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- Education of both authors and new students
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Peer Review

Journal of Cellular & Molecular Anesthesia
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Peer Review Report for "A Case of Malignant Hyperthermia Induced by Volatile Anesthetics: Clinical Management and Treatment"

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Review Timeline:

Submit Date:	11 Jun 2025
Revised Date:	27 Aug 2025
Accepted Date:	27 Aug 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE : Reviewer — 9 Jul 2025

Dear AE,
This is a good clinical case report; however, the manuscript should be fully revised fundamentally, with a "cellular and molecular" approach. A schematic cellular and molecular figure would also be very helpful.
Kind Regards

REFEREE : Reviewer — 15 Jul 2025

Dear AE,
• The case report's dosing is significantly lower than the discussion's claim and

current guidelines (initial dose: 2.5 mg/kg, repeated until symptoms resolve).
• The case report states "remifentanil (0.1 mcg/kg/hour)". The standard unit for remifentanil is mcg/kg/min. A rate of 0.1 mcg/kg/hour would be subtherapeutic.
• The discussion states thyroid storm was ruled out due to lack of history, but thyroid storm can occur without prior history. This point could be strengthened with additional clinical evidence (e.g., thyroid function tests).
Kind Regards

REFEREE : Associate Editor

22 Jul 2025

Dear EIC,
The case report presents an interesting clinical scenario with potential educational value. However, it requires substantial revisions to meet publication standards. Below are detailed critiques and recommendations.
Strengths:
1. Clinical Relevance: The case addresses an uncommon or diagnostically challenging presentation, which could benefit other clinicians.
2. Educational Potential: Highlights key learning points regarding diagnosis, management, or pathophysiology.
3. Multidisciplinary Approach: If applicable, demonstrates collaboration across specialties (e.g., surgery, radiology, pathology).

Major Concerns:

Provide a clear chronological narrative (e.g., symptom onset, diagnostic steps, interventions, outcomes).

Management: Detail treatments (drugs, doses, procedures) and rationale for choices.

Compare the case to published reports. Address:
- How does this case align with or deviate from typical presentations?
- What novel insights does it offer?
- Limitations: Acknowledge gaps (e.g., incomplete follow-up, atypical presentation).

Final Recommendation:
Please ask the authors to revise and resubmit after addressing the above concerns.
Kind Regards
AE

Ali Dabbagh : EIC

22 Jul 2025

Dear Authors
Thank you for your contribution.

Based on the comments by the reviewers, the manuscript needs major revisions. Please revise accordingly and resubmit. Thank you for the great cooperation.

Kind Regards

EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor in chief

We sincerely thank the reviewers and the associate editor for their thorough and constructive comments. We have carefully revised the manuscript according to each suggestion. Below is a point-by-point response.

Reviewers' Comments:

Reviewer 2:

This is a good clinical case report; however, the manuscript should be fully revised fundamentally, with a "cellular and molecular" approach. A schematic cellular and molecular figure would also be very helpful.

Author response: We have revised the manuscript to incorporate a detailed cellular and molecular explanation of MH in the **Background** and **Discussion** sections. Specifically, we described the role of RYR1 and CACNA1S gene mutations, calcium dysregulation, and the mechanism of action of dantrolene. Additionally, we have included a **schematic figure (Figure 1)** illustrating the molecular pathophysiology of MH (lines 29-36 ,line 61 :figure 1, and 121-124).

Reviewer 3:

* The case report’s dosing is significantly lower than the discussion’s claim and current guidelines (initial dose: 2.5 mg/kg, repeated until symptoms resolve).

Author response: We corrected the reported dantrolene dosing in the Case Report section to reflect the recommended initial dose of 2.5 mg/kg IV, repeated as needed up to a maximum of 10 mg/kg, as per current guidelines (Riazi et al., Can J Anesth 2018). (lines 85-88).

* The case report states "remifentanil (0.1 mcg/kg/hour)". The standard unit for remifentanil is mcg/kg/min. A rate of 0.1 mcg/kg/hour would be subtherapeutic.

Author response: Thank you for noting this. The unit has been corrected to **mcg/kg/min** in the revised manuscript. (line 76).

* The discussion states thyroid storm was ruled out due to lack of history, but thyroid storm can occur without prior history. This point could be strengthened with additional clinical evidence (e.g., thyroid function tests).

Author response: We have addressed this point in the Discussion by adding that thyroid function tests (TSH, T3, T4) were performed and were within normal range, further supporting the exclusion of thyroid storm in this patient. (lines 112-114).

Associate Editor's Comments:

Associate Editor:

The case report presents an interesting clinical scenario with potential educational value. However, it requires substantial revisions to meet publication standards. Below are detailed critiques and recommendations.

