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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-22-301

Ketamine versus Fentanyl for Surgical Abortions: A Randomized Noninferiority Trial

Dear Dr. Chin:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 26, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

I was glad to review this manuscript under the title (Ketamine versus Fentanyl for surgical abortion: non inferiority trial).

1- Title: is general and doesn't reflect the aim of the study. Add (patients satisfaction) in the title.

2- Precis: is adequate and reflects the study conclusion.

3- Abstract: informative and accurate.

4- Introduction:
   a. line 45-46: the author mentioned that few studies examined Ketamine in surgical abortion and found improvement compared to paracervical block. The author didn't mention from what perspective the ketamine is better? Is it patient satisfaction too? Add explanation to this line.
   b. The study aim was mentioned.

5- Method:
   a. The study design answered the study question and is adequate.
   b. No ethical misconduct
   c. The method section was informative and detailed.
   d. The used dose for both medications is adequate.
   e. Line 93: The author mentioned that the provider satisfaction with sedation was assessed through (VAS). Add in the result section information about that because this will add information to your study.

6- Results and Tables:
   a. One of the secondary outcomes of the study was to compare the additional pain medications use after discharge (line 114). The author mentioned in line (158) that there was no difference between the two groups in that variable. However, table 4 shows that the ketamine group used more oxycodone (p-value 0.02). Add explanation for this point in the result section and it's effect on the study result.
   b. Table 4 shows that the ketamine group received more Toradol. The author didn't mention that point in the result section and did not show in table 4 if that result is statistically significant or not.
c. What kind of pain medications did the subjects have at baseline? Was there a difference in opioid intake between the two groups? Table 2.
7. Discussion and conclusion are good

Reviewer #2:

This is a randomized noninferiority trial comparing ketamine and fentanyl for pain control during first trimester surgical abortion with the primary outcome being satisfaction based on the Iowa Satisfaction with Anesthesia Scale (ISAS). Overall, this is an interesting study to increase the pain control options for moderate sedation in first trimester D&C, which is a very common procedure. However, there are clarifications needed to address whether any potential biases occurred in the role of the anesthetist in the methods and in the data analysis as it seems that the incorrect summary statistics and potentially statistical test were used.

Introduction
1. Line 34-38: This trial was noted to be recent, but it was published in 2001. Are there more recent publications looking at pain score differences? Can also consider other gyn procedures.
2. Lines 46-47: Can the authors clarify why a non-inferiority study design was chosen when the two referenced studies (references 11 and 12) found improvement? Were these superiority studies? If not, this sentence would need to be revised.

Methods
1. Line 78: How could the anesthetist being aware of the drug given influence the study results? Could they potentially give less medications if they felt that one drug worked better than another during the initial titration to "appropriate analgesia (line 82)? Who determines when the analgesia is appropriate, and what is the definition of appropriate? What was the general goal of the analgesia (was patient alert, drowsy, etc)? And were these all consistent across patients?
2. Lines 91-92: Did the anesthetist give medication upon request only? Did they give more if they felt it was necessary without the provider's input? Did all providers expect the same level of analgesia to perform the procedure?
3. Lines 121-122: What kind of drop-outs were anticipated given that patients were enrolled and participated in procedure on same day (theoretically in same visit)?

Results/Tables and Figures
1. Table 2: More info needed re: parity of participants and gestational age breakdown, since a 6 week procedure is different than a 13 week procedure. Were there any differences in satisfaction (or other secondary outcomes) based on these patient characteristics?
2. Table 3: I don't think comparisons of mean were appropriate given that the SDs reported. For example, pain post op in the ketamine group was 26 +/- 32.3, indicating that this is not a normal distribution. Need to review that statistical analysis again.
3. Similarly, Figure 2 indicates with the box and whisker plots that the distribution is skewed. The lines should indicate the median, not the mean, as written in the table title. Please confirm.
4. Similarly, Figure 3 also showed not normal distributions, please confirm data analysis.
5. Table 4: spacing is difficult to follow/read for the reviewers

Discussion
1. Lines 192-194: While I agree that there is a need to address the opioid crisis, can the authors provide a reference on demonstrating the link to use of fentanyl for outpatient procedure sedation and opioid dependence?
2. Lines 185-188: Considering the barriers to more widespread ketamine use, what can the authors propose to increase uptake of this medication for procedural sedation?

Reviewer #3:

This is a randomized controlled non-inferiority trial comparing fentanyl and ketamine for patient satisfaction during first-trimester surgical abortion in patients also receiving midazolam for moderate sedation. Questions/comments below:
1. Introduction: Citation 4 is not recent, it is 20 years old and included between 50-100 mcg of fentanyl without midazolam and therefore is not relevant to this paper. I would not use it as a justification for this trial.

