

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of the cerebroprotective effect of inhalation anaesthesia and total intravenous anaesthesia in patients undergoing cardiac surgery with cardiopulmonary bypass: A systematic review and meta-analysis
AUTHORS	Chen, Feng; Duan, You; Wu, Xi; Zuo, Yi; Li, Hong

VERSION 1 - REVIEW

REVIEWER	Emine O Bayman University of Iowa, USA
REVIEW RETURNED	01-Nov-2016

GENERAL COMMENTS	<p>Authors should clearly define the primary and secondary outcomes of the study. Currently, they are not defined. However, on the Discussion section (P15L26-28), authors interpret the primary and secondary analyses. Meta analyses should be performed for the primary and secondary analyses. Currently authors are presenting 6 different sets of results on figures 2 to 7. They also examined results in various subgroups. The reader misses the main goal of the study. I highly recommend identifying a primary outcome variable and a few secondary outcome variables and presenting results only for those variables. This way, the findings of the study will be more clear.</p> <p>I recommend authors to receive a professional assistance from an English editor. Some sentences are incomplete (P3L8-16), and some sentences are not clear (P15L6-11).</p> <p>P5L34-39: searches for "cardiopulmonary bypass", "bypass cardiopulmonary", "bypasses cardiopulmonary" and "cardiopulmonary bypasses" should all return the same list of publications. It is also true for 5 varieties of "heart-lung bypass."</p> <p>P7L19-21: we do not need to know who performed the quantitative meta-analyses.</p> <p>P7L49: "If the p-value ... publication bias WAS ASSUMED existed." would be more appropriate.</p> <p>P7L56 to P8L4: not clear.</p> <p>Figure 1: "articles not randomized" maybe "articles from not randomized studies"?</p>
-------------------------	---

REVIEWER	Sarvesh Pal Singh All India Institute of Medical Sciences India
REVIEW RETURNED	02-Nov-2016

GENERAL COMMENTS	<p>Comments</p> <p>The authors have done a very elaborate Meta-analysis to address relation between anaesthetic agents and cerebral protection. The Methodology and Statistics are good. I would advise the authors to use help for English grammar from a professional so as to correct minor grammatical mistakes. Please do not use complicated statements as Point 4 in Abstract. This is a Scientifically reasoned paper so avoid using words like some . Page 3, line 42</p> <p>Page 3 line 52, the references quoted do not conclude Neurological dysfunction as major cause of mortality. Kindly revise.</p> <p>Page 4, Line 21. Reference 10 is about Jugular venous oximetry. Kindly quote the original reference quoted in the paper.</p> <p>Page 6, Line 6. Inclusion Criteria : Rewrite the first statement. AllTIVA group.</p> <p>Page 10 Line 37. D (a-j)O2 What is this ?</p> <p>Page 12, Figure 6 legend: D(a-v)O2 ; Are you using D(a-v)O2 and D (a-j)O2 interchangeably? Kindly clarify</p> <p>Page 16, line 7 and 40. Please don't use terminology like " As we know"</p> <p>Page 16; line 45 . " The neuroprotectionresponse". Unless supported by reference this is just authors opinion.</p> <p>Page 17, para 1. The authors are repeatedly discussing the same thing that Inhalational anaesthesia have cerebral protective effects. Kindly rewrite the paragraph.</p> <p>Page 17, Para 2. Grammar check. Line 2 : various application methods ???</p> <p>Page 18, Para 1 , line 1. "Additionally, a recent meta-analysiscomplications" reference please.</p>
-------------------------	---

REVIEWER	Gudrun Kunst King's College Hospital NHS Foundation Trust United Kingdom
REVIEW RETURNED	12-Mar-2017

