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OPEN PEER REVIEW

Comparison of Prophylactic Antiemetic Effects of Ondansetron Versus Haloperidol in Patients Undergoing Mastectomy: A Double-Blind Randomized 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

6 comments · 19 May 2025 – 31 May 2025

Referee 1 Reviewer

MINOR REVISION 19 May 2025

Dear Authors
Please explain the limitations of your plan.

Referee 2 Reviewer

MINOR REVISION 22 May 2025

Thank you for the manuscript.
I have two questions:
1- Please add the formula for sample size determination and the related calculations.
2- Is there any relationship between this research and the content at the following link?
https://www.cochranelibrary.com/es/central/doi/10.1002/central/CN-02687442/full?contentLanguage=en

Maryam Shahsavari Reviewer

MINOR REVISION 24 May 2025

Hi dear Author
All parts of the article were reviewed, and I think it is a very good and perfect piece of work. It would be better to mention in the title that the article is a randomized clinical trial.

Referee 3 Reviewer

MAJOR REVISION 25 May 2025

1. Title & Abstract
• Title: Consider rewording for clarity:
"Comparison of prophylactic antiemetic effects of ondansetron versus haloperidol in patients undergoing mastectomy: A double-blind randomized trial"
• Abstract:
o The P-values in the results section should be formatted consistently (e.g., *P = 0.65* instead of *P=0.65*).
o Specify that this was a transgender population (since this is a key aspect of the study).
2. Introduction/Background
• Rationale for Haloperidol:
o Expand on why haloperidol was chosen (beyond just being a dopamine antagonist).
o Mention cost differences (haloperidol is cheaper than ondansetron in many settings).
• PONV in Mastectomy:
o Clarify why mastectomy patients are high-risk (hormonal factors? opioid use?).
3. Methods
• Sample Size Justification:
o The calculation assumes a 30% absolute reduction in PONV, which seems optimistic.
o Was this based on prior literature? Cite a reference.
• Anesthesia Protocol:
o Propofol TIVA was used, which itself reduces PONV. Did this affect outcomes?
o Opioid use (morphine post-op) is a major PONV risk factor. Was this balanced between groups?

• Adverse Effects Monitoring:
o Haloperidol can cause QT prolongation/extrapyramidal symptoms—was ECG monitoring done?
o Ondansetron can cause headaches/constipation—were these recorded?
4. Results
• Table 1:
o The "PNOV" abbreviation is confusing—it should be "PONV" throughout.
o Mean age: The groups were young (26-27 years). Was this representative of typical mastectomy patients?
• Figure 3:
o The graph is unclear. Consider a line graph showing PONV trends over time.
• Statistical Trends:
o At 2 hours, haloperidol had lower PONV (20% vs. 44%, *P = 0.06*). This near-significance should be discussed.
5. Discussion
• Comparison with Prior Studies:
o The discussion cites Apfel et al. (2004) but does not explain why their findings differ.
o Lee et al. (2007) found haloperidol = ondansetron, which aligns with this study—emphasize this.
• Limitations:
o Small sample size (n=50) limits power to detect small differences.
o Single-center study may affect generalizability.
o No assessment of side effects (e.g., QT prolongation, sedation).
o Fixed dosing (2 mg haloperidol vs. 4 mg ondansetron)—was this optimal?
6. Conclusion
• Clinical Takeaway:
o "Both drugs are equally effective, so choice should depend on patient risk factors, cost, and side effect profile."
• Future Research:
o Suggest a larger multicenter trial with dose-ranging and safety monitoring.

Final Verdict
• Publishable with minor revisions.
• The study adds value by showing haloperidol is a viable alternative to ondansetron for PONV prophylaxis in mastectomy.
• Key revisions needed:
1. Clarify statistical methods and sample size justification.
2. Discuss limitations (side effects, dosing, population selection).
3. Improve graphs/tables for readability.
Would you like me to help refine any specific section further?

Associate Editor

MAJOR REVISION 31 May 2025

The study addresses an important clinical issue—Postoperative Nausea and Vomiting (PONV)—which significantly impacts patient recovery and satisfaction, particularly in mastectomy patients. The randomized, double-blind clinical trial design is robust and appropriate for comparing the efficacy of haloperidol and ondansetron. The use of block randomization, blinding, and standardized anesthesia protocols enhances the validity of the findings.
Moreover, the evaluation of PONV at multiple time points (0.5h to 24h) provides a detailed understanding of the temporal effects of both drugs.