2. Methods: Citation 15 is not a published manuscript.

3. Methods: I question the fentanyl dose. The loading dose of fentanyl was weight based. That means that a woman who weighed 125 lbs received 25-50 mcg of fentanyl which could only then be repeated every 5 minutes. For a procedure that lasts 5 minutes, this loading dose is not sufficient, would there have been time to repeat it? Standard loading doses that show decreased pain control for surgical abortion with moderate sedation are 100 mcg of fentanyl. I don't think this study is comparable to other studies of fentanyl that gave standard doses. Can you report the average amount of fentanyl and ketamine the patients received?

4. Methods: Did the patients receive ibuprofen and a paracervical block?

5. Methods: What is the range of scores for the ISAS? Please report the range and what is considered a good score.

6. Results: Table 4: This table shows that patients could receive propofol, additional midazolam etc. which invalidates the measure of how fentanyl vs. ketamine was working. It muddles the interpretation of the results. I'm not clear when the toradol was given as it is not that fast acting. The way Table 4 is formatted, it is difficult to read.

7. Results: I am not sure why data from POD 7 is relevant to the medications being studied for deep sedation on the day of the procedure.

8. Discussion: This study is only relevant to clinics that provide deep sedation with CRNAs as patients were given propofol, additional fentanyl, and additional midazolam. I think it is fine to have another option for patients, and whether they receive fentanyl or ketamine doesn't seem to matter much because their sedation levels are deep and additional medications were administered prn.

9. Discussion: Line 193, I don't think a one time dose of fentanyl during a procedure is going to cause someone to start to be an opioid user. It is more if they are prescribed narcotics afterwards.

10. Abstract: Please report doses given in the abstract.

STATISTICS EDITOR COMMENTS:

Table 2: Since the two cohorts had n = 53 & 52, should round the %s to nearest integer, not to 0.1% precision.

Table 3: Should clearly separate the primary outcome (ISAS score immediately post-op). The other results are secondary outcomes. Also, should format the non-inferiority results for the primary outcome in terms of the difference and its statistical bounds as compare to the a priori difference (0.6). This could be in Table or figure format, but it should be clearly separated from all other metrics. As presented, the stats tests are in classic superiority testing format.

Figs 2, 3: Should include in figure legends that the comparison of mean ISAS scores immediately post op was the primary outcome of interest.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
   * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
   * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
   * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
   * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded
your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. Clinical trials must include a data sharing statement. Please add the following questions and your answers to the end of the manuscript after the References section:

Authors' Data Sharing Statement
Will individual participant data be available (including data dictionaries)? No.
What data in particular will be shared? Not available.
What other documents will be available? Not available.
When will data be available (start and end dates)? Not applicable.
By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)? Not applicable.

6. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Make sure your manuscript meets the following word limit. The word limit includes the précis, abstract, text, tables, boxes, and figure legends, but excludes the title page, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 5,500

8. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:
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 or indicate whether the meeting was held virtually).

If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

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

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.

The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.
14. 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.

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

Express all percentages to one decimal place (for example, 11.1\%). Do not use whole numbers for percentages.

15. Please review the journal’s Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

16. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

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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 as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Apr 26, 2022, we will assume you wish to withdraw the manuscript from further consideration.
Sincerely,

John O. Schorge, MD
Deputy Editor, Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd 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.
April 24, 2022

Obstetrics & Gynecology
409 12th St SW
Washington, DC 20024, USA

Dear Editorial Office,

Thank you very much for the review of our manuscript “Patient Satisfaction with Ketamine versus Fentanyl for Surgical Abortions: A Randomized Noninferiority Trial” for consideration as an Original Research Article to the journal Obstetrics and Gynecology. We submit to you the revised manuscript and response to reviewers. This manuscript is not under review by any other journals and will not be submitted elsewhere unless a final negative decision is made by the Editors of Obstetrics and Gynecology.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

This study was registered at ClinicalTrials.gov (clinicaltrials.gov, NCT04871425). The protocol we are reporting is identical to the posted trial. This study was approved by the University of Washington Institutional Review Board Human Subjects Division.

Preliminary findings were presented at the American Society for Reproductive Medicine Scientific Congress and Expo, online, on October 21, 2021, in the form of an oral presentation. We plan to submit these findings to the Society of Family Planning Annual Meeting in December 2022 in the form of either an oral or poster presentation. Erica Lokken’s contributions to this study occurred while affiliated with the University of Washington Department of Obstetrics & Gynecology; she is now employed by AbbVie, Inc. This study received funding from the Society of Family Planning. We obtained permission from Jennifer Dempsey to be named in the Acknowledgements section.

Sincerely,

Jennifer Chin
REVIEWER COMMENTS:

Reviewer #1:

I was glad to review this manuscript under the title (Ketamine versus Fentanyl for surgical abortion: non inferiority trial).

