Author’s response to reviews

Title: Dexmedetomidine Prevents Acute Kidney Injury After Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

Authors:

Yang Liu (liuyang2002whu@whu.edu.cn)
Bo Sheng (13718303769@163.com)
Suozhu Wang (153226464@qq.com)
Feiping Lu (leafreding@126.com)
Jie Zhen (13811799239@139.com)
Wei Chen (heart2008whu@163.com)

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Author’s response to reviews:

Cover Letter

Dear Editor,

Thank you for your letter and the reviewers’ comments about our manuscript entitled “Dexmedetomidine Prevents Acute Kidney Injury After Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials” BANE-D-17-00312. These comments are appreciated and very useful for the revision of our paper. We have read comments carefully and made corresponding revisions which are marked in red in the resubmitted manuscript. We have listed the responses point by point according to your concerns in a separate letter-“Responses to the comments”. The authors have declared that no competing interests exist.

We hope that these corrections will meet with the suggestions. Looking forward to your new advice about our content.

Once again, thank you very much for your comments!

Yours sincerely,

Wei Chen

Respond to the Comments
Editor Comments:

The meta analysis performed is of clinical interest. However further methodological improvements are mandatory, as suggested by the reviewer. Furthermore, AKI in cardiac surgery is common and may have several different causes. It is difficult to really establish a sure protective role for dexmedetomidine. this should be better discussed in the manuscript.

Re: Thank you for the advices. We admitted that many risk factors for AKI were not included in our meta analysis, such as iodinated contrast administration, emergency surgery, hemodynamic instability, and use of starches and transfusions. However, it is very difficult for us to ask for the data not reported in the published articles. We added these issues as a limitation in the limitation section, and further methodological improvements have been done, as suggested by the reviewer.

Special thanks for your constructive advices.

Reviewer 1:

Mean and standard deviation when not calculated were estimated according to accepted, published methods. Although such estimation contains error when samples are not normally distributed (Bland, 2015; Kwon & Reis, 2015), which is usually when median and range or interquartile range are reported, Bland has convincingly argued that the overestimation is mostly in the standard deviation. That will increase the error term, which will make it more difficult to reject the null hypothesis in a meta-analysis. Given that all of the meta-analytic results favor dexmedetomidine, the overestimation should not affect the conclusions. The authors may want to add a footnote, or include in the limitations section, an indication that the Hozo et al. (2005) estimation method may have limited their statistical ability to detect differences. The authors should add a reference for Hozo et al. (2005).

Re: Thank you for the concerns. We have added these issues as a limitation in the Limitation section: "Fifth, Bland [32]and Kwon & Reis [33]have argued that the statistical method of Hozo et al may have limited their statistical ability to detect differences. when samples are not normally distributed. So the effect of dexmedetomidine may be overestimation, especially for negative findings " (Page 12,Line 7-11)

We also have added as a reference for Hozo et al. (2005) (Page 16,Line 4-6).

Special thanks for your constructive advices.

Reviewer 2:

1. The Authors reported to have assessed quality of included trials according to Cochrane Risk of Bias tool. However, the items suggested by the Cochrane Handbook are slightly different
from those reported by the Authors. In particular, Cochrane Handbook recommend to distinguish between blinding of participants and personnel, and blinding of outcome assessors; attrition bias (dropout and intention-to-treat) is grouped together; selective outcome reporting and possible other biases are also assessed. More importantly, a final judgement on overall risk of bias should be provided. In my opinion, the Authors should perform this assessment. After that, a sensitivity analysis including only low risk of bias trials should be performed.

Re: Thank you for your advice. We have revised these information according to Cochrane Risk of Bias tool suggested by the Cochrane Handbook listed in a new Table 3. Moreover, the Jadad scale was used for a final judgment on overall risk of bias, and subgroup analysis for Jadad scale≥3 VS Jadad scale<3 have been done in Table 5.

2. The primary endpoint of the study was incidence of AKI defined by RIFLE, AKIN or KDIGO criteria. Does this mean that studies reporting AKI defined according to other criteria were excluded? If yes, this should be specified.

Re: Thank you for the concern. We have revised it in the Method section and defined all AKI followed RIFLE, AKIN or KDIGO criteria (Page 6, Line 5-6).

3. The Authors reported to have analyzed data using random-effects model for the potential clinical inconsistency. However, they do not describe any method for assessing possible inconsistency. I think that methods for assessing heterogeneity (e.g., I^2) should be described. If analysis suggest possible heterogeneity, the Authors should try to identify possible sources of inconsistency (e.g., different baseline characteristics? Different study drug dosing scheme)

Re: Sorry for the missing statement. Heterogeneity was assessed with the inconsistency statistic (I2), and we have added the information in the methods section (Page 6, Line 16-17). Subgroup analyses for the potential sources of heterogeneity was listed in Table 5.

