank for your observation. %s were rounded to nearest integer % as seen in table 1.

Analysis of BMI effect on concentrations was not done. In pharmacokinetics, the effect of covariates is usually performed on the pharmacokinetic parameters rather than the concentrations. Such an analysis for bupivacaine is planned, however it is out of the scope of this manuscript.

Point 2

Editor’s comment: Table 2: Should include the "n" for each time point and should include the range, rather than 80% CI, since the samples are small and the estimates of %-tiles are imprecise. Are the concentrations precise to nearest 0.01 ng/ml (lines 162-171)? If not, should round to more appropriate precision level.

Authors’ response: Thank you for your suggestion. We have now included “n” of samples for each time point as well as the range.

In this table we reported geometrical means and 80% CIs of the concentrations to closest 0.1 ng/ml.

Geometrical means and 80% CIs of the concentrations were used to calculate AUC means and AUC 80% CI, respectively. We chose to report CIs as they are more representative of the population compared with ranges.

For reproducibility purposes, we reported 80% CIs of the concentrations which were used to calculate the AUC 80% CI.

Suggested edits were all addressed as seen in table 2.

Point 3

Editor’s comment: Table 3: The AUC is dependent on both the concentrations and the time points. What precision was the time interval recorded? That will limit the precision of estimation of milk and plasma AUC. Again, should cite the N for each time interval and the mean and range, not 80%=tiles.

Authors’ response: We have used a linear trapezoidal rule to calculate the AUCs rather than using an integrator.
Hence the time points used for AUC calculations were the nominal time points recorded by the study coordinators.

As seen in figure 2, geometrical means and CIs closest to 0.1 ng/ml at each time point reported in Table 2 were used to drive AUC calculation. Each mean (n=1) and CIs (upper, n=1; lower, n=1) at each time point represents a point (and associated CIs) on the exposure curve. Trapezoidal rule was used to calculate mean AUC (and associated AUC CIs) for both plasma and milk. In table 3, we did not report summary statistics on AUC and Milk/plasma ratio, rather we reported geometrical means and CIs. This results in 3 values (geometric mean, lower CI and upper CI) for each time point of both milk/plasma AUC and milk/plasma ratio. Therefore, the n=1 and hence neither nor ranges were reported.

Suggested edits were all addressed as seen in table 3.

**Point 4**

*Editor’s comment:* Table 4: The calculation of infant dosage is based on the assumption of 150 mL/kg/24hr of milk consumption and that the concentration in breast milk is independent of amount of milk produced. So, while a useful exercise, it is not based on actual data. Again, the precision of estimates for dosages seems too precise.

*Authors’ response:* We agree with the reviewer that the milk consumption was not coming from actual data and may vary among infants and varies with the age. However, the 150 ml/kg/24h is well established in the pharmacokinetic literature and it does provide a standard by which drugs can be compared with each other according to Anderson et al. 2016 (referenced in the manuscript).

Since the study was conducted on infants of 0-4 days of age, using 150 ml/kg/24h of milk consumption might be considered a high rate relative to the rate reported by Anderson et al. 2016, Figure 2, for the same age group. Hence, when using this higher rate we might be overestimating the infant daily dose and therefore our recommendation is considered safe.

**Point 5**

*Editor’s comment:* Figs 1, 2: As can be seen from these figures, the range of concentrations is wide, complicating precise estimation of population pharmacokinetics.

*Authors’ response:* We agree with the editor that the range of concentrations is wide. However, population pharmacokinetics has the ability to not only give us estimates of population means, but help us identify
covariates that are contributing to the overall variability. Literature shows population models for breastfeeding is possible even with a small sample size (Tanoshima R et al. BJCP 2014.). Additionally, population pharmacokinetics also provides us the opportunity to borrow information from the literature to build models when current data is less informative.