Journal of Cellular & Molecular Anesthesia
Volume 11 · Issue 1 · e165641

OPEN PEER REVIEW

Opioid Free Anesthesia and Its Effects on Clinical Outcomes in Thoracoscopic Surgery: A Clinical Trial Study

Moein Daneshmand, Alireza Jahangirifard, Seyedeh Mahta Mirkhani, Kobra Rafie Badi, Alireza Salimi, Seyed Bashir Mirtajani, Lida Fadaizadeh

SUBMITTED	REVISED	ACCEPTED	DOI
11 Nov 2025	4 Feb 2026	4 Feb 2026	10.5812/jcma-165641

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.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Referee 2, Referee 3, Associate Editor, Editor-in-Chief 2
2 **Revision 1** Referee 3, Referee 1, Referee 2, Editor-in-Chief 7
Authors' reply to reviewers 8
Reviewer and editor comments 13
3 **Revision 2** Referee 3, Referee 1, Referee 2, Associate Editor, Editor-in-Chief 15
Authors' reply to reviewers 16
Reviewer and editor comments 18
4 **Revision 3** Associate Editor, Editor-in-Chief 20
Authors' reply to reviewers 21
Reviewer and editor comments 22
5 **Revision 4** Associate Editor, Editor-in-Chief 23
Authors' reply to reviewers 24
Reviewer and editor comments 25

1 Original submission

5 comments · 14 Nov 2025 – 22 Nov 2025

Referee 1 Reviewer

MAJOR REVISION 14 Nov 2025

This randomized controlled trial (RCT) evaluates opioid-free anesthesia (OFA) using ketamine and dexmedetomidine versus opioid-based anesthesia (OBA) with fentanyl in 60 patients undergoing thoracoscopic surgery. The study reports improved pain control and hemodynamic stability with OFA but unexpectedly higher postoperative inflammatory (CRP) and renal (BUN, creatinine) markers, with no difference in complications or rescue analgesia. Overall, the work contributes to the emerging OFA literature in thoracic surgery but is undermined by methodological flaws, statistical inconsistencies, reporting errors, and limited generalizability. Below is a structured critique.

Strengths

• Clinical Relevance and Timeliness
• Randomized Design and Ethics
• Multimodal Outcomes
• Feasible Protocol

Major Weaknesses

1- Inconsistent Terminology and Labeling Errors:

• The groups are referred to interchangeably as “intervention/non-opioid/non-narcotic” vs. “control/Opium” (likely a translation error for “opioid”). This is confusing and unprofessional (e.g., Abstract: “Opium group”; Results: “Opium”).
• The Abstract claims that HR was lower in the non-opioid group at 6, 8, and 12 hours (correct per Table 2), but that VAS was lower “during recovery, 2, 12, and 18 hours” (Table 2 shows significance at recovery and at 2, 12, and 18 hours—consistent, but the phrasing is imprecise).
• The keywords list “Opioid” (should be “opioids”) and omit “ketamine/dexmedetomidine.”

2- Statistical and Analytical Issues:

• Multiple Testing Without Correction: ~40 comparisons in Table 2 (hemodynamics/VAS across 8 time points), plus those in Table 3 (preoperative/postoperative laboratory values), increase the risk of Type I error. No Bonferroni or similar adjustment is reported; the claimed significance at $p < 0.05$ for isolated time points (e.g., HR at 6/8/12 hours) may be spurious.
• Inappropriate Tests: The manuscript states that the Kolmogorov-Smirnov test was used to assess normality but uses t-tests/Mann-Whitney tests. High SDs (e.g., BUN-A: OFA 52.2 ± 46.6 vs. OBA 32.9 ± 8.5) suggest skewness/outliers; box plots or evidence of normality are not shown.
• Baseline Imbalances Ignored: Preoperative CRP tends to be higher in the OFA group (39.1 ± 24.8 vs. 25.8 ± 15.3, $p = 0.054$)—a near-significant difference. Postoperative differences ($p = 0.038$) may reflect baseline confounding, not treatment. No ANCOVA adjusting for baseline values is reported.
• Underpowered for Key Outcomes: n = 30/group allows detection of large effects but not subtle differences in complications (rare events: itching 0% vs. 6.7%) or rescue acetaminophen use (Figure 2: no SDs/error bars; the manuscript claims “no difference” without a test/p-value).
• Selective Reporting: ALT/AST are unchanged but included; no effect sizes (e.g., Cohen’s d) or CIs for differences are reported.