GENERAL COMMENTS	<p>The authors of this systematic review and meta-analysis compare neuroprotective effects of volatile and intravenous anesthetics in patients undergoing cardiac surgery with cardiopulmonary bypass.</p> <p>Major comments:</p> <p>1) Introduction, there are many studies demonstrating that CPB does not increase morbidity and mortality postoperatively in patients undergoing CABG surgery (Lamy et al. 2013). This should be mentioned.</p> <p>2) S100 has been described as an un-suitable serum marker for neurocognitive function or neurological outcomes in cardiac surgery, due to S100 contamination of pericardial suction blood, which is often re-transfused or processed in the cell saver and then re-transfused (e.g. Svenmarker et al. 2004). These important results of several studies should be considered in the discussion of the results</p>
-------------------------	--

	<p>and under limitations of the study. Did the studies included in the meta-analysis use the commonly used technique of re-transfusion and cell salvage?</p> <p>3) Methods, regarding patients in the volatile anaesthesia group, did these patients also receive propofol during CPB, or no propofol at all? Would propofol in the volatile group have a potential effect on neuroprotection? Please discuss.</p> <p>4) Abstract, methods and results, at what time points were cerebral blood flow and MMSE assessed in the study groups? Postoperative MMSE varies according to the time-point of assessments. Therefore, exact time-points of the MMSE assessments in the analysed studies should be listed, and discussed.</p> <p>5) It is also not clear at what time the other variables, such as oxygen consumption, jugular bulb oxygen saturation and cerebral oxygen extraction were assessed in the studies, during CPB, after CPB, or both?</p> <p>6) Discussion, page 18, line 11-12: please list relevant references.</p> <p>Minor comments: Abbreviations will need to be explained in the abstract, and also in the figures. Throughout the manuscript there is lack of sufficient grammar and other factors in the English language which will need to be thoroughly revised and corrected.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Emine O Bayman

Institution and Country: University of Iowa, USA

Please state any competing interests: None declared

Please leave your comments for the authors below

1) Authors should clearly define the primary and secondary outcomes of the study. Currently, they are not defined. However, on the Discussion section (P15L26-28), authors interpret the primary and secondary analyses. Meta analyses should be performed for the primary and secondary analyses. Currently authors are presenting 6 different sets of results on figures 2 to 7. They also examined results in various subgroups. The reader misses the main goal of the study. I highly recommend identifying a primary outcome variable and a few secondary outcome variables and presenting results only for those variables. This way, the findings of the study will be more clear.

Response: Sincerely thanks for the reviewer's thoughtful suggestions. We have revised the statements regarding the outcomes in the method section in the revision manuscript. (Page 7, lines 2 to 10)

Increased S100B concentrations in serum and cerebrospinal fluid were observed after brain infarction or injury, and thus S100B was one of the most commonly used and acceptable biomarker for neurocognitive function or neurological outcomes in many previous studies. (Br J Anaesth. 2000; 85:287-98. ; Rev Bras Cir Cardiovasc. 2014;29:630-41. Biomed Res Int. 2015; 2015:402959.) And in the study S100B level was considered as primary outcome. In addition, the other included variables such as MMSE, cerebral blood flow and cerebral metabolic rate of oxygen consumption, etc., were demonstrated that may reflect or affect patients' neurological function after the cardiac surgery. Therefore, these variables were considered as secondary outcomes in the current analysis.

2) I recommend authors to receive a professional assistance from an English editor. Some sentences are incomplete (P3L8-16), and some sentences are not clear (P15L6-11.)

Response: We have sought a professional English editing company to improve the English usage throughout the manuscript including the sentence (P15L6-11.) in the revision manuscript. (Page 17, lines 5 to 9) And we have revised the "Strengths and Limitations section" and deleted the incomplete sentences (P3L8-16) according to the Editorial Requirements. (Page 3, lines 6 to 20)

3) P5L34-39: searches for "cardiopulmonary bypass", "bypass cardiopulmonary", "bypasses cardiopulmonary" and "cardiopulmonary bypasses" should all return the same list of publications. It is also true for 5 varieties of "heart-lung bypass."

Response: We have deleted the redundant terms and only use one in the revision manuscript. (Page 5, line 22 to Page 6, line 1)

4) P7L19-21: we do not need to know who performed the quantitative meta-analyses.