My recommendations are as follows:
With 25 patients per group, the study may be underpowered to detect small but clinically meaningful differences. A post-hoc power analysis would strengthen the conclusions. Also provide the sample size calculation method.
The manuscript does not systematically report adverse effects (e.g., extrapyramidal symptoms for haloperidol or headaches for ondansetron), which are critical for evaluating the safety profile of these drugs.
Fixed doses of haloperidol (2 mg) and ondansetron (4 mg) were used.
The statistical methods are appropriate, but the lack of significant differences may reflect the small sample size rather than true equivalence. How do the authors justify this?
The trend toward ondansetron's superior efficacy at 2 hours (p=0.06) warrants discussion about whether a larger study might yield significant results.
The discussion adequately contextualizes the findings within existing literature but could better address the limitations (e.g., sample size, population specificity).
The conclusion that both drugs are "equally effective" should be tempered with acknowledgment of the study's limitations in detecting small differences.

My decision:

Major Revisions Required (with emphasis on expanding limitations discussion, reporting adverse effects, and clarifying population rationale).

Editor-in-Chief MAJOR REVISION 31 May 2025

Dear authors. Thank you for the submission. Based on the reviewers' comments, the manuscript needs major revision. Please rewrite it according to the journal's rules.

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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.

Dear Editor-in-Chief, thank you for your valuable comments. All comments have been reviewed, and the article has been revised according to the reviewer's comments.

Reviewers' Comments:

Reviewer 1:

Dear Authors

Please explain the limitations of your plan.

Response: Thank you. The manuscript revised accordingly.

Reviewer 2:

Thank you for the manuscript.

I have two questions

1- Please add the formula for sample size determination and the related calculations.

Response: Thank you. The manuscript revised accordingly.

2- Is there any relationship between this research and the following link:

https://www.cochranelibrary.com/es/central/doi/10.1002/central/CN-02687442/full?contentLanguage=en

Response: The cited review (CN-02687442) compares *ondansetron vs. placebo*, not haloperidol. Our study directly compares two active drugs, adding new evidence for alternatives to 5-HT3 antagonists.

Reviewer 3:

1. Title & Abstract

• Title: Consider rewording for clarity:

"Comparison of prophylactic antiemetic effects of ondansetron versus haloperidol in patients undergoing mastectomy: A double-blind randomized trial"

Response: Thank you. The manuscript revised accordingly.

• Abstract:

o The P-values in the results section should be formatted consistently (e.g., *P = 0.65* instead of *P=0.65*).

Response: Thank you. The manuscript revised accordingly.

o Specify that this was a transgender population (since this is a key aspect of the study).

Response: Thank you. The manuscript revised accordingly.

2. Introduction/Background

• Rationale for Haloperidol:

o Expand on why haloperidol was chosen (beyond just being a dopamine antagonist).

Response: Thank you. The manuscript revised accordingly.

o Mention cost differences (haloperidol is cheaper than ondansetron in many settings).

Response: Thank you. The manuscript revised accordingly.

• PONV in Mastectomy:

o Clarify why mastectomy patients are high-risk (hormonal factors? opioid use?).

Response: Thank you. The manuscript revised accordingly.

3. Methods

• Sample Size Justification:

o The calculation assumes a 30% absolute reduction in PONV, which seems optimistic.

o Was this based on prior literature? Cite a reference.

Response: Thank you. The Sample Size formula clarified in the manuscript.

• Anesthesia Protocol:

o Propofol TIVA was used, which itself reduces PONV. Did this affect outcomes?

o Opioid use (morphine post-op) is a major PONV risk factor. Was this balanced between groups?

Response: Given that the anesthesia protocol was the same for all patients and all received the same medications after surgery, the two groups were similar in this regard, and the results did not change.

• Adverse Effects Monitoring:

o Haloperidol can cause QT prolongation/extrapyramidal symptoms—was ECG monitoring done?

Response: Yes, ECG monitored for QTc and EPS assessed via Simpson-Angus Scale; there was no any of mentioned adverse effects.

o Ondansetron can cause headaches/constipation—were these recorded?

Response: Yes, there was no any of mentioned adverse effects.

4. Results

• Table 1:

o The "PNOV" abbreviation is confusing—should be "PONV" throughout.

Response: Thank you. The manuscript revised accordingly.

o Mean age: The groups were young (26-27 years). Was this representative of typical mastectomy patients?

Response : Yes, most mastectomy candidates are in this age range.

• Figure 3:

o The graph is unclear. Consider a line graph showing PONV trends over time.

Response: Thank you. The manuscript revised accordingly.

• Statistical Trends:

o At 2 hours, haloperidol had lower PONV (20% vs. 44%, *P = 0.06*). This near-significance should be discussed.

Response: Thank you. The manuscript revised accordingly.

5. Discussion

• Comparison with Prior Studies:

o The discussion cites Apfel et al. (2004) but does not explain why their findings differ.

o Lee et al. (2007) found haloperidol = ondansetron, which aligns with this study—emphasize this.

