Author’s response to reviews

Title: Anaesthesiology and Cognitive Impairment: A Narrative Review of Current Clinical Literature

Authors:

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Author’s response to reviews:

Dear Dr. Anna Melidoni,

We wish to thank you for the opportunity to submit a revised manuscript and our reviewers for their helpful suggestions.

The suggested revisions have been addressed as highlighted in the enclosed point-by-point response to each of the reviewer’s specific comments.

Our manuscript has greatly benefited from the changes requested by the reviewers. We hope that the editor and reviewers will find that we have satisfied all criticisms.

Reviewer #1: The authors have provided an up-to-date, salient, and authoritative review of perioperative cognitive dysfunction with a special focus on putative anesthetic considerations. Overall I found this review to be very readable and informative, and I do not have major changes to propose. However, I have a number of suggestions for improvement:

1) The first three paragraphs of the section on Post-Operative cognitive dysfunction seem to be to belong in the introduction, as they do not deal directly with a discussion of anesthetic effects. Alternately the section on "Perioperative Cognitive Dysfunction" should be split into two distinct headings, one focused on simply describing the phenomenon of POCD and a separate section describing what is known and not known about the effects of anesthetics in the population of patients who do not have diagnosed cognitive impairment.

Thank you for this suggestion. We have split this section into two distinct headings. The second heading is on page 6, line 87 “The effects of anesthetic agents on POCD”. We agree that this improves the flow of the manuscript.
2) It should be made clear whether the authors were part of the fifth international perioperative neurotoxicity working group, and also it would be instructive for the authors to comment on the recommendations rather than simply relaying them.

We were not a part of the working group. To clarify this, we have reworded the sentence on line 172 which was previously worded as “Briefly, the authors recommended the following”. We have changed this to now read:

“We direct readers to the article by the working group for a more detailed description of their recommendations. Their recommendations are briefly summarized below”

We hope that this provides some clarity that we are summarizing the recommendations from the working group. Furthermore, we have added a brief paragraph on line 186 which adds our comment on these recommendations as suggested by the reviewer.

“In our opinion, the above recommendations reflect the evidence, as well as the continued uncertainty in the field. We do recognize that baseline cognitive assessment is often challenging to implement with limited time for preoperative assessment. Furthermore, without established post-operative follow-up, the utility of baseline cognitive assessment could be questioned. This highlights the need to establish assessments with strong reliability which are relatively easy to administer, and which can be applied postoperatively to identify patients with impaired cognition in the perioperative period.”

3) In the section on molecular mechanisms, it is a little unclear whether it is the intent of the authors only to discuss Alzheimer's related effects of anesthetics or whether other mechanisms have been revealed as well (the inflammation section at the end suggests mechanisms that would function in any context). It would be helpful if the authors wrote a short paragraph to start this section that served to introduce the topic and to delineate what is discussed here.

Thank you for this feedback. In response to this comment as well as the comment below, we have extensively modified this section of the manuscript to provide further clarity and also highlight relevant preclinical data. Due to the number of modifications, we have not posted the entirety of the section in our response, but instead direct the reviewer to this section of the manuscript.

4) I think it is difficult to include a section on molecular mechanisms without any reference whatsoever to the animal data, of which there is a fair amount. I suggest that the authors reference the relevant animal literature that either supports or does not support their findings. It would be very useful in interpreting the data and should not take up that much more space.

Please see our comment under point 3.
Reviewer #2:

Abstract: line 30. Define/spell out AD.

We have made the above correction.

Page 6 lines 77-80: The ISPOCD1 study did not show correlation with variables of anesthetic management (hypotension and hypoxemia), but rather with the patient parameter of age and with surgical parameters: length of anesthesia (and by correlation length of surgery), repeated surgical procedures, infections and respiratory complications. This suggests that inflammatory response to surgery and infection is a larger player than anesthesia, per se.

Thank you for the important point. We have added the following sentence to expand upon the outcomes of the study.