4. The analysis of continuous outcome should be better described. Did all the trials reported mean and standard deviations? I understand that included trials reported either mean and SD or median (IQR) or median (range), and mean/SD were then estimated by the Authors according to the method by Hozo et al. (Hozo et al, BMC Medical Research Methodology 2005, 5:13. doi:10.1186/1471-2288-5-13). However, Hozo method only allow to estimate mean and SD from median and range. I believe that Authors may have actually used the updated Wan et al method (Wan et al, BMC Medical Research Methodology 2014, 14:135. doi:10.1186/1471-2288-14-135)

Re: Thank you for the concerns. We have added these issues as a limitation in the Limitation section: "Fifth, Bland [32]and Kwon & Reis [33] have argued that the statistical method of Hozo et al may have limited their statistical ability to detect differences. When samples are not normally distributed. So the effect of dexmedetomidine may be overestimation, especially for negative findings." (Page 12, Line 7-11)
5. The Authors reported to have analyzed data with Stata; however, manuscript figures seems to me to have been generated with Review Manager

Re: Thank you for the concern. We have revised it in the Method section as followed: “All statistical analyses were performed in REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 9.0; StataCorp LP)”. (Page 6, Line 19-20)

6. In addition to the study flow-chart, I think that Authors should provide a complete list of 88 excluded studies together with references and reason for exclusion, ideally as Supplementary Appendix.

Re: Thank you for your advice, we have uploaded a complete list of 88 excluded studies together with references and reason for exclusion as a supplemental material.

7. Was need for RRT reported only in? If not, I think that analyzing the effect of dexmedetomidine on need for RRT might be a very interesting analysis.

Re: Thank you for the concern. You have proposed a quite high-level analytic idea for our meta-analysis. It is a pity for us not doing the analysis because the renal replacement therapy was reported only in the trial by Djaiani et al

8. There are some subgroup analyses which might be interesting to performed, with particular reference to Authors' conclusions: the Authors could assess whether a subgroup effects exist in pre/intraoperative versus postoperative dexmedetomidine administration, loading dose vs no loading dose use, and low vs high dose continuous infusion. Additional analyses could be CABG only surgery, and studies using placebo as control.

Re: Thank you for the concerns. We added a subgroup analysis in the Table 5 and described in the in the Result section as followed: Subgroup analyses for the potential sources of heterogeneity was listed in Table 5. We divided study participants into 11 groups according to different characteristics such as age(year)≥60.0 versus < 60.0, proportion of males ≥60% versus < 60.0%, proportion with diabetes ≥25% versus < 25%, CPB duration(min) ≥100 versus < 100, statin use ≥60% versus < 60.0%, loading dose use or not, low versus high dose continuous infusion, studies using placebo versus control, pre/intraoperative versus postoperative dexmedetomidine administration, CABG only surgery versus Combined surgery, JADAD score ≥3 versus <3. Overall, no significant differences existed in incidence of AKI. (Page 8, Line 5-13)

9. Additional sensitivity analyses for the primary outcome which could be performed include removing each trial at a time and reanalyzing the remaining dataset (to assess whether
results are heavily influenced by a single trial), changing analysis method (Mantel-Haenszel or Inverse Variance) or changing summary statistics (RR vs OR vs RD).

Re: Thank you for the concern. We have added these issues in the Result section as followed: “Sensitivity analysis excluding each included study 1 at a time revealed that the Cho 2015 study were inconsistent with the direction and size of the overall AKI-reducing effect of dexmedetomidine ($P = 0.34$),and the other studies were consistent with the direction and size of the overall AKI-reducing effect of dexmedetomidine ($P$ for all $< 0.04$)” (Page 8, Line 14-18).

Different analysis method (Mantel-Haenszel or Inverse Variance) or different summary statistics (RR vs OR vs RD) was listed in Table 4 and described in the Result section as followed: “Different analysis method (Mantel-Haenszel or Inverse Variance) or different summary statistics (RR vs OR vs RD) was listed in Table 4”. (Page 8, Line 2-3)

10. Two recent experts consensus article on AKI have been recently published (Joannidis et al, Intensive Care Med. 2017 Jun;43(6):730-749. doi: 10.1007/s00134-017-4832-y; and Bellomo et al, Ann Intensive Care. 2017 Dec;7(1):49. doi: 10.1186/s13613-017-0260-y), which discussed also new possible therapies/preventive measures. I think that Authors should discuss their results also in light of current evidence as summarized by these two articles.

Re: Thank you for your advice, We have added these issues in the Discussion section as followed: “Two recent expert consensus articles on AKI have been recently published, which discussed also new possible therapies/preventive measures[30,31]. Our results was in keeping with one of the article conducted by M. Joannidis and colleagues, which showed dexmedetomidine was promising to reduce the rate of AKI, although no recommendation can be given on the basis of current data”. (Page 11, Line 16-20)