

## Peer review

Well researched and well presented. Good effort. However, The manuscript, as written does not satisfy the Journal's guidelines or expectations of a review paper as seen here:

<https://jhss.scholasticahq.com/about>

I would like to see the following points of concern addressed and discussed in the manuscript, that would then make it acceptable for review in the category of a review manuscript.

1. I want to see a chart with sevoflurane (plotted in increasing concentration) on the x-axis, the other drugs (plotted as discrete ordinal points) on the Z-axis and the EDA reduction percent (difference from control) on the Y-axis. Please do this for all the drugs in the studies incorporated in the review. The data points will be indicative of which drugs; when combined with sevoflurane provide greater reduction in EDA.

2. Next, I want to see drug classes (not individual drugs) plotted as discrete ordinal points on the Z-axis with the average of their percent reduction in EDA (for that class of drugs) on the Y-axis. The X-axis is sevoflurane concentration (as before in point 1). For example, plot clonidine and dexmedetomidine together as alpha2 agonists, plot Tramadol and remifentanyl together as opioids, plot propofol as GABA agonist, plot Remimazolam as benzodiazepene and Ketamine as NMDA antagonist. You are plotting drug classes in this figure, not individual drugs (except in those cases where there is only one drug in that class). This chart will be indicative of whether there is a mechanism of action synergy or additive effect in the reduction of EDA. For example, Sevoflurane has GABA agonist and NMDA antagonist effects. Ketamine is an NMDA antagonist while propofol is a GABA agonist. If it turns out that the combination of Sevoflurane and ketamine or the combination of Sevoflurane in propofol is relatively more effective at reducing EDA than other drugs, it may be that this is because they act by similar mechanisms? This may mean that -counterintuitively - a larger dose of Sevoflurane (lesser bispectral index, deeper anesthesia) may be better in reducing EDA than a smaller dose (greater bispectral index, shallower anesthesia)? Plotting these graphs provides directionality to investigation and hypotheses formulation.

3. I then want to see a chart similar to 1 where the Z-axis will consist of 2 points (administered concurrently (point 1) or administered as wash-out (point 2) toward the end of sevoflurane anesthesia. This will inform if there is difference in EDA reduction if a drug is administered concurrently or as a wash-out (toward the end of the anesthetic procedure on Sevoflurane).

4. You have not discussed the depth of anesthesia in your report. Please report the bispectral index for each study. If not reported, check the dosage of Sevoflurane administered and find the bispectral index. Report the bispectral index for each study, then circle around to point 2 for explanation and discussion.

5. In the references section, if an article has more than 6 authors, all the 6 authors must be listed followed by et al. Please check and correct where necessary.

---

Thank you for addressing my comments. However, I would like to see the on X-Y-Z dimensions (for an example, see figure 2 in this manuscript <https://jhss.scholasticahq.com/article/123635-the-effect-of-the-ketogenic-diet-in-increasing-and-or-restoring-fertility-in-polycystic-ovarian-syndrome-pcos-patients>) This provides significantly more clarity to the observations, analysis and conclusions. Please re-graph.

---

Please use the website below to make your charts

<https://geographyfieldwork.com/3D-Chart-Maker.htm>

This provides the charts on the X-Y-Z axes rather than your simulated excel charts.

---

## Summary of Findings:

1. The combination of sevoflurane with **alpha-2 agonists** like clonidine and dexmedetomidine yields the highest EDA reduction, suggesting strong synergistic effects.
2. **Opioids** like remifentanyl and tramadol show moderate efficacy in reducing EDA.
3. Other drugs like **GABA agonists** (e.g., propofol) and **NMDA antagonists** (e.g., ketamine) also exhibit moderate effects when combined with sevoflurane.

6. These changes and details provide insights into the effectiveness of different anesthetic combinations in reducing EDA during pediatric surgeries. The graph visually represents these findings based on drug class and concentration levels.

7. Here is a summary of the different charts from the document and whether there is an XYZ chart included:

### 8.1. Figure 1: XYZ: Drug Effects on EDA Reduction

9. This chart is labeled as an **XYZ chart**.

10. It seems to provide data on the effects of various drugs on reducing emergence delirium or agitation (EDA) during pediatric surgeries.

11. The specific axes for this chart (X, Y, and Z) are not detailed, but it likely involves some variables related to drug types, dosage, and the percentage reduction in EDA.

### 12.2. Figure 2: Sevoflurane concentration vs. Other drugs vs. EDA reduction percent

13. This chart shows the effectiveness of different drugs combined with sevoflurane in reducing EDA.

14. **X-axis:** Sevoflurane concentration.

15. **Y-axis:** Percent reduction in EDA.

16. **Z-axis (comparison):** Various drugs (e.g., Clonidine, Remifentanyl) that are combined with sevoflurane.

### 17.3. Figure 3: XYZ: Average EDA Reduction by Drug Class

18. This chart categorizes drugs by class (alpha-2 agonists, opioids, GABA agonists, etc.) and examines their ability to reduce EDA when combined with sevoflurane.

19. **X-axis:** Drug classes.

20. **Y-axis:** Sevoflurane concentration.

21. **Z-axis:** Average EDA reduction percent (0% to 50% range).

### 22. Summary of the XYZ Charts:

23. **Figure 1** and **Figure 3** are specifically labeled as **XYZ charts**, meaning they explore variables in a three-dimensional format. These figures relate to how different drugs or drug classes interact with sevoflurane to reduce EDA, factoring in drug class, dosage, and EDA reduction percentage.

