

## 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

<b>TITLE (PROVISIONAL)</b>	The effect of dexmedetomidine on postoperative nausea and vomiting in patients under general anesthesia: an updated meta-analysis of randomized controlled trials
<b>AUTHORS</b>	Zhao, Weihong; Li, Jianli; Wang, Na; Wang, Zhibin; Zhang, Meng; Zhang, Huanhuan; Liu, Meinv; He, Jinhua; Yu, Dongdong

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Kateryna Bielka Bogomolets National Medical University, Anesthesiology and intensive care
<b>REVIEW RETURNED</b>	19-Aug-2022

<b>GENERAL COMMENTS</b>	The review update information on PONV prevention, using DEX, and is of great interest. The goal, methods and results of the review are clear, although need minor native english speaker correction.
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<b>REVIEWER</b>	Kannan Sridharan Seth GS Medical College and KEM Hospital, Department of Clinical Pharmacology
<b>REVIEW RETURNED</b>	18-Sep-2022

<b>GENERAL COMMENTS</b>	<ol style="list-style-type: none"><li>1. Please provide in the results section (and also in abstract) how this systematic review is concluding something new compared to the previous meta-analysis.</li><li>2. Please adhere to PRISMA and submit filled-in checklist as the Electronic supplementary file.</li><li>3. In Table 1, please include demographic features of the study participants, dosing regimen of dexamedetomidine, nature of scale used for assessing nausea/vomiting.</li><li>4. Please get the manuscript edited by a native English speaker/professional language editing company.</li><li>5. Please provide Grading of key outcomes.</li></ol>
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<b>REVIEWER</b>	Marcin Wasowicz University Health Network, Anesthesia and Pain Management
<b>REVIEW RETURNED</b>	18-Sep-2022

<b>GENERAL COMMENTS</b>	<p>Thank you for an opportunity to read your manuscript. It is interesting meta-analysis investigating reduction of PONV with use of dexmedetomidine after surgery performed under general anesthesia.</p> <p>The analysis is well conducted with use of an appropriate methods. I have two main concerns reg. your manuscript.</p> <ol style="list-style-type: none"><li>1. Your introduction is too long. Several statements are well know</li></ol>
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	<p>facts and it is enough to reference it. In general your introduction should not be longer than 1 page</p> <p>2. Discussion. Needs to be re-written. Please avoid repeating your results in discussion.</p> <p>I would suggest following scheme</p> <ol style="list-style-type: none"> <li>The main finding of your study</li> <li>How do your results compare to other similar studies, put more attention into description of 2 other meta analyses</li> <li>Clinical significance of your results</li> <li>limitations</li> <li>Conclusions</li> </ol> <p>Other comments</p> <ol style="list-style-type: none"> <li>I would avoid word obvious while referring to your results (for example abstract line 18) or discussion</li> </ol>
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<b>REVIEWER</b>	Jiyoung Lee CHA University
<b>REVIEW RETURNED</b>	05-Oct-2022

<b>GENERAL COMMENTS</b>	<p>Page 11 Line 7-9 Can DEX also prevent perioperative stress response by regulating heart rate and blood pressure? Is it right? Are cause and effect, correct? Is reference 23 right?</p> <p>What is the definition of bradycardia? Is the definition of bradycardia the same across studies?</p> <p>How did you measure opioid consumption? Did all studies use the same opioid? Was it calculated and used as a morphine equivalent dose?</p> <p>Why do you think the extubation time was short in the DEX group? Did your studies set the depth of anesthesia using BIS? Or is DEX added to the same dose of inhaled anesthetic or TIVA? DEX has a sedation effect, so it is interesting to reduce the extubation time in your study.</p>
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<b>REVIEWER</b>	Holger Schielzeth Friedrich-Schiller-Universitat Jena
<b>REVIEW RETURNED</b>	30-Nov-2022

