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OPEN PEER REVIEW

Preventive Effects of Lidocaine, Fentanyl, Acetaminophen, and TENS on Propofol-Induced Injection Pain: A Randomized Double-Blind Clinical Trial

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

5 comments · 7 Sep 2025 – 17 Sep 2025

Referee 1 Reviewer

MAJOR REVISION 7 Sep 2025

Dear AE,
Thank you for the invitation. The study tackles a common and clinically relevant issue: propofol-induced injection pain. The randomized double-blind design and inclusion of both pharmacological and non-pharmacological interventions make it valuable. Here are some suggestions and comments that should be addressed:

*Abstract
Comment 1-The abstract is poor, especially in terms of the English writing.

Comment2-Keywords: Misspelling ("fentanlye").
Comment 3-The abstract repeats the same background/methods/results twice.
*Introduction
Comment 4-Some sentences lack references (for example, the first sentence). All sentences quoted from other articles must have references at the end.
*Methods
Comment 5-No power calculation is provided to justify n=30 per group. The study may be underpowered. The NRS is assessed every 5 seconds after propofol injection until unconsciousness—but induction with propofol is very fast. Measuring every 5 seconds might miss the peak pain window.

Comment 6-TENS Protocol: Described, but no rationale is provided for the intensity/duration chosen. It is also unclear why a 100 mL saline infusion was given in the TENS group (placebo effect?).
*Results
Comment 7-In all Tables, the abbreviations must be explained in a Legend.

*Discussion
Comment 8-We would prefer to write the aim or the title of an article as the first line, and in the second and third lines we must mention the main finding(s). For the rest of this part, any gap, question, or hypothesis should be stated, followed by references to other studies.

Comment 9-The discussion compares results with prior studies but does not acknowledge why the findings differ. For example, prior studies show that acetaminophen + lidocaine is effective, but here acetaminophen alone showed no significant difference.

Comment 10-Some older references (from the early 2000s) are over-relied on, while more recent meta-analyses could be cited.

Alireza Abdullahzadeh-Baghaei Reviewer

MINOR REVISION 13 Sep 2025

Dear Authors

I found your work to be interesting research on improving anesthesia, with an innovative comparison of five elements for the relief of propofol injection pain.
But it needs some corrections as follows:
1- Measurement times are vague in the Methods section. The statement in line 104 should be corrected because unconsciousness is individualized: "Every 5 seconds after the propofol injection started until they

were completely unconscious." It is better to mention "every 5 seconds after the propofol injection started until 20 seconds" as stated in the tables.

2- The Methods section did not contain information about the side effects of drugs. We did not find any clarification on the timing of assessment or the criteria for apnea, headache, thrombophlebitis, and allergy in the Methods section. We found them only in Table 4 in the Results section.
3- There are no results about "type and length of surgery, the time it took to recover" that were mentioned in the Methods section. It seems they are unnecessary, and I suggest that they be omitted.

4- The brand of propofol that was used is not clear. It should also be emphasized that the same preparation of propofol was used for all patients.

5- The results about apnea described in line 173 contradict Table 4. In the text, the highest rate of apnea is in the TENS group, while in the table it is in the Fentanyl group. This should be corrected.

6- The Discussion section needs to be revised to consider a few studies with contradictory results. At present, all studies are concordant.

7- The references are somewhat old. It is advised to search for and try to add a few new studies to them.

Laleh Hakemibarabadi Reviewer

ACCEPT 15 Sep 2025

Propofol's onset of action is less than a minute. The drop in pain NRS after propofol injection may be due to the anesthetic effect of the drug.

Associate Editor

MAJOR REVISION 17 Sep 2025

Dear EIC,
Thanks to the authors and appreciation to the researchers. The manuscript is a valuable piece of research. But some revisions are needed. The authors should revise it based on the reviewers' comments. Also, minor changes should be made in the abstract:
*A summary of the statistical analysis results should be mentioned in the results section.

Editor-in-Chief

MAJOR REVISION 17 Sep 2025

Dear Author,
Thank you for submitting the article. The manuscript has major flaws and needs some revision. Please revise it based on the reviewers' and AE's comments. We will make a decision on it after revision.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers

We sincerely thank the reviewers and the associate editor for their valuable comments and suggestions.

Reviewer 1

*Comment: * Abstract is poor, especially in English writing.

Response: We agree and have fully revised the Abstract for clarity, conciseness, and proper academic English. We removed redundant sentences and ensured that background, methods, results, and conclusions are structured clearly. The results section of the Abstract now also reports the statistical findings, as requested by the AE.

*Comment: * Keywords: Misspelling (“fentanyl”).