Response: Thank you. The manuscript revised accordingly.

• Limitations:

o Small sample size (n=50) limits power to detect small differences.

o Single-center study may affect generalizability.

o No assessment of side effects (e.g., QT prolongation, sedation).

o Fixed dosing (2 mg haloperidol vs. 4 mg ondansetron)—was this optimal?

Response: Thank you. The manuscript revised accordingly.

6. Conclusion

• Clinical Takeaway:

o "Both drugs are equally effective, so choice should depend on patient risk factors, cost, and side effect profile."

• Future Research:

o Suggest a larger multicenter trial with dose-ranging and safety monitoring.

Response: Thank you. The manuscript revised accordingly.

Reviewer 4:

Hi dear Author

All parts of the article were reviewed and I think it is a very good and perfect work.It would be better to mention in the title that the article is a randomized clinical trial.

Response: Thank you. The manuscript revised accordingly.

Associate Editor's Comments:

Associate Editor 1:

The study addresses an important clinical issue—Postoperative Nausea and Vomiting (PONV)—which significantly impacts patient recovery and satisfaction, particularly in mastectomy patients. The randomized, double-blind clinical trial design is robust and appropriate for

comparing the efficacy of haloperidol and ondansetron. The use of block randomization, blinding, and standardized anesthesia protocols enhances the validity of the findings. Moreover, the evaluation of PONV at multiple time points (0.5h to 24h) provides a detailed understanding of the temporal effects of both drugs.

My recommendations are as following:
With 25 patients per group, the study may be underpowered to detect small but clinically meaningful differences. A post-hoc power analysis would strengthen the conclusions. Also provide the sample size calculation method.

Response: Thank you. The manuscript revised accordingly.

The manuscript does not systematically report adverse effects (e.g., extrapyramidal symptoms for haloperidol or headaches for ondansetron), which are critical for evaluating the safety profile of these drugs.

Response: Thank you. The manuscript revised accordingly. Multiple complications, such as QT prolongation/extrapyramidal symptoms and headache, were monitored, and no adverse events were observed in either group.

Fixed doses of haloperidol (2 mg) and ondansetron (4 mg) were used.
The statistical methods are appropriate, but the lack of significant differences may reflect the small sample size rather than true equivalence. How do the authors justify this?

Response: Thank you. The small sample size was the one of the main limitations of current study. Due to operational limitations, we were unable to obtain a larger sample size. However, according to the statistical formula and considering a power of 80% and a difference of 40% between the two groups, this number was utilized. This formula was intended to determine the minimum sample size, and a larger number could have been achieved, which was discussed in the study limitations.

The trend toward ondansetron’s superior efficacy at 2 hours (p=0.06) warrants discussion about whether a larger study might yield significant results.
The discussion adequately contextualizes the findings within existing literature but could better address the limitations (e.g., sample size, population specificity).

The conclusion that both drugs are "equally effective" should be tempered with acknowledgment of the study’s limitations in detecting small differences.
Response: Thank you. The recommendations were considered.

My decision:

Major Revisions Required (with emphasis on expanding limitations discussion, reporting adverse effects, and clarifying population rationale).

Response: Thank you. The recommendations were considered.

2 Revision 1

3 comments · 12 Jun 2025 – 1 Jul 2025

Referee 2 Reviewer

ACCEPT 12 Jun 2025

Dear Editor in Chief
Thank you for choosing me as a reviewer.
In my opinion, the revised version has addressed all the critiques, and so the manuscript could be accepted for publication in the journal.

Associate Editor

MINOR REVISION 30 Jun 2025

The revised manuscript presents a well-designed randomized controlled trial comparing the efficacy of haloperidol and ondansetron for preventing postoperative nausea and vomiting (PONV) in transgender patients undergoing bilateral mastectomy. The authors have addressed most reviewer concerns, including methodological clarity, statistical reporting, and ethical considerations. The study is clinically relevant, particularly given the high risk of PONV in mastectomy patients and the need for cost-effective alternatives to ondansetron. However, some areas require minor refinements to enhance clarity and rigor.

The expanded discussion on haloperidol's cost-effectiveness and dopaminergic mechanism is excellent. Consider adding a sentence about its historical use in PONV (e.g., "Haloperidol, though less studied than ondansetron, has shown promise in PONV prophylaxis due to its D2 antagonism").
The hormonal and opioid-related risk factors are well explained in the introduction. A brief mention of transgender-specific factors (e.g., hormone therapy effects on PONV risk) would strengthen the rationale.
Regarding the assessment timeline in the methods, please include it as a table and specify the different time units.
Sample Size Calculation: The formula and assumptions (30% absolute reduction) are now clearly stated. However, the expected PONV incidence (50% in controls) seems high. Cite a reference for this estimate (e.g., a prior mastectomy study).
Postoperative morphine (a PONV risk factor) was given to all patients. Was the dose standardized based on weight?
The manuscript now states that QT prolongation and extrapyramidal symptoms were monitored, but the results section could explicitly report "zero events" for clarity.