Response: We have deleted these sentences in the revision manuscript.

5) P7L49: "If the p-value ... publication bias WAS ASSUMED existed." would be more appropriate.

Response: Thanks the reviewer and we have revised this statement as the suggestion. (Page 8, lines 15 to 16)

6) P7L56 to P8L4: not clear.

Response: We have sought a professional English editing company to improve the English usage to make it much clearer. (Page 8, lines 19 to 21)

7) Figure 1: "articles not randomized" maybe "articles from not randomized studies"?

Response: We have revised this statement of Figure 1.

Reviewer: 2

Reviewer Name: Sarvesh Pal Singh

Institution and Country: All India Institute of Medical Sciences, India

Please state any competing interests: None declared

Please leave your comments for the authors below

Comments

1) The authors have done a very elaborate Meta-analysis to address relation between anaesthetic agents and cerebral protection.

The Methodology and Statistics are good.

I would advise the authors to use help for English grammar from a professional so as to correct minor grammatical mistakes.

Please do not use complicated statements as Point 4 in Abstract.

This is a Scientifically reasoned paper so avoid using words like some . Page 3, line 42

Response: Thanks for reviewer's suggestion regarding the manuscript. We have sought a professional English editing company to improve the English usage throughout the manuscript.

2) Page 3 line 52, the references quoted do not conclude Neurological dysfunction as major cause of mortality. Kindly revise.

Response: We have quoted appropriate references in the revision manuscript. (Page 4, line 9)

3) Page 4, Line 21. Reference 10 is about Jugular venous oximetry. Kindly quote the original

reference quoted in the paper.

Response: We have quoted the original reference in the revision manuscript. (Page 4, line 18)

4) Page 6, Line 6. Inclusion Criteria : Rewrite the first statement. AllTIVA group.

Response: We have rewritten this statement and sought a professional English editing company to improve the English usage. (Page 6, lines 14 to 16)

5) Page 10 Line 37. D (a-j)O₂ What is this ?

6) Page 12, Figure 6 legend: D(a-v)O₂ ; Are you using D(a-v)O₂ and D (a-j)O₂ interchangeably?
Kindly clarify

Response: Sorry for the write errors regarding this terms. Actually, it should be “D(a-v)O₂”, which represents “arteriovenous oxygen content difference” in the manuscript. We have unified the terms throughout the manuscript.

7) Page 16, line 7 and 40. Please don't use terminology like “ As we know” 润色

Response: We have revised these English usages throughout the manuscript.

8) Page 16; line 45 . “ The neuroprotectionresponse”. Unless supported by reference this is just authors opinion.

Response: We have deleted this sentence in the revision manuscript.

9) Page 17, para 1. The authors are repeatedly discussing the same thing that Inhalational anaesthesia have cerebral protective effects. Kindly rewrite the paragraph.

Response: We have deleted this paragraph in the revision manuscript.

10) Page 17, Para 2. Grammar check. Line 2 : various application methods ???

Response: We have revised this sentence in the revision manuscript. (Page 19, lines 9 to 13)

11) Page 18, Para 1 , line 1. “Additionally, a recent meta-analysiscomplications” reference please.

Response: We have added the reference (Anesthesiology. 2016. 124: 1230-45.) in the revision manuscript. (Page 19, line 19)

Reviewer: 3

Reviewer Name: Gudrun Kunst

Institution and Country: King's College Hospital NHS Foundation Trust, United Kingdom

Please state any competing interests: None declared

Please leave your comments for the authors below

The authors of this systematic review and meta-analysis compare neuroprotective effects of volatile and intravenous anesthetics in patients undergoing cardiac surgery with cardiopulmonary bypass.

Major comments:

1) Introduction, there are many studies demonstrating that CPB does not increase morbidity and

mortality postoperatively in patients undergoing CABG surgery (Lamy et al. 2013). This should be mentioned.