Strengths:

1. Clinical Relevance: The case addresses an uncommon or diagnostically challenging presentation, which could benefit other clinicians.

2. Educational Potential: Highlights key learning points regarding diagnosis, management, or pathophysiology.

3. Multidisciplinary Approach: If applicable, demonstrates collaboration across specialties (e.g., surgery, radiology, pathology).

Author response: Thank you, the manuscript revised accordingly. (lines 165-172).

Major Concerns:

Provide a clear chronological narrative (e.g., symptom onset, diagnostic steps, interventions, outcomes (.

Author response :Thank you, the manuscript revised accordingly. (lines 68-102).

Management: Detail treatments (drugs, doses, procedures) and rationale for choices.

Author response: Thank you, the manuscript revised accordingly. (lines 84-95).

Compare the case to published reports. Address:

- How does this case align with or deviate from typical presentations?

Author response :Thank you, the manuscript revised accordingly (lines 173-175).

- What novel insights does it offer?

Author response :Thank you, the manuscript revised accordingly (lines 176-186).

- Limitations: Acknowledge gaps (e.g., incomplete follow-up, atypical presentation(.

Author response: Thank you, the manuscript revised accordingly. (lines 187-195).

OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer — 11 Aug 2025

Dear AE,

• Genetic testing (e.g., RYR1/CACNA1S mutation analysis) or contracture testing was not performed to confirm MH susceptibility.

• Axillary temperature (42.5°C) was used instead of core temperature (e.g., esophageal/rectal). Axillary measurements are less reliable and may underestimate true hyperthermia.

• CPK was 744 U/L (line 89), which is moderately elevated but not markedly high for MH-associated rhabdomyolysis. The timing of CPK measurement (e.g., peak vs. initial) is unspecified, which limits clinical interpretation.

• Serum myoglobin and urine myoglobin were not reported, critical for assessing rhabdomyolysis severity.

• No long-term follow-up (e.g., renal function, recurrence risk) due to patient loss to follow-up.

Kind Regards

REFEREE : Reviewer — 11 Aug 2025

Dear AE,

The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.

Thanks

REFEREE : Reviewer — 15 Aug 2025

Dear AE,

There are some comments which should be addressed by the author:

Please revise the keywords and don’t use one medical term in two different writing patterns.

Case Report:

- Please mention to the past surgical history of the patient.
- Case presentation part, needs more details of the patients.

Management and Treatment:

- Please mention the time of ABG
- Given the importance of timing and immediate treatment in this case, please mention to the timing of the any intervention also the time of each lab test.
- It would be of higher quality if all of these items convince as a timeline diagram.

- CASE REPORT GUIDELINES: Timeline – Historical and current information from this episode of care organized as a timeline (figure or table)
- Did you check the TFT before the surgery in pre-op evaluation? If yes please mention to Lab TFT details.
- Did you check TFT during this event or after treatment of MH?

References:

- Please use more recent references.

Kind Regards

REFEREE : Associate Editor

20 Aug 2025

Dear EIC,

This is a well-written and clinically significant case report that describes a classic presentation of malignant hyperthermia with a successful outcome due to prompt recognition and management. The authors have been highly responsive to the reviewers' and editor's comments, substantially improving the manuscript. The revisions have successfully incorporated a cellular and molecular perspective, corrected dosing errors, strengthened the differential diagnosis, and provided a more comprehensive discussion. The manuscript is now much stronger and is suitable for publication pending minor revisions.

Strengths:

1. Clinical Relevance and Educational Value: The case is a quintessential example of an MH crisis and serves as an excellent teaching tool. It underscores the "can't miss" nature of this diagnosis and the life-saving importance of protocol-driven care.
2. Successful Revisions: The authors have effectively addressed all major concerns from the previous review.

Minor Concerns and Suggestions for Improvement:

1. Figure 1 Citation and Legend:

The figure is excellent and informative. However, its legend ("Schematic representation of cellular and molecular changes in malignant hyperthermia") is too brief. Please expand the legend to explicitly connect the figure to the case. And ensure the figure is cited at the first relevant point in the text (likely in the Background around line 37) and again in the Discussion where pathophysiology is mentioned.

2. The management details are good, but the timeline could be slightly more precise. How quickly after the rise in $ETCO_2$ was dantrolene administered? This emphasizes the "swift action" highlighted in the conclusion.

Accept with Minor Revisions.

The manuscript has been greatly improved and meets the standards for a valuable clinical case report. The minor suggestions above are intended to further polish an already strong paper.

Kind Regards
AE

Ali Dabbagh : EIC

21 Aug 2025

Dear Authors
I really appreciate your great contribution in the JCMA.
Based on the reviewers' comments, I kindly ask you to consider the comments. The reviewers' have asked ONLY minor comments.
Thank you

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear editor in chief

Thank you for the valuable comments. All comments studied point by point and applied in the manuscript.