3- Methodological Limitations:

• No Blinding Details: Patients/surgeons were likely unblinded (different induction drugs); whether assessors/outcome raters were blinded is not specified, creating a risk of bias in subjective VAS scores.
• Short Follow-Up: A 24-hour follow-up misses delayed opioid effects (e.g., ileus, hyperalgesia) or chronic pain

—critical considerations for OFA claims.
• Homogeneous Cohort: The study is single-center (Iran), includes patients aged 18–70, and excludes high-risk patients (e.g., those with ICP issues or addiction). A BMI of ~19–20 (low) is atypical for Western populations, limiting extrapolation.
• No Nociception Monitoring: OFA requires titration (e.g., ANI/SPI); no nociception monitoring is mentioned, creating a risk of underdosing.
• Rescue Analgesia Protocol: The protocol for IV acetaminophen for VAS > 3 is identical in both groups; the absence of opioids as rescue analgesia biases against detecting OFA's opioid-sparing benefit.
4- Unexpected Results and Interpretation Gaps:
• Higher postoperative CRP/BUN/Cr levels in the OFA group contradict the literature (dexmedetomidine/ketamine are often anti-inflammatory/renal-protective). The authors speculate about confounders (ventilation, fluids) but provide no data (e.g., surgery duration, blood loss, fluids—entirely missing).
• No clinical correlation: Elevated Cr (OFA: 1.91 ± 2.33 vs. 1.04 ± 0.23) is driven by outliers (SD > mean); no AKI diagnosis or follow-up is reported.
• Hemodynamic "stability": Is lower HR in the OFA group beneficial? Baseline HR tends to be lower (73 vs. 93.5, p = 0.054), but no bradycardia events are reported.
5- Reporting and Presentation Flaws:
Typos/Grammar: "Opium" for opioid; "patients were randomly divided into two intervention and control groups" (awkward); "same surgical" (incomplete); "non-narcotic patients" (vs. group).
Tables/Figures: Table 1: Weight p = 0.082 (a trend toward imbalance). Table 2: SBP/DBP/RR results are mostly nonsignificant and overwhelm the significant findings. Figure 2: Bar heights are ~1 g in both groups, but the manuscript claims "no difference"—provide means/SDs/p-value.
Introduction Mismatch: The stated aim is to "systematically evaluate current evidence" (sounds like a review), but this is a primary RCT.
References: A mix of classics (e.g., #1 2008) and recent references; #6 addresses PRISMA for reviews (irrelevant); no thoracic OFA meta-analyses are cited.

Referee 2 Reviewer

MAJOR REVISION 21 Nov 2025

Dear AE,
The manuscript claims to be a randomized clinical trial but fails to describe the randomization method, block size, allocation concealment, or who performed the allocation.

There is no description of blinding (patients, clinicians, assessors). The absence of blinding greatly increases the risk of bias, particularly for VAS measurement.

It is unclear whether intraoperative analgesic titration was standardized (depth of anesthesia, nociception monitoring, adjunct use).

"Patients in both groups underwent surgery by the same surgical." → The wording is unclear and incomplete; details about the surgeon, technique standardization, and type of thoracoscopic surgery are missing.

There is no mention of one-lung ventilation, lung isolation technique, pleural analgesia, the number of chest tubes, or other operative variables that strongly affect postoperative pain.

The authors do not report an a priori power analysis. The study risks being severely underpowered, particularly for secondary outcomes (CRP, BUN/Cr, complications).

Complications are mentioned, but no definition or grading system (e.g., Clavien-Dindo) is provided despite the citation of Clavien-Dindo in the references.

It is unclear whether respiratory depression was objectively measured.

There is no information on baseline comparability for comorbidities (COPD, renal disease, hypertension).

IV acetaminophen alone, given PRN for VAS > 3, is not an acceptable analgesic regimen in thoracic surgery trials. The lack of multimodal analgesia or regional blocks strongly biases the study toward the OFA regimen.

The manuscript states that CRP, BUN, and Cr were "significantly higher in the non-opioid group," but no clinical interpretation is provided, neither baseline renal status nor the perioperative fluid strategy is described, and the observed increase in Cr (mean 1.9 mg/dL) seems clinically meaningful, yet the authors dismiss it without justification.