Response: Thanks for the reviewer's thoughtful suggestions regarding the manuscript. We have rewritten this sentence of the introduction. Cardiopulmonary bypass (CPB) is a necessary and common procedure to support the patient's circulation during cardiac surgery. Although previous studies (N Engl J Med. 2013. 368: 1179-88; N Engl J Med. 2016. 375: 2359-68.) reported that CPB does not increase the postoperative morbidity and mortality in patients undergoing coronary artery bypass graft (CABG) surgery, it was demonstrated that the incidence of some postoperative complications for these patients remains high.(up to 14.0% one year after the surgery and 23.6% after five year) We have added this statement in the revision manuscript (Page 4, lines 2 to 8)

2) S100 has been described as an un-suitable serum marker for neurocognitive function or neurological outcomes in cardiac surgery, due to S100 contamination of pericardial suction blood, which is often re-transfused or processed in the cell saver and then re-transfused (e.g. Svenmarker et al. 2004). These important results of several studies should be considered in the discussion of the results and under limitations of the study. Did the studies included in the meta-analysis use the commonly used technique of re-transfusion and cell salvage?

Response: Increased S100B concentrations in serum and cerebrospinal fluid were observed after brain infarction or injury, and thus S100B was one of the most commonly used and acceptable biomarker for neurocognitive function or neurological outcomes in many previous studies. (Br J Anaesth. 2000; 85:287-98. ; Rev Bras Cir Cardiovasc. 2014;29:630-41. Biomed Res Int. 2015; 2015:402959.) Although it is inevitable for S100B contamination due to the pericardial suction blood (Svenmarker et al. 2004), a strict control of clinical procedures between two groups may decrease its potential effect on difference of S100B detection in the study. Nevertheless, the possible effect of re-transfusion and cell salvage should not be neglected. And in the included studies, the use of the technique of re-transfusion and cell salvage were not mentioned. Therefore, as your suggestion, we have added this in the limitations of the study in the discussion section.

3) Methods, regarding patients in the volatile anaesthesia group, did these patients also receive propofol during CPB, or no propofol at all? Would propofol in the volatile group have a potential effect on neuroprotection? Please discuss.

Response: In the include studies of the current meta-analysis, patients did not receive propofol during CPB in the volatile anaesthesia group at all, and thus the potential effect of propofol on neuroprotection could be avoided. And we have added the statement "In the included studies, patients in the 'volatile anaesthesia' group had not received propofol, thiopental, or ketamine during during the surgery and CPB." in the results section of revision manuscript to clarify this potential issue. (Page 9, line 10 to page 10, line 2)

4) Abstract, methods and results, at what time points were cerebral blood flow and MMSE assessed in the study groups? Postoperative MMSE varies according to the time-point of assessments. Therefore, exact time-points of the MMSE assessments in the analysed studies should be listed, and discussed.

Response: Thanks for the reviewer's caution regarding the time-points of included variables. We have carefully checked the time-points of all included variables again and again. In all the included studies with MMSE testing, the tests of three studies (Huaping Yuan. 2015; Shudong Ma. 2015; Jiying Zhong. 2010) were performed at 24 hours after the surgery while another study (Lei Li. 2010) was at 96 hours after the surgery. Thus to eliminate the effect of time-points on MMSE we have deleted this study (Lei Li. 2010) from the analysis (fig 3), and we have added the description regarding the time-point for MMSE in the revision manuscript. (Page 7, line 6) In addition, cerebral blood flow was tested at cooling and rewarming during CPB. (Page 7, line 10)

5) It is also not clear at what time the other variables, such as oxygen consumption, jugular bulb

oxygen saturation and cerebral oxygen extraction were assessed in the studies, during CPB, after CPB, or both?

Response: We have added the assessing time points of the included variables including cerebral metabolic rate of oxygen consumption; arteriovenous oxygen content difference; cerebral oxygen extraction and jugular bulb oxygen saturation in the revision manuscript. All these variables were tested at cooling and rewarming during CPB. (Page 7, line 10)

6) Discussion, page 18, line 11-12: please list relevant references.