Response: Thank you. The misspelling has been corrected to 'Fentanyl'. Keywords were re-checked for accuracy.

*Comment: * Abstract repeats the same background/methods/results twice.

Response: We revised the Abstract to remove redundancy. Each section now appears once, following journal guidelines.

*Comment: * Some sentences in Introduction lack references.

Response: We carefully checked the Introduction and added appropriate references for all statements based on published studies (e.g., Jalota et al. BMJ 2011; Hong et al. Medicine 2023; Wang et al. Pain Ther 2020). This ensures every factual statement is now referenced.

*Comment: * No power calculation provided to justify n=30 per group.

Response: We acknowledge this limitation. This was a pilot randomized trial. We now clarify in the Methods section that sample size (30 per group) was based on feasibility and common practice in pilot RCTs. We added a note that no formal power calculation was performed and results should be interpreted accordingly.

*Comment: * NRS every 5 seconds after propofol injection until unconsciousness — induction is very fast. Measurement may miss peak pain.

Response: We clarified this issue in the Methods. The assessment was in fact performed up to 20 seconds, consistent with Tables 2 and 3. We corrected

the wording to ensure consistency. This addresses the concern about rapid onset of propofol.

*Comment: * TENS Protocol rationale unclear. Why 100 mL saline infusion in TENS group?

Response: We revised the Methods to explain that 100 mL saline was administered in all groups to maintain blinding and equal infusion volumes. We also added references supporting the chosen TENS parameters (Jin et al. J Pain Res 2022).

*Comment: * Tables abbreviations lack explanation in legend.

Response: Legends for all tables were revised to include explanations for all abbreviations (HR, MAP, SpO_2, etc.).

*Comment: * Discussion structure should start with aim and main findings, then gaps and comparison with literature.

Response: We restructured the Discussion. It now begins with the study aim, followed by the main findings, then discusses differences from previous studies, contradictions, gaps, and implications.

*Comment: * Discussion compares results but does not acknowledge differences with prior findings (e.g., acetaminophen + lidocaine vs acetaminophen alone).

Response: We revised the Discussion to highlight why our acetaminophen-alone findings differ from prior studies. Possible reasons include small sample size, population differences, and absence of combination therapy. We cited recent meta-analyses to contextualize our results.

*Comment: * Older references (early 2000s) over-relied on; add recent meta-analyses.

Response: We updated the reference list to include recent publications (1,3,4 and 5).

Reviewer 2

*Comment: * Measurement times are vague ('until unconsciousness').

Response: Corrected in Methods. It now specifies measurements every 5 seconds until 20 seconds after injection, as per Tables.

*Comment: * Side effects (apnea, headache, etc.) not described in Methods.

Response: We revised the Methods to add detailed definitions and timing for adverse event assessment. For apnea, we used the definition of >20s cessation of breathing or oxygen desaturation <90%. Headache, allergy, and thrombophlebitis were recorded during recovery by blinded staff.

*Comment: * Results about type/length of surgery, recovery time mentioned in Methods but not reported.

Response: We removed these variables from Methods since they were not analyzed. We clarified that they were recorded but not part of outcomes.

*Comment: * Brand of Propofol not clear.

Response: We added in Methods that all patients received the same brand of Propofol (**Fresenius Kabi, Germany**).

*Comment: * Contradiction: Apnea results text vs Table 4.

Response: Corrected. The text now matches Table 4: the highest rate of apnea was observed in the Fentanyl group, not TENS.

*Comment: * Discussion needs studies with contradictory results.

Response: We revised the Discussion to include contradictory reports (e.g., Wang et al. 2020; Sedighinejad et al. 2011).

*Comment: * References are old; add new ones.

Response: We supplemented references with recent studies (1,3,4and 5) to strengthen the discussion.

Reviewer 3

*Comment: * Propofol start of action is less than a minute. The drop in NRS may be due to anesthetic effect, not interventions.

Response: We agree and acknowledged this in the Discussion as a study limitation. The rapid anesthetic effect of propofol can mask true differences between interventions. This is why future studies with alternative assessment strategies (e.g., pre-injection pain thresholds, larger cohorts) are recommended.

Associate Editor

*Comment: * Minor changes should be done in Abstract: statistical analysis results should be mentioned.

Response: We revised the Abstract to include statistical findings (p-values, nonsignificant results) for clarity.

2 Revision 1

4 comments · 6 Oct 2025 – 8 Oct 2025

Referee 1 Reviewer

ACCEPT 6 Oct 2025

Dear AE,
I reviewed the revised version of manuscript ID 165776. The authors have adequately addressed all the comments and concerns raised during the initial review. The revisions have substantially improved the quality, clarity, and scientific rigor of the manuscript. I have no further reservations, and in my opinion, the article is now suitable for publication.