Extremely large SDs (e.g., Cr SD 2.3278) indicate high variance or data entry errors.

The abstract states, "CRP, BUN, Cr indices after surgery had significant difference."
Table 3 shows that CRP-B and BUN-B are not significantly different.

Table 2 indicates near-significant differences ($p \approx 0.05$), but the authors report them as meaningful without adjusting for multiple comparisons.

There is no adjustment for multiple time-point comparisons (≥8 time points × multiple variables = dozens of comparisons).

Normality is assessed using only the K-S test (not recommended for small samples).

Repeated-measures data are analyzed with multiple t-tests rather than a methodologically appropriate approach.

Continuous variables are presented as mean ± SD despite skewed distributions.

BMI values (19.90 vs. 19.40) are implausibly low for average thoracic surgery patients.

The flow diagram is minimal and does not include detailed reasons for exclusion, analysis exclusions, protocol violations, or safety data.

OFA usually includes multimodal techniques (lidocaine infusion, magnesium, NSAIDs, β-blockers, regional blocks). The authors use only ketamine + dexmedetomidine, yet generalize the results to "OFA" broadly.

There is no justification for dosing (dexmedetomidine 0.6 μg/kg/h is unusually high for thoracoscopic surgery).

No nociception index or BP/HR-guided titration is described.

Was depth of anesthesia monitored? Was BIS used? Was MAC targeted?

HR in the control group during recovery (93.5 bpm) is extremely high for anesthetized post-thoracoscopy patients unless inadequate analgesia occurred.

Baseline RR (17.6) is unusually high for the immediate postoperative period in patients receiving controlled ventilation.

There are numerous grammatical and syntactic errors.

Group names vary:
"Non opioid", "non-opioid", "Non-opioid group", "Opium", "Opiate", "Opioid", "narcotic", "narcotic group."

"Opium group" is scientifically incorrect. These patients did not receive opium.

The introduction over-cites basic opioid concepts and under-cites thoracic anesthesia evidence.

The literature discussion is overly general; some references are irrelevant (PRISMA guidelines in an RCT?).

Reference 6 (PRISMA) is irrelevant to the clinical trial.

Referee 3 Reviewer — MINOR REVISION — 21 Nov 2025

Dear Associate Editor
Thank you for your kindness.

Title:
- Identify the study as a randomized trial in the title.
Keyword:
- Please add VATS (video-assisted thoracic surgery), which is the type of surgery being studied, to the keywords.

Methods:
- The inclusion and exclusion criteria need to be revised: bradycardia, psychological disorders.
- Please provide more details about the study method.
- As you know, multimodal pain management methods are usually used in thoracic surgeries because some patients may need more pain relief and do not respond to intravenous medications. In this study, if a patient complained of pain despite taking acetaminophen, how was the pain relieved?

Sample size:
- Please explain how the sample size was determined.
- When applicable, please explain any interim analyses and stopping guidelines.

Randomization - Sequence generation:
- Please describe the method used to generate the random allocation sequence.
- Please describe the type of randomization and provide details of any restrictions (such as blocking and block size).
- Please describe the mechanism used to implement the random allocation sequence (such as sequentially numbered containers), including any steps taken to conceal the sequence until interventions were assigned.
Blinding:
- If blinding was performed, please state who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.
Harm:
Please report all important harms or unintended effects in each group (for specific guidance, see CONSORT for harms).

The manuscript needs to be reviewed by a native English speaker.

Associate Editor — MAJOR REVISION — 22 Nov 2025

Dear EIC,
This manuscript presents a single-center randomized controlled trial comparing opioid-free anesthesia (OFA) with a ketamine-dexmedetomidine regimen to traditional opioid-based anesthesia (OBA) in patients undergoing thoracoscopic surgery. The authors report that OFA provided superior analgesia at specific time

points and better hemodynamic stability (lower heart rate) but also note higher postoperative levels of CRP, BUN, and creatinine in the OFA group.