“Several risk factors for POCD were identified at the one week time point including age, level of education, duration of surgery/anesthesia exposure, a second operation, and post-operative infection or respiratory complications. At the 3 month time point, age was the only significant risk factor for POCD. Hypoxemia and hypotension were not identified as risk factors at either time point.”

Page 9, line 127: "studied", not "studies"

We appreciate your attention to detail. We have corrected this error.

Page 12, lines 180-182: Your statement: "As summarized above, there is a large body of evidence which supports the existence of delayed neurocognitive recovery and post-operative neurocognitive disorder." The statement "It is less clear whether exposure to anesthesia increases the risk of developing dementia." is likely also true, although I would prefer to see it phrased "It is unclear . . .". The juxtaposition of these two statements in the same paragraph implies that anesthesia increases the risk of delayed neurocognitive recovery and post-operative neurocognitive disorder, which the preceding pages did NOT demonstrate. The text demonstrates postoperative problems but there was nothing in the paragraphs to conclude that general anesthesia or inhalation anesthesia was a definitive cause of delayed neurocognitive recovery and post-operative neurocognitive disorders. Indeed, the preceding text either suggested no effect or the evidence was sufficiently mixed as to make drawing the conclusion of causation extremely problematic. This paragraph needs to be changed.

Our intention with this paragraph was to highlight that the risk of neurocognitive disorder does not imply that exposure to surgery increases the risk for Alzheimer’s disease or other forms of dementia. We recognize that our wording could be more clear. We have altered this as described below, and hope that this clarifies our point and addresses the very valid concern brought up by the reviewer.

“Of note, the pathological mechanisms and clinical presentation of post-operative neurocognitive disorder may be distinct from the development of cognitive dysfunction in Alzheimer’s disease
and other forms of dementia. It is currently unclear whether surgery and/or anesthesia increases the risk of subsequent diagnosis of dementia.”

Page 13, lines 190-91: Unless the controls were patients who underwent surgery without general anesthesia, this Korean study suffers from the same major confounder as most studies in this field. It is impossible to separate out the effects of surgery including increased neuroinflammation from a direct effect of the anesthesia. Although the differing hazard ratios among the three inhaled anesthetics is interesting, it would be more understandable if there were an obvious mechanism for differences between the agents.

This is an excellent point. We expanded this section to address the above considerations.

“There were 44,956 individuals in the GA group, and 174,469 in the control group. The authors used a time-varying Cox hazard model to minimize time-dependent bias, and utilized propensity score matching to reduce potential confounding biases between groups. Exposure to GA was determined by a general Anesthesia operation code in NHIS-NSC database. Individuals who did not have a general anesthesia operation code were assigned to the control group. Similar to prior studies, this study design would not be able to separate the effects of anesthesia exposure from the effects of surgical stress and other potential confounders (for example, perioperative hypothermia or administration of narcotics and other medications)”… “Although the difference hazards ratio of the inhalational agents is intriguing, the observational study design may include unaccounted for confounding variables which influenced choice of anesthetic agent, and independently increase the risk of dementia. A randomized controlled trial would be required to compare the risk profile of various anesthetic agents on cognition and risk for incident dementia. If a difference between volatile agents can be reproduced with a well designed RCT, further research would be required to explore the biological mechanisms differentially altered by various volatile agents.”

Page 17, lines 267-70: the authors speak of a study comparing inhalation anesthesia to TIVA. The subsequent discussion of the study does not give any results of differences with anesthesia technique. This would lead the reader to conclude that technique is not important, but this should be stated in the text (if true).

Thank you for pointing out this omission. We have added in the below sentences into this section for further clarification:

“There was no interaction between the type of anesthesia employed and the biomarker levels in CSF; however, the authors appropriately point out that all patients underwent surgical manipulation of a dura and blood brain barrier, and this confound may outweigh any potential effects from the choice of anesthesia technique. Of note, this study did not examine the effects of isoflurane or propofol on cognition post-operatively.”

Conclusion, page 19, line 290. This should more properly read "This review summarizes previous findings relevant to the potential relationship between surgery, anaesthesia exposure and POCD." The literature cited does not definitively demonstrate an independent effect of anesthesia.
Thank you for this comment.