The small sample size and single-center design are appropriately noted as limitations. Consider adding that the transgender population, while clinically relevant, may limit generalizability to other groups.

Overall Recommendation: Accept with Minor Revisions.

Editor-in-Chief

MINOR REVISION 1 Jul 2025

Dear authors
Please consider minor revisions.

3

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.

Dear editor in chief

Thank you for the valuable comments, all comments, studied point by point and apllied in the manuscript.

Comments 1:

"Consider adding a sentence about its historical use in PONV (e.g., 'Haloperidol, though less studied than ondansetron, has shown promise in PONV prophylaxis due to its D2 antagonism')."

Response:
Thank you for your helpful suggestion. We have added a sentence to the Background section to highlight haloperidol's historical role in PONV prophylaxis. The revised text reads:

"Historically, haloperidol, though less extensively studied than ondansetron, has shown promise in PONV prophylaxis due to its D2 receptor antagonism, particularly in high-risk surgical patients."

Comment 2:

"The hormonal and opioid-related risk factors are well-explained in introduction. A brief mention of transgender-specific factors (e.g., hormone therapy effects on PONV risk) would strengthen the rationale."

Response:
We appreciate this insightful comment. We have added a sentence to the Background section addressing transgender-specific risk factors:

"Additionally, transgender individuals receiving gender-affirming hormone therapy may exhibit altered susceptibility to PONV, as estrogen and testosterone modulate neurotransmitter sensitivity in emetogenic pathways, including serotonin and dopamine systems."

Comment 3:

"Regarding the assessment timeline in methods please include it as a table and specify the different time units."

Response:
Thank you for your suggestion. The manuscript revised accordingly.

Comment 4:

"Sample Size Calculation: The formula and assumptions (30% absolute reduction) are now clearly stated.d However, the expected PONV incidence (50% in controls) seems high. Cite a reference for this estimate (e.g., a prior mastectomy study)."

Response:
Thank you for your suggestion. The manuscript revised accordingly.

Comment 5:

"Postoperative morphine (a PONV risk factor) was given to all patients. Was the dose standardized based on weight?"

Response:
We have clarified this in the Methods section:

“Postoperative analgesia included a standardized morphine dose of 0.1 mg/kg IV, ensuring consistency across patients.”

Comment 6:

"The manuscript now states that QT prolongation and extrapyramidal symptoms were monitored, but the results section could explicitly report 'zero events' for clarity."

Response:
We appreciate this comment and agree that explicit reporting improves clarity. The following sentence was added to the Results section:

“Specifically, no cases of QT prolongation or extrapyramidal symptoms occurred in either group.”

Comment 7:

"The small sample size and single-center design are appropriately noted as limitations. Consider adding that the transgender population, while clinically relevant, may limit generalizability to other groups."

Response:
Thank you for this important point. We have added the following sentence to the Limitations section:

“Moreover, the study of transgender population, while clinically relevant, may limit the generalizability of these findings to other groups"

3 Revision 2

4 comments · 15 Jul 2025 – 22 Jul 2025

Referee 2 Reviewer — ACCEPT 15 Jul 2025

Dear AE
Following the revisions requested in the previous round of review, I think the revised manuscript is well prepared and the current version is acceptable for publication in the JCMA.

Maryam Shahsavari Reviewer — ACCEPT 22 Jul 2025

Hi dear Authors
The revision has been well done.

Associate Editor — ACCEPT 22 Jul 2025

The revised manuscript presents a well-designed, double-blind randomized trial comparing haloperidol and ondansetron for PONV prophylaxis in transgender patients undergoing mastectomy. The authors have addressed most reviewer comments comprehensively, enhancing clarity, rationale, and methodological rigor. The study fills a niche in PONV literature by focusing on a high-risk, understudied population.

Strengths:
1. Novel Population
2. Robust Methodology
3. Ethical Compliance
4. Balanced Discussion

Areas for Improvement:
Correct Typos:
- Page 3: "ondanse tron" → "ondansetron" (repeated error).
- Page 12: "PNOV" → "PONV."
Figure 2: Label y-axis as "% PONV Incidence" for clarity.

Final Recommendation
Accept. The manuscript is methodologically sound and makes a valuable contribution to PONV literature.

Editor-in-Chief — ACCEPT 22 Jul 2025

Congratulations!
The manuscript is ready for publication in the Journal.