- The results section of the abstract states: "The CRP index after surgery (P=0.038), and BUN (P=0.027) and Cr (P=0.040) indices after surgery had a significant difference in the two groups." The authors should explicitly state that these values were significantly higher in the OFA group and provide the p-values as well.
The term "Opium group" should be replaced with "opioid-based anesthesia (OBA) group" or "control group" for scientific accuracy.
- A major methodological weakness is the lack of a description of blinding. Were the patients, surgeons, anesthesiologists, or outcome assessors blinded to the group allocation? If blinding was not performed, this must be stated as a significant limitation. If it was, the specific methods used must be described.
- The manuscript does not mention a pretrial sample size or power calculation. How was the sample size of 60 patients determined? A post hoc power analysis may be necessary to justify the conclusions, especially for outcomes for which no difference was found (e.g., complication rates).
- The manuscript alternates between "Non opioid," "non-narcotic," and "OFA" for one group and between "Opium" and "OBA" for the other. This should be standardized.
- Table 2 is extensive and difficult to interpret. Consider presenting a simplified version.
- The results for CRP, BUN, and Cr are the most surprising part of the study. The text (Page 7) states they were "significantly higher in the non-opioid group." This must be emphasized with the actual mean ± SD values from Table 3 in the results text for clarity (e.g., "Postoperative CRP was 45.0 ± 23.1 in the OFA group vs. 32.0 ± 18.1 in the OBA group, p=0.038").
- For non-normally distributed data, the median and interquartile range (IQR) should be reported instead of the mean ± SD. The manuscript states that both were used, but the tables report only the mean ± SD. Please verify and correct the presentation of data where nonparametric tests were used.
- The discussion of the elevated CRP, BUN, and Cr levels is speculative, which is appropriate. However, the authors should more strongly consider and discuss the possibility of baseline imbalance. Table 3 shows that preoperative CRP and BUN were already higher in the OFA group (39.1 vs. 25.8 and 30.9 vs. 36.8, respectively), though these differences were not statistically significant. With a small sample size, these baseline differences could explain the postoperative findings. An analysis of covariance (ANCOVA) adjusting for baseline values would be a much stronger statistical approach to address this concern.
The discussion should comment on the clinical significance of the observed differences.

Recommendation:
Major revision
Addressing the major concerns regarding blinding, sample size justification, and clarity of results is essential for the validity and impact of this work.

Editor-in-Chief

MAJOR REVISION 22 Nov 2025

Dear Authors
Thank you for your manuscript. Based on the reviewers' comments, the manuscript needs a "MAJOR revision". Please consider revising it based on the provided comments.
Thank you for your contribution to the JCMA.

2

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

Comment

- No blinding details; patients/surgeons likely unblinded, outcome assessors not specified as blinded, risking bias in subjective VAS.
- **Response:**
  We thank the reviewer for this important comment. We acknowledge that complete blinding of anesthesiologists was not feasible due to the use of different induction agents in the two study arms. However, patients were not informed about group allocation, and postoperative data collection, including VAS pain scores and complication assessment, was performed by a trained nurse who was blinded to the anesthetic regimen. We have now clarified the blinding procedures in the Methods section and acknowledged the potential risk of performance bias in the Limitations section.
  -Manuscript revision:
  A statement regarding assessor blinding and the limitation of anesthesiologist non-blinding has been added to the Methods and Limitations sections.

Comment

- Short follow-up (24 hours) misses delayed opioid effects or chronic pain outcomes.
- **Response:**
  We agree with the reviewer that a 24-hour follow-up does not capture delayed opioid-related adverse effects or chronic postoperative pain. The primary objective of this study was to evaluate early postoperative analgesia and immediate clinical outcomes following thoracoscopic surgery. Longer-term outcomes were beyond the scope of the present trial. This limitation has now been explicitly acknowledged, and we have emphasized the need for future studies with extended follow-up periods.
- **Manuscript revision:**
- The limitation of short-term follow-up has been added to the Limitations section.

Comment

- Homogeneous cohort (single-center, narrow BMI, exclusion of high-risk patients) limits generalizability.
- **Response:**
  We acknowledge that the single-center design and strict inclusion/exclusion criteria limit the external validity of our findings. The relatively low mean BMI reflects the demographic characteristics of our study population and regional referral patterns. We have revised the Discussion to explicitly state that extrapolation to Western or high-risk populations should be performed with caution.

Comment 4

- No nociception monitoring (ANI/SPI) despite OFA claims.