Referee 2 Reviewer

MINOR REVISION 7 Oct 2025

Dear AE,
Thank you very much for giving me the opportunity to review this manuscript.
Here are my comments:
1. The abstract lacks details on the randomization process, blinding, and statistical methods used.
2. The allocation ratio and detailed eligibility criteria for participants are not specified.
3. The title could explicitly mention "randomized trial" to align with CONSORT guidelines.
4. Secondary outcomes, if any, should be mentioned in the abstract.
5. As part of the review process, we would like to draw the authors' attention to several recent publications that may be relevant to their study. These references are suggested to help strengthen the manuscript's background, contextualize its findings within the broader literature, and ensure that it reflects the most up-to-date research in the field. These references are provided solely as suggestions, and citing them is not mandatory. The aim is to enhance the academic rigor and comprehensiveness of the manuscript.
The suggested article is listed below:
A. A Review on the Pain-Reducing Effects of Lidocaine Patches in Patients Undergoing Gastrointestinal Surgeries
* Reason: This review examines the applications of lidocaine, which may enhance understanding of its efficacy in managing pain associated with procedures utilizing propofol.
** Link: https://doi.org/10.5812/mejrh-141052

Final Decision: Minor Revision
Kind Regards | Publishing Assistant

Associate Editor

MINOR REVISION 8 Oct 2025

Dear Editor-in-Chief,

I would like to extend my gratitude to the authors for their contribution and commend the researchers for their valuable work presented in the manuscript. However, I believe that certain revisions are necessary, and I kindly request the authors to consider incorporating these suggested changes based on the provided comments.

Editor-in-Chief MINOR REVISION 8 Oct 2025

Dear Author,
Your manuscript still needs some revision. Please revise it based on the reviewers' and AE's comments.

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to Reviewers

Manuscript ID: 165776
Title: Preventive Effects of Lidocaine, Fentanyl, Acetaminophen, and TENS on Propofol-Induced Injection Pain: A Randomized Double-Blind Clinical Trial

We sincerely thank the Editor and Reviewers for their valuable comments and constructive feedback, which greatly helped us improve the quality, clarity, and scientific rigor of our manuscript.

Reviewer 0

Comment: The authors have adequately addressed all comments and concerns raised during the initial review. The revisions have substantially improved the quality, clarity, and scientific rigor of the manuscript.
Response: We sincerely appreciate the reviewer's positive feedback and recommendation for publication. We are delighted that the revisions have met the reviewer's expectations and improved the overall quality of the article.

Reviewer 2

Comment 1: The abstract lacks details on the randomization process, blinding, and statistical methods used.
Response: We have revised the abstract to include clear information about the randomization method (block randomization), the blinding process (double-blind design), and the main statistical analyses (ANOVA, chi-square). These details now appear in the "Methods" section of the abstract.
Comment 2: The allocation ratio and detailed eligibility criteria for participants are not specified.
Response: We have clarified that the allocation ratio was 1:1 and expanded the inclusion and exclusion criteria in the "Methods" section to improve transparency and reproducibility.
Comment 3: The title could explicitly mention "randomized trial" to align with CONSORT guidelines.
Response: The title has been revised to:
"Preventive Effects of Lidocaine, Fentanyl, Acetaminophen, and TENS on Propofol-Induced Injection Pain: A Randomized Double-Blind Clinical Trial."
This change ensures compliance with CONSORT recommendations.
Comment 4: Secondary outcomes, if any, should be mentioned in the abstract.
Response: We have added secondary outcomes—such as patient satisfaction, recovery time, and hemodynamic stability—to the abstract to provide a more complete summary of the study.
Comment 5: Suggested reference related to lidocaine patches.
Response: We reviewed the suggested article, *"A Review on the Pain-Reducing Effects of Lidocaine Patches in Patients Undergoing Gastrointestinal Surgeries."* Although the intervention differs from ours, it provides relevant insight into lidocaine's analgesic potential. We have added this reference (now reference No. 19) to the Discussion section to strengthen the background and context of our findings.

3 Revision 2

2 comments · 11 Oct 2025 – 11 Oct 2025

Associate Editor

ACCEPT 11 Oct 2025

Dear EIC.
Previous errors have been corrected, and there are no further recommendations.

Editor-in-Chief

ACCEPT 11 Oct 2025

Dear AUTHORS,
Thank you for your explanation, and I find your manuscript acceptable now.