<b>GENERAL COMMENTS</b>	<p>The manuscript uses formal meta-analyses to investigate the effect DEX on postoperative nausea and vomiting. The manuscript is not always and easy read, which may be partly due to differences among fields (I was asked to assess the statistical analysis in specifically), but I do think the manuscript would benefit from some language editing. A particularly interesting phrase appears in P4, L14-15 (“no updated analysis ... was performed during general anesthesia”) – I hope not all meta-analyses in the field are done under anesthesia. Anyway, the meta-analysis seems competently done and is well documented. I cannot access the preregistration (CRD 42022341548), but by the sounds of it, the meta-analysis was performed as planned.</p> <p>My biggest questions is why the number of included studies is lower than in two previous meta-analyses that seem to address the exact</p>
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	<p>same topic: Liang et al. 2015. Int J. Clin. Exp. Med 8: 8450-8471 with 82 included trials and Jin et al. 2017. Medicine 96: e5770 with 22 included trials – as compared the total of 18 trials included in the current meta-analysis. The manuscript claims that there are now more trials (which I would expect after 5+ years), it is thus not clear why the number of included trials is lower. It does not seem to me that the selection criteria are more stringent. The differences should at least be explained and justified. I would also think that a screening and possibly a forward search on previous meta-analyses should be part of the data collection process.</p> <p>P5, L9: The search terms seem to be redundant (e.g. “nausea” should include all hits from “postoperative nausea”). Also, there should be brackets around (“nausea and vomiting”) although this is also redundant. I’m also a bit confused about the search strings in Supplement 2. The Embase search seems to be filtered by (“postoperative AND nausea AND vomiting”) and the Cochrane search by (“postoperative nausea and vomiting”). This is both more restrictive and different from the search strategy presented in the methods section. Please clarify.</p> <p>The analysis seems competently done. Personally, I wouldn’t make the use of random or fixed effect models conditional on the significance test for <math>I^2</math> – and would use a random effects model throughout – but such model selection procedures are widespread and I don’t think it makes a difference here.</p> <p>Table 1: I would think the included studies should be properly cited and included in the reference list. (See also Item #17 from PRISMA Checklist)</p> <p>Table 1: Suggest to replace “Number” by “Sample size” and “Nausea and vomiting” by “Nausea and/or vomiting”.</p> <p>Figure captions: All captions are a bit too brief to stand alone. For example: A funnel plot of what?</p> <p>Figure 2: I guess it should read: “1724 duplicates removed”. Also, I think there is a box missing for the studies excluded at the abstract screening stage. It would be good to break down exclusion by specific criteria. Finally, suggest to replace “endpoint” by “outcome”</p> <p>Figure 3: Suggest to replace “Experimental” by “Treatment” or “DEX treatment”</p> <p>Figure 8: I was looking for the axis labels, but now I see there are very small, but they are there. This could be made a bit more obvious.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1:

1. The review update information on PONV prevention, using DEX, and is of great interest. The goal, methods and results of the review are clear, although need minor native english speaker correction.

Response: Thank you for your important comment. We improved the quality of the English throughout our manuscript and the revised parts were highlighted in red.

Reviewer 2:

1. Please provide in the results section (and also in abstract) how this systematic review is concluding something new compared to the previous meta-analysis.

Response: Thank you for your important comment. In fact, we mainly focused on the adult patient population under general anesthesia, and the intervention was perioperative intravenous DEX, in addition, our study involved a number of updated RCTs. The relevant information was added in the revised manuscript, please see Page 2, lines 15-16, and Page 7, lines 6-7.

2. Please adhere to PRISMA and submit filled-in checklist as the Electronic supplementary file.

Response: Thanks for your important comment. In fact, our meta-analysis adhered to the PRISMA and we submitted the filled-in checklist as Supplementary document 1 in the origin manuscript, please see Page 5, lines 1-2 and Supplementary document 1.

3. In Table 1, please include demographic features of the study participants, dosing regimen of dexmedetomidine, nature of scale used for assessing nausea/vomiting.

Response: Thank you for your comment. We added the relevant information in the revised manuscript. Please see Table 1.

4. Please provide Grading of key outcomes.

Response: Thank you for your comment. Four studies mentioned about the grading of PONV. The grading of PONV was shown in last column of Table 1. Because of the different criteria for assessing the severity and the specific grading of PONV, the severity degree and grading of PONV was not quantified in this analysis. We mentioned it in limitation part of origin manuscript. Please see Page 14, lines 7-9.