- **Response:**
  We agree that advanced nociception monitoring tools such as ANI or SPI can optimize analgesic titration in OFA. Unfortunately, these monitors were not available at our institution during the study period. Intraoperative analgesia was titrated based on standard clinical parameters (heart rate, blood pressure, and anesthesiologist judgment). This limitation has been added to the manuscript.

Comment 5

- Rescue analgesia protocol (IV acetaminophen only) biases against detecting opioid-sparing benefit.
- **Response:**
  We appreciate this insightful comment. A uniform rescue analgesia protocol using intravenous acetaminophen was intentionally applied to both groups to avoid confounding postoperative outcomes with additional opioid exposure. However, we acknowledge that this approach may have limited the ability to demonstrate opioid-sparing effects. This issue is now discussed as a methodological limitation.

Comment 6

- Unclear standardization of intraoperative analgesic titration and anesthesia depth.
- **Response:**
  We thank the reviewer for highlighting this point. Anesthesia depth was standardized using MAC-targeted isoflurane (up to 1 MAC), and intraoperative adjustments were guided by hemodynamic responses. Although BIS or nociception indices were not used, anesthetic management followed a predefined institutional protocol. Additional details have been added to the Methods section.

Comment

- Lack of thoracic-specific operative variables (OLV, lung isolation, chest tubes, pleural analgesia).
- **Response:**
  We agree that these variables influence postoperative pain. In this study, all patients underwent thoracoscopic surgery with one-lung ventilation using a double-lumen endotracheal tube, and standard chest tube placement was performed by the same surgical team. No regional pleural analgesia was used. These details have now been added to the Methods section.

Comment 8

- Complications not defined or graded despite citing Clavien–Dindo.
- **Response:**
  We appreciate this comment. Postoperative complications were recorded as minor adverse events (nausea, vomiting, pruritus) and did not include major surgical complications. We

acknowledge that formal Clavien–Dindo grading was not applied, and the citation has been removed to avoid confusion. This has been clarified in the revised manuscript.

Comment

- Respiratory depression not objectively defined.
- **Response:**
  We agree that objective criteria should be specified. Respiratory depression was defined as a respiratory rate <10 breaths/min or oxygen saturation <90% on room air. No patient met these criteria. This definition has now been included in the Methods section.

Comment

- IV acetaminophen alone is not an acceptable analgesic regimen for thoracic surgery trials.
- **Response:**
  We acknowledge that multimodal and regional analgesia are standard in thoracic surgery. However, all patients underwent thoracoscopic surgery and to isolate the effects of the anesthetic technique itself, regional blocks and additional systemic analgesics were intentionally avoided. This design choice may limit real-world applicability and is now clearly acknowledged as a study limitation.

Comment

- CRP, BUN, and creatinine significantly higher in OFA group without adequate interpretation; Cr ~1.9 mg/dL clinically relevant.
- **Response:**
  We thank the reviewer for this important observation. All patients had normal baseline renal function. Perioperative fluid therapy was standardized; however, subtle differences in hydration status or surgical stress response may have contributed to transient postoperative elevations. We agree that the creatinine increase is clinically relevant and have revised the Discussion to emphasize that this finding warrants caution and further investigation rather than dismissal.

Comment

- No adjustment for multiple comparisons.
- **Response:**
  We acknowledge that multiple time-point analyses increase the risk of type I error. Given the exploratory nature of this trial and limited sample size, no formal correction was applied. This has now been explicitly stated as a statistical limitation.

Comment

- Normality assessed using K–S test only.
- **Response:**
  We agree that the Kolmogorov–Smirnov test has limited sensitivity in small samples. We have clarified that normality was also assessed using graphical methods (box plots and normal probability plots), and this has been revised in the Statistical Analysis section.

Comment

- Implausibly low BMI values.
- **Response:**
  We appreciate this observation. The BMI values reflect the actual measurements of our patient cohort and are consistent with the local population undergoing thoracic surgery at our center. This has been clarified in the Discussion as a factor limiting generalizability.

Comment

- Overgeneralization of results to OFA despite limited regimen (ketamine + dexmedetomidine only).
- **Response:**
  We agree and have revised the manuscript to specify that our findings apply specifically to a ketamine–dexmedetomidine–based OFA protocol rather than OFA in general.

Comment

- No justification for dexmedetomidine dosing (0.6 μg/kg/h).
- **Response:**
  The selected dose was based on prior clinical studies demonstrating effective analgesia and hemodynamic stability without excessive bradycardia. We have added a justification and relevant references in the Methods section.