Reviewers' Comments:

Reviewer 0:

Case Report:

- Please mention to the past surgical history of the patient.

Author's response: Thank you for the valuable comments. Its revised accordingly.

- Case presentation part, needs more details of the patients.

Author's response: Thank you for the valuable comments. Its revised accordingly

Management and Treatment:

- Please mention the time of ABG

Author's response: Thank you for the valuable comments. Its revised accordingly . this sentence added in manuscript " The initial arterial blood gas (ABG) and creatine phosphokinase (CPK) tests were drawn immediately following the onset of hypermetabolic signs (e.g., hypercapnia, tachycardia)."

- Given the importance of timing and immediate treatment in this case, please mention to the timing of the any intervention also the time of each lab test.

- It would be of higher quality if all of these items convince as a timeline diagram.

- CASE REPORT GUIDELINES: Timeline – Historical and current information from this episode of care organized as a timeline (figure or table)

Author's response: We thank the reviewer for this excellent suggestion. We have now added a detailed timeline of events as **Table 1** in the revised manuscript, which includes the timing of ABG, CPK measurement, and all major interventions."

- Did you check the TFT before the surgery in pre-op evaluation? If yes please mention to Lab TFT details.
- Did you check TFT during this event or after treatment of MH?

Author's response We thank the reviewer for this important question. Preoperative thyroid function tests (TFTs) were not performed as the patient was a healthy, asymptomatic young woman with no personal or family history of thyroid disease and no clinical signs of thyroid dysfunction upon physical examination. Therefore, it was not indicated per our standard preoperative protocol. However, **TFTs were checked after the MH event to rule out thyroid storm as a differential diagnosis, and the results were within normal limits.** This has been explicitly stated in the revised manuscript."

References:

- Please use more recent references.

Author's response: Thank you for the valuable comments. Some reffrencess changed with more recent references.

Reviewer 1:

• Genetic testing (e.g., RYR1/CACNA1S mutation analysis) or contracture testing was not performed to confirm MH susceptibility.

Author's response: Thank you for the valuable comments .We acknowledge that genetic testing is the gold standard for confirming susceptibility. While it was not available for this case, the clinical presentation was classic and met the established criteria for an MH crisis."

• Axillary temperature (42.5°C) was used instead of core temperature (e.g., esophageal/rectal). Axillary measurements are less reliable and may underestimate true hyperthermia.

Author's response: Thank you for the valuable comments. We agree that core temperature monitoring is superior. Unfortunately, it was not readily available at the time of the acute crisis, and axillary measurement was used as the best available alternative. We have acknowledged this as a limitation in the discussion.

• CPK was 744 U/L (line 89), which is moderately elevated but not markedly high for MH-associated rhabdomyolysis. The timing of CPK measurement (e.g., peak vs. initial) is unspecified, which limits clinical interpretation.

• Serum myoglobin and urine myoglobin were not reported, critical for assessing rhabdomyolysis severity.

Author's response: Thank you for the valuable comments .We have clarified that the reported CPK level (744 U/L) was the initial value drawn during the acute phase. We also acknowledge that serum myoglobin was not measured due to laboratory constraints and have included this as a limitation.

• No long-term follow-up (e.g., renal function, recurrence risk) due to patient loss to follow-up.
Author's response: Thank you for the valuable comments .We agree that follow-up is ideal. However, the patient was lost to follow-up after discharge. Importantly, malignant hyperthermia itself does not typically require long-term follow-up unless organ damage occurred during the acute crisis, which it did not in this case, as all parameters normalized before discharge

Associate Editor's Comments:

Minor Concerns and Suggestions for Improvement:

1. Figure 1 Citation and Legend:
The figure is excellent and informative. However, its legend ("Schematic representation of cellular and molecular changes in malignant hyperthermia") is too brief. Please expand the legend to explicitly connect the figure to the case. And ensure the figure is cited at the first relevant point in the text (likely in the Background around line 37) and again in the Discussion where pathophysiology is mentioned.
2. The management details are good, but the timeline could be slightly more precise. How quickly after the rise in $ETCO_2$ was dantrolene administered? This emphasizes the "swift action" highlighted in the conclusion.

- We thank the Associate Editor for the positive and constructive feedback. We have expanded the caption for Figure 1 as suggested and have ensured it is cited in both the Background and Discussion sections. We have also added a precise timeline of interventions (**Table 1**), which includes the approximate time of dantrolene administration (~80 minutes post-induction)."By implementing these specific changes, you will have thoroughly and professionally addressed all comments, significantly strengthening your manuscript for final acceptance

OPEN PEER REVIEW

Revision (2)

Ali Dabbagh : EIC

27 Aug 2025

Congratulations!

The manuscript is accepted for publication.