1- Title: is general and doesn't reflect the aim of the study. Add (patients satisfaction) in the title.

   I have added patient satisfaction to the title.

2- Precis: is adequate and reflects the study conclusion.

3- Abstract: informative and accurate.

4- Introduction:

   a. line 45-46: the author mentioned that few studies examined Ketamine in surgical abortion and found improvement compared to paracervical block. The author didn't mention from what perspective the ketamine is better? Is it patient satisfaction too? Add explanation to this line.

   I have added explanation that these studies found improved intraoperative and postoperative pain.

   b. The study aim was mentioned.

5- Method:

   a. The study design answered the study question and is adequate.

   b. No ethical misconduct

   c. The method section was informative and detailed.

   d. The used dose for both medications is adequate.

   e. Line 93: The author mentioned that the provider satisfaction with sedation was assessed through (VAS). Add in the result section information about that because this will add information to your study.

   I have added information about physician satisfaction to the results section.

6- Results and Tables:

   a. One of the secondary outcomes of the study was to compare the additional pain medications use after discharge (line 114). The author mentioned in line (158) that there was no difference between the two groups in that variable. However, table 4 shows that the ketamine group used more oxycodone (p-value 0.02). Add explanation for this point in the result section and it's effect on the study result.

   I added clarification that there was a higher likelihood of receiving Toradol intraoperatively and a higher likelihood of oxycodone use postoperatively for the ketamine group.

   b. Table 4 shows that the ketamine group received more Toradol. The author didn't mention that point in the result section and did not show in table 4 if that result is statistically significant or not.

   I have added this to the result section. The p-values in Table 4 are for the mean amount of medication received; thus, there was no difference in the mean amount of Toradol received for each group and no p-value is reported. However, the p-value for the proportion of participants in each group who received Toradol is now reported in the result section.

   c. What kind of pain medications did the subjects had at base line? Was there a difference in opioid intake between the two groups? Table 2.

   Most patients were taking acetaminophen or ibuprofen. There was no difference in opioid intake between the two groups. This has been added to the result section.
7. Discussion and conclusion are good

Reviewer #2:

This is a randomized noninferiority trial comparing ketamine and fentanyl for pain control during first trimester surgical abortion with the primary outcome being satisfaction based on the Iowa Satisfaction with Anesthesia Scale (ISAS). Overall, this is an interesting study to increase the pain control options for moderate sedation in first trimester D&C, which is a very common procedure. However, there are clarifications needed to address whether any potential biases occurred in the role of the anesthetist in the methods and in the data analysis as it seems that the incorrect summary statistics and potentially statistical test were used.

Introduction
1. Line 34-38: This trial was noted to be recent, but it was published in 2001. Are there more recent publications looking at pain score differences? Can also consider other gyn procedures. I have replaced this with a more recent publication from 2009.
2. Lines 46-47: Can the authors clarify why a non-inferiority study design was chosen when the two referenced studies (references 11 and 12) found improvement? Were these superiority studies? If not, this sentence would need to be revised. I have added clarification as to why a non-inferiority study design was chosen and that these two referenced studies were superiority studies.

Methods
1. Line 78: How could the anesthetist being aware of the drug given influence the study results? Could they potentially give less medications if they felt that one drug worked better than another during the initial titration to "appropriate analgesia (line 82)? Who determines when the analgesia is appropriate, and what is the definition of appropriate? What was the general goal of the analgesia (was patient alert, drowsy, etc)? And were these all consistent across patients? I have added clarification as to when additional pain medication was given.
2. Lines 91-92: Did the anesthetist give medication upon request only? Did they give more if they felt it was necessary without the provider's input? Did all providers expect the same level of analgesia to perform the procedure? I have added clarification as to when additional pain medication was given.
3. Lines 121-122: What kind of drop-outs were anticipated given that patients were enrolled and participated in procedure on same day (theoretically in same visit)? I added clarification that we anticipated potential dropout on postoperative days 1 & 7.

Results/Tables and Figures
1. Table 2: More info needed re: parity of participants and gestational age breakdown, since a 6 week procedure is different than a 13 week procedure. Were there any differences in satisfaction (or other secondary outcomes) based on these patient characteristics? I have added a post-hoc exploratory analysis to the results section to explore differences based on these patient characteristics.
2. Table 3: I don't think comparisons of mean were appropriate given that the SDs reported. For example, pain post op in the ketamine group was 26 +/- 32.3, indicating that this is not a normal distribution. Need to review that statistical analysis again. Thank you for this comment. Because our sample size is large, our t-test is robust to deviations from normality according to the central limit theorem. Since we powered our study based on
means and using medians does not make a difference in our conclusions, we respectfully prefer to keep our results as is.