Comment

- No nociception index or HR/BP-guided titration described.
- **Response:**
  We have clarified that analgesic titration was guided by hemodynamic responses and clinical judgment due to unavailability of nociception indices.

Comment

- Depth of anesthesia monitoring unclear (BIS/MAC).
- **Response:**

Depth of anesthesia was controlled using MAC-targeted isoflurane. BIS monitoring was not used. This has now been explicitly stated.

Comment

- High HR and RR values suggest inadequate analgesia.
- **Response:**
  We acknowledge that higher HR and RR values in the opioid group may reflect increased sympathetic activation or pain. This observation supports, rather than undermines, the potential analgesic efficacy of the OFA regimen and is now discussed accordingly.

Comment

- Inclusion/exclusion criteria need revision (bradycardia, psychological disorders).
- **Response:**
  We agree and have revised the exclusion criteria to include baseline bradycardia and significant psychiatric disorders.

Comment

- Request for more detailed methods and rescue analgesia beyond acetaminophen.
- **Response:**
  If patients experienced persistent pain despite acetaminophen, additional analgesic management was provided according to institutional protocols; however, no patient required escalation beyond acetaminophen. This clarification has been added to the Methods section.

2 Revision 1

4 comments · 19 Dec 2025 – 19 Dec 2025

Referee 3 Reviewer

MINOR REVISION 19 Dec 2025

Dear Associate Editor
Thank you for your kindness.

Title:
Same as the previous version.
- Identification as a randomized trial in the title.

Sample size:
- How the sample size was determined.
- When applicable, an explanation of any interim analyses and stopping guidelines.

Randomization - Sequence generation:
“Participants were randomly allocated into two equal groups using a random number table”
Please provide more details.
- Method used to generate the random allocation sequence.
- Type of randomization; details of any restriction (such as blocking and block size).
- Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned.

Referee 1 Reviewer

MAJOR REVISION 19 Dec 2025

Dear Associate Editor
I acknowledge the authors' considerable efforts to improve the manuscript. However, a considerable number of the comments and critiques concern fundamental flaws in the original study and therefore could not be resolved.
Some other items have been fully addressed.

My final suggestion is to convert the manuscript to a "brief communication" and then accept it for publication.

Referee 2 Reviewer

MAJOR REVISION 19 Dec 2025

The manuscript does not clearly report the basis for sample size determination. A formal power analysis, including the primary outcome, expected effect size, alpha level, and statistical power, should be explicitly stated. Without this information, it is difficult to assess whether the study was adequately powered to detect clinically meaningful differences.

Although multiple outcomes were assessed (HR, VAS, CRP, BUN, creatinine), the manuscript does not clearly distinguish between primary and secondary endpoints.

The opioid-free anesthetic regimen requires a more precise description. While the concept of OFA is central to the study, the following details should be presented clearly to improve reproducibility and external validity: 1. Exact drugs and dosages, 2. Timing of administration, 3. Rationale for drug selection.

Although the authors state that no patient required escalation beyond acetaminophen, the protocol for rescue analgesia should be described more explicitly. It should be clarified whether additional non-opioid analgesics were allowed and how pain escalation thresholds were defined.

The clinical relevance of differences in CRP, BUN, and creatinine should be discussed more cautiously. While statistical significance is reported, the magnitude and clinical implications of these changes remain unclear. It would be helpful to indicate whether changes exceeded clinically meaningful thresholds.

Some terminology is inconsistent (e.g., use of “Opium group” instead of “opioid-based anesthesia group”).

The discussion could be strengthened by a more direct comparison with recent high-quality trials or meta-analyses on OFA in thoracic or minimally invasive surgery.

OFA is not a one-size-fits-all solution. It is most appropriate for minimally invasive surgeries, short-duration procedures, or patients at high risk for opioid-related complications, such as those with a history of opioid use disorder, sleep apnea, or other respiratory issues. However, in more invasive surgeries where pain management is a major concern, complete opioid avoidance may lead to worse outcomes and increased pain.

Editor-in-Chief

MAJOR REVISION 19 Dec 2025

Dear authors
Thank you for the revision. Several of the critiques have been addressed; however, some important ones remain.
Due to the design of the study and some basic critical issues, we could accept the manuscript as a "Brief Communication" ONLY after the current concerns raised by the reviewers have been addressed.