Response: We have added the reference (Anesthesiology. 2016. 124: 1230-45.) in the revision manuscript. (Page 19, line 19)

7) Minor comments:

Abbreviations will need to be explained in the abstract, and also in the figures.

Throughout the manuscript there is lack of sufficient grammar and other factors in the English language which will need to be thoroughly revised and corrected.

Response: We have added the annotation for the abbreviations in the abstract and the figures in the revision manuscript. And we have sought a professional English editing company to improve the English usage throughout the manuscript.

We thank you and the reviewers for your thoughtful suggestions and insights, which have enriched the manuscript and produced a more balanced and improved account of the research. We hope that the revised manuscript is now suitable for publication in your journal.

VERSION 2 – REVIEW

REVIEWER	Emine O Bayman University of Iowa
REVIEW RETURNED	03-May-2017

GENERAL COMMENTS	<p>P7L3, 4: Are there 3 outcome variables in the study; S100B at pre-op, post-CPB and 24 hours post-operatively? It is not clear from this sentence.</p> <p>Whenever authors present a meta-analysis result, they should also indicate the number of studies and the total number of patients. For example, on P11L21, “Based on 6 studies from NN patients, S100B levels” This would be helpful on assessing the generalizability of the results.</p> <p>Meta-analysis from figures 4 and 5 are based on only 2 studies each with small sample sizes. I recommend presenting those studies only descriptively, and maybe moving the related tables and figures as supplementary materials, instead of conducting meta-analysis for these outcomes. Accordingly, the discussion about these outcomes should be removed from the Results section.</p> <p>No discussion of the heterogeneity among studies in the Results section.</p>
-------------------------	---

REVIEWER	Gudrun Kunst King's College Hospital NHS Foundation Trust United Kingdom
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	All my comments have been addressed. The manuscript reads well and I have no more recommendations.
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Emine O Bayman

Institution and Country: University of Iowa

Please state any competing interests: None declared

Please leave your comments for the authors below

P7L3, 4: Are there 3 outcome variables in the study; S100B at pre-op, post-CPB and 24 hours post-operatively? It is not clear from this sentence.

Response: “In the included studies, S100B levels in serum were detected before CPB (pre-CPB), after CPB (post-CPB) and 24 hours postoperatively. And the primary outcomes were protein S100B levels in serum post-CPB and 24 hours postoperatively.” We have revised this sentence in the revision manuscript. (Page 6, lines 22 and Page 7, lines 1 to 3)

Whenever authors present a meta-analysis result, they should also indicate the number of studies and the total number of patients. For example, on P11L21, “Based on 6 studies from NN patients, S100B levels” This would be helpful on assessing the generalizability of the results.

Response: Thanks for the reviewer’s suggestion, and we have revised these statements in the revision manuscript. (Page 11, lines 7,8 and 11)

Meta-analysis from figures 4 and 5 are based on only 2 studies each with small sample sizes. I recommend presenting those studies only descriptively, and maybe moving the related tables and figures as supplementary materials, instead of conducting meta-analysis for these outcomes. Accordingly, the discussion about these outcomes should be removed from the Results section.

Response: Thanks the reviewer and we have removed the figures 4,5 and related tables from the Results section. Also we have removed the discussion about these outcomes from the Results section and presented those studies only descriptively in Discussion section. (Page 14, lines 10 to 20)

No discussion of the heterogeneity among studies in the Results section.

Response: Thanks the reviewer, we have added the description of heterogeneity in results section (Page 11, lines 5 to 7 and 14,15). Also we have discussed the heterogeneity among studies in the discussion section.(Page 15, lines 18 to 21)

We thank you and the reviewers again for your thoughtful suggestions and insights. And we hope that the revised manuscript is now suitable for publication in your journal.

VERSION 3 – REVIEW

REVIEWER	Emine O Bayman University of Iowa, USA
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	I do not have any further comments.
-------------------------	-------------------------------------