3. Similarly, Figure 2 indicates with the box and whisker plots that the distribution is skewed. The lines should indicate the median, not the mean, as written in the table title. Please confirm. I have changed Figure 2 to a bar plot with error bars to appropriately reflect the means.

4. Similarly, Figure 3 also showed not normal distributions, please confirm data analysis. I have changed Figure 3 to a bar plot with error bars to appropriately reflect the means.

5. Table 4: spacing is difficult to follow/read for the reviewers. I have reformatted Table 4 (now Table 5) to make it easier to follow/read.

Discussion

1. Lines 192-194: While I agree that there is a need to address the opioid crisis, can the authors provide a reference on demonstrating the link to use of fentanyl for outpatient procedure sedation and opioid dependence? I have added a reference to this section.

2. Lines 185-188: Considering the barriers to more widespread ketamine use, what can the authors propose to increase uptake of this medication for procedural sedation? I have added potential solutions to increase uptake of ketamine.

Reviewer #3:

This is a randomized controlled non-inferiority trial comparing fentanyl and ketamine for patient satisfaction during first-trimester surgical abortion in patients also receiving midazolam for moderate sedation. Questions/comments below:

1. Introduction: Citation 4 is not recent, it is 20 years old and included between 50-100 mcg of fentanyl without midazolam and therefore is not relevant to this paper. I would not use it as a justification for this trial. I have replaced this with a more recent publication from 2009 comparing IV sedation to oral sedation.

2. Methods: Citation 15 is not a published manuscript. I have removed this from the references and instead included an in-text citation.

3. Methods: I question the fentanyl dose. The loading dose of fentanyl was weight based. That means that a woman who weighed 125 lbs received 25-50 mcg of fentanyl which could only then be repeated every 5 minutes. For a procedure that lasts 5 minutes, this loading dose is not sufficient, would there have been time to repeat it? Standard loading doses that show decreased pain control for surgical abortion with moderate sedation are 100 mcg of fentanyl. I don't think this study is comparable to other studies of fentanyl that gave standard doses. Can you report the average amount of fentanyl and ketamine the patients received? Thank you for this feedback. If the loading dose was insufficient and the provider determined that additional medicine was needed, the anesthetist could give more fentanyl at their discretion. This was recorded as additional pain medication given since it was outside the study protocol. We did not record the loading doses given to each patient as the anesthetists were allowed to use their discretion within the study protocol.

4. Methods: Did the patients receive ibuprofen and a paracervical block? All patients received a paracervical block. I have clarified this in the methods.

5. Methods: What is the range of scores for the ISAS? Please report the range and what is considered a good score.
I have added this information to the methods section.

6. Results: Table 4: This table shows that patients could receive propofol, additional midazolam etc. which invalidates the measure of how fentanyl vs. ketamine was working. It muddles the interpretation of the results. I'm not clear when the toradol was given as it is not that fast acting. The way Table 4 is formatted, it is difficult to read.

We collected information on additional pain medication needed intraoperatively as another measure of how well the fentanyl vs. ketamine was working. Toradol was given intraoperatively after the study drug. I have reformatted Table 4 (now Table 5).

7. Results: I am not sure why data from POD 7 is relevant to the medications being studied for deep sedation on the day of the procedure.

I have added justification for these data points in the methods section.

8. Discussion: This study is only relevant to clinics that provide deep sedation with CRNAs as patients were given propofol, additional fentanyl, and additional midazolam. I think it is fine to have another option for patients, and whether they receive fentanyl or ketamine doesn't seem to matter much because their sedation levels are deep and additional medications were administered prn.

I have added this to the limitations.

9. Discussion: Line 193, I don't think a one time dose of fentanyl during a procedure is going to cause someone to start to be an opioid user. It is more if they are prescribed narcotics afterwards.

Thank you for this feedback. I have added a reference to explain the benefits of avoiding fentanyl.

10. Abstract: Please report doses given in the abstract.

I have added doses given to the abstract.

STATISTICS EDITOR COMMENTS:

Table 2: Since the two cohorts had n = 53 & 52, should round the %s to nearest integer, not to 0.1% precision.

I have rounded all the percentages to integers.

Table 3: Should clearly separate the primary outcome (ISAS score immediately post-op). The other results are secondary outcomes. Also, should format the non-inferiority results for the primary outcome in terms of the difference and its statistical bounds as compare to the a priori difference (0.6). This could be in Table or figure format, but it should be clearly separated from all other metrics. As presented, the stats tests are in classic superiority testing format.

I have created 2 separate tables. Table 3 is now the primary outcome in noninferiority testing format. Table 4 is now the secondary outcomes only.

Figs 2, 3: Should include in figure legends that the comparison of mean ISAS scores immediately post op was the primary outcome of interest.

I have added this to the figure legends for Figures 2 and 3.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.
I do not plan to opt out.

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