Thank you for your kind cooperation with the JCMA.

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.

Response to reviewers

Comment

- The type of study, which is RCT, should be added at the end of the title.
- **Response:**
  It was changed to "Opioid free Anesthesia and its effects on clinical outcomes in Thoracoscopic surgery-a clinical trial study".

Comment

- The aim of the study is not clear, and the authors might mention the type of surgery early in the abstract.
- **Response:**
  The text "Therefore, the present study was designed and implemented with the aim of evaluating Opioid-free Anesthesia and its effects on clinical outcomes in Thoracoscopic surgery" was added.

Comment

- Consider using a single terminology for groups. Opioid-free is the best choice for the group who did not receive opioids. There is an inconsistency about the naming of the control group as well (“Opium group” vs “opioid group”).
- **Response:**
  Corrections have been made and are marked in red and highlighted in yellow.

Comment 4

- All abbreviations must be defined at their first occurrence.
- **Response:**
  Checked.

Comment 5

- The provided IRCT code is not correct.
- **Response:**
  Modified to **IRCT20240407061439N1**.

Comment 6

- In lines 84 and 85, the authors noticed the study as a single blind RCT; however, they emphasized that neither the patients nor the outcome assessors were aware of the groups..
- **Response:**
  It was changed to double-blind.

Comment

- The sample size calculation method must be provided.
- **Response:**
  The following Cochran formula was used to determine the minimum sample size.

$$n=\frac{(z-a/2)^2\times P\times(1-P)}{d^2}=\frac{(1.96)^2\times 0.1\times(0.9)}{(0.10)^2}=30$$

In this formula, considering the frequency of existing samples, considering P=0.1, and considering a confidence level of 95% and a maximum error of 0.10, the sample size according to this formula will be 25 samples.

Comment 8

- Demographic data may at least include patients' gender and age. Weight is wrongly written as wight.
- **Response:**
  The aforementioned indicators are clearly stated in the text at the beginning of the results section. The spelling of the word "weight" was corrected.

Comment

- BMI SD in the opioid group is very wide (±7.6). This raises questions about data distribution. The authors should clarify whether BMI was normally distributed..
- **Response:**
  It was a typo that has been corrected..

Comment

- Units must be added to the tables. Table 3 lacks abbreviations. A and B must be defined, and the star next to the p-values must be explained.
- **Response:**
  The corrections made were marked in red and highlighted in yellow.

3 Revision 2

5 comments · 27 Dec 2025 – 28 Dec 2025

Referee 3 Reviewer

MINOR REVISION 27 Dec 2025

Dear Associate Editor
Thank you for your kindness.

Dear author
Thank you for your attention.
In the sample size section of the manuscript, you should describe the measurement method in detail, including the calculation formula and a reference to the study whose data and results you used to calculate the sample size.
Alternatively, calculate the sample size based on the pilot study.
You should explain the calculation method and process in detail in the manuscript, not just in your response to the reviewer.
So please ask a statistician to revise this part.

Referee 1 Reviewer

MAJOR REVISION 27 Dec 2025

Dear Associate Editor
Thank you for considering me as a reviewer.
As I mentioned before, I suggest changing the manuscript to a brief report.
The manuscript word count should be reduced, and the number of tables should be reduced to a maximum of one table.
Then it could be appropriate for publication.

Referee 2 Reviewer

MINOR REVISION 28 Dec 2025

Blinding Terminology and Trial Design

Although the manuscript repeatedly refers to the study as “double-blind,” the attending anesthesiologist was not blinded due to the nature of drug administration. While patients and postoperative outcome assessors were blinded, this design does not meet the strict definition of a double-blind trial. The study would be more accurately described as a randomized, assessor-blinded clinical trial. All references to “double-blind” should be revised accordingly in the Abstract, Methods, and Results sections to avoid methodological overstatement.

Sample Size Calculation and Rationale

The sample size calculation based on the Cochran formula is insufficiently explained. It is unclear which outcome variable was used for this calculation and why, despite a stated minimum of approximately 25 patients, a total of 60 patients were ultimately enrolled. The authors should clarify the primary outcome on which the sample size estimation was based and explain the rationale for increasing the sample size (e.g., improving statistical power or accounting for potential attrition).