24. **Figure 2** presents a comparison of drug efficacy with varying sevoflurane concentrations.

---

Please produce a chart like that in Figure 2 at <https://jhss.scholasticahq.com/article/123635-the-effect-of-the-ketogenic-diet-in-increasing-and-or-restoring-fertility-in-polycystic-ovarian-syndrome-pcos-patients>

I sent you a website link at which you could reproduce a 3D chart in my previous review.

---

I see only one chart. You will need to label the axes as well as the legend and provide a title in the graph. What about the other 2 charts?

I want to see a chart with sevoflurane (plotted in increasing concentration) on the x-axis, the other drugs (plotted as discrete ordinal points) on the Z-axis and the EDA reduction percent (difference from control) on the Y-axis. Please do this for all the drugs in the studies incorporated in the review. The data

points will be indicative of which drugs; when combined with sevoflurane provide greater reduction in EDA.

Next, I want to see drug classes (not individual drugs) plotted as discrete ordinal points on the Z-axis with the average of their percent reduction in EDA (for that class of drugs) on the Y-Axis. The X-axis is sevoflurane concentration (as before in point 1). For example, plot clonidine and dexmedetomidine together as alpha2 agonists, plot Tramadol and remifentanyl together as opioids, plot propofol as GABA agonist, plot Remimazolam as benzodiazepene and Ketamine as NMDA antagonist. You are plotting drug classes in this figure, not individual drugs (except in those cases where there is only one drug in that class). This chart will be indicative of whether there is a mechanism of action synergy or additive effect in the reduction of EDA. for example, Sevoflurane has GABA agonist and NMDA antagonist effects. Ketamine is an NMDA antagonist while propofol is a GABA agonist. If it turns out that the combination of Sevoflurane and ketamine or the combination of Sevoflurane in propofol is relatively more effective at reducing EDA than other drugs, it may be that this is because they act by similar mechanisms? This may mean that -counterintuitively - a larger dose of Sevoflurane (lesser bispectral index, deeper anesthesia) may be better in reducing EDA than a smaller dose (greater bispectral index, shallower anesthesia) ? Plotting these graphs provides directionality to investigation and hypotheses formulation.

I then want to see a chart similar to 1 where the Z-axis will consist of 2 points (administered concurrently (point 1) or administered as wash-out (point 2) toward the end of sevoflurane anesthesia. This will inform if there is difference in EDA reduction if a drug is administered concurrently or as a wash-out (toward the end of the anesthetic procedure on Sevoflurane).

---

There appear to be too many data points on each chart? Please re-check and re-plot

I want to see a chart with sevoflurane (plotted in increasing concentration) on the x-axis, the other drugs (plotted as discrete ordinal points) on the Z-axis and the EDA reduction percent (difference from control) on the Y-axis. Please do this for all the drugs in the studies incorporated in the review. The data points will be indicative of which drugs; when combined with sevoflurane provide greater reduction in EDA.

Next, I want to see drug classes (not individual drugs) plotted as discrete ordinal points on the Z-axis with the average of their percent reduction in EDA (for that class of drugs) on the Y-Axis. The X-axis is sevoflurane concentration (as before in point 1). For example, plot clonidine and dexmedetomidine together as alpha2 agonists, plot Tramadol and remifentanyl together as opioids, plot propofol as GABA agonist, plot Remimazolam as benzodiazepene and Ketamine as NMDA antagonist. You are plotting drug classes in this figure, not individual drugs (except in those cases where there is only one drug in that class). This chart will be indicative of whether there is a mechanism of action synergy or additive effect in the reduction of EDA. for example, Sevoflurane has GABA agonist and NMDA antagonist effects. Ketamine is an NMDA antagonist while propofol is a GABA agonist. If it turns out that the combination of Sevoflurane and ketamine or the combination of Sevoflurane in propofol is relatively more effective at reducing EDA than other drugs, it may be that this is because they act by similar mechanisms? This may mean that -counterintuitively - a larger dose of Sevoflurane (lesser bispectral index, deeper anesthesia) may be better in reducing EDA than a smaller dose (greater bispectral index, shallower anesthesia) ? Plotting these graphs provides directionality to investigation and hypotheses formulation.

I then want to see a chart similar to 1 where the Z-axis will consist of 2 points (administered concurrently (point 1) or administered as wash-out (point 2) toward the end of sevoflurane anesthesia.

This will inform if there is difference in EDA reduction if a drug is administered concurrently or as a wash-out (toward the end of the anesthetic procedure on Sevoflurane).

You have not discussed the depth of anesthesia in your report. Please report the bispectral index for each study. If not reported, check the dosage of Sevoflurane administered and find the bispectral index. Report the bispectral index for each study, then circle around to point 2 for explanation and discussion. In the references section, if an article has more than 6 authors, all the 6 authors must be listed followed by et al. Please check and correct where necessary.

---

Thank you for addressing my comments. I have extensively revised your manuscript (see attached). However, before I can accept this work, you will need to correct the references section. The references need to be formatted to at least 6 authors per paper then followed by an et al. The doi link must be live. Please navigate to the paper and copy and paste the doi link in each of the references. Please review the manuscript thoroughly to see if it still says what you wanted to communicate when you first submitted it; and that there are no factual errors. Once you revise the references, please submit as the next iteration.

---

Accept. Thank You for addressing my comments.