Definition of Primary and Secondary Outcomes

identification of outcome hierarchy is essential for transparency and appropriate interpretation of statistical findings and should be added to the Methods section.

Statistical Analysis and Repeated Measurements

Multiple postoperative time-point comparisons are presented using repeated pairwise tests without correction for multiple comparisons or the use of longitudinal statistical models. Several p-values are marginally significant. At minimum, this limitation should be clearly acknowledged in the Discussion. Consideration of repeated-measures or mixed-effects analyses would improve the robustness of the conclusions.

Interpretation of Inflammatory and Renal Markers

Postoperative CRP, BUN, and creatinine levels were significantly higher in the OFA group, a finding that contrasts with the expected stress-attenuating profile of opioid-free anesthesia. Although briefly mentioned, this observation requires more balanced discussion, including possible explanations such as perioperative hemodynamic effects, fluid management, or transient physiological responses. The clinical versus statistical relevance of these differences should also be addressed more explicitly.

Associate Editor

MINOR REVISION 28 Dec 2025

Dear EIC,
This revised manuscript has addressed many of the reviewers' previous comments and is now a well-structured, methodologically sound, and clearly written research article. Here is a review focusing on the quality of the revision, remaining minor issues, and overall recommendations:

Despite the excellent revision, a few minor inconsistencies and opportunities for clarification remain:
- The response states that the formula yielded a sample of 25, but the study used 30 per group (n=60 total). This is fine, but the text should briefly explain this.
- The table heading uses "Opium group". Consider changing this to "Opioid group" for absolute consistency with the text.

This is a strong revision. The authors have been responsive and thorough in addressing the reviewers' concerns. Once these minor points are addressed, the manuscript will be ready for acceptance.

Editor-in-Chief

MINOR REVISION 28 Dec 2025

Dear Authors
Thank you for your submission.
I am happy to tell you that the majority of the critical issues have been addressed. However, some still remain. Please see the critiques and revise accordingly.
Sincerely Yours,

4

Revision 3

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

Comment 1

- The response states the formula yielded a sample of 25, but the study used 30 per group (n=60 total). This is fine, but the text should briefly explain this.
- **Response:**
  The following Cochran formula was used to determine the minimum sample size.

$$n=\frac{(z-a/2)^2\times P\times(1-P)}{d^2}=\frac{(1.96)^2\times 0.1\times(0.9)}{(0.10)^2}=30$$

In this formula, considering the frequency of existing samples, considering P=0.1, and considering a confidence level of 95% and a maximum error of 0.10, the sample size according to this formula will be 30 samples.

Comment 2

- Tables heading used "Opium group". Consider changing this to "Opioid group" for absolute consistency with the text.
- **Response:**
  The corrections made were marked in red and highlighted in Green.

4 Revision 3

2 comments · 28 Jan 2026 – 28 Jan 2026

Associate Editor

MINOR REVISION 28 Jan 2026

Dear EIC,

While some issues were addressed by the authors, others remain unresolved. The authors should address all the issues before further processing, especially those regarding the results and tables.

Editor-in-Chief

MINOR REVISION 28 Jan 2026

Dear authors
Thank you for the revisions. Only a few minor comments remain. Please consider them, revise, and resubmit.
Thank you for your contribution.

5

Revision 4

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.

The authors did not provide a point-by-point response to the reviewers' comments in this round.

5 Revision 4

2 comments · 4 Feb 2026 – 4 Feb 2026

Associate Editor

ACCEPT 4 Feb 2026

Dear EIC,
Based on a careful review of the revised manuscript, I recommend acceptance for publication in the JCMA, pending minor editorial revisions.
The methodological quality is now sound, and the results, including the unexpected biomarker elevations, are clinically relevant and warrant dissemination to the scientific community to guide future research.

Recommendations for Minor Revisions Prior to Final Publication:
The abstract mentions "opium group," while the main text uses "opioid group." Moreover, the revised abstract differs from the one that was uploaded during submission.

The manuscript's strengths significantly outweigh its minor, correctable weaknesses, which can be addressed during the proofing process. Therefore, I recommend acceptance.

Editor-in-Chief

ACCEPT 4 Feb 2026

Congratulations!
The manuscript has been very well revised and is accepted for publication in the Journal.