Reviewer 3:

1. Your introduction is too long. Several statements are well know facts and it is enough to reference it. In general your introduction should not be longer than 1 page.

Response: Thank you for your comment. We shortened the introduction in revised manuscript. Please see Page 3, lines 13-22 and Page 4, lines 1-18.

2. Discussion. Needs to be re-written. Please avoid repeating your results in discussion.

I would suggest following scheme.

- a. The main finding of your study
- b. How do your results compare to other similar studies, put more attention into description of 2 other meta analyses
- c. Clinical significance of your results
- d. limitations
- e. Conclusions

Response: Thank you for your important comment. We removed the repeating results in discussion and revised the discussion in revised manuscript according to the scheme that you suggested. Please see Page 13, lines 12-22 and Page 14, lines 1-3.

3. I would avoid word obvious while referring to your results (for example abstract line 18) or discussion.

Response: Thank you for your suggestion. We removed the word in our revised manuscript.

Reviewer 4:

1. Can DEX also prevent perioperative stress response by regulating heart rate and blood pressure?  
Is it right? Are cause and effect, correct?  
Is reference 23 right?

Response: Thank you for your important comment. In fact, we think there is causal relationship between the stress response and hemodynamic changes. And we think the reference 23 is right that reported that the direct laryngoscopy and tracheal intubation following induction of anesthesia were also related to the hemodynamic changes due to increased sympathoadrenal activity, which was attenuated by DEX.

2. What is the definition of bradycardia?  
Is the definition of bradycardia the same across studies?

Response: Thank you for your important comment. The definition of bradycardia was different across studies. In total of eight trials described the incidence of bradycardia. Four of these trials defined bradycardia as heart rate less than 50 beats/min. One of these trials defined bradycardia as heart rate less than 45 beats/min. Another trial defined bradycardia as heart rate less than 40 beats/min and two trials did not describe the definition of bradycardia. We collected the incidence of bradycardia from the RCTs and used the standardized mean difference (SMD) to express the data because of the dissimilar definition of bradycardia.

3. How did you measure opioid consumption?  
Did all studies use the same opioid?  
Was it calculated and used as a morphine equivalent dose?

Response: Thank you for your comment. We collected the data of intraoperative opioid consumption from the included RCTs. In total of eight trials described the opioid consumption. There were five trials used the fentanyl, and three trials used the remifentanyl. Although we did not use the morphine equivalent dose to calculate it, we used the SMD to analyze the opioid consumption to decrease influence on the results.

4. Why do you think the extubation time was short in the DEX group?  
Did your studies set the depth of anesthesia using BIS?  
Or is DEX added to the same dose of inhaled anesthetic or TIVA?  
DEX has a sedation effect, so it is interesting to reduce the extubation time in your study.

Response: Thank you for your comment. Four studies described the extubation time, there were two studies set the depth of anesthesia using BIS and two studies did not. There were two studies described DEX could decrease the propofol consumption. We thought that DEX shortened the time to extubation by reducing the use of perioperative other anesthetic drugs, like propofol. In our meta-analysis we found that DEX shortened the time to extubation, but because of the limited data and substantial heterogeneity among studies, the result might be interpreted cautiously. And we added the relevant information in the part of discussion. Please see Page 13, lines 8-11.

Reviewer 5:

1. My biggest question is why the number of included studies is lower than in two previous meta-analyses that seem to address the exact same topic: Liang et al. 2015. *Int J. Clin. Exp. Med* 8: 8450-8471 with 82 included trials and Jin et al. 2017. *Medicine* 96: e5770 with 22 included trials – as

compared the total of 18 trials included in the current meta-analysis. The manuscript claims that there are now more trials (which I would expect after 5+ years), it is thus not clear why the number of included trials is lower. It does not seem to me that the selection criteria are more stringent. The differences should at least be explained and justified. I would also think that a screening and possibly a forward search on previous meta-analyses should be part of the data collection process.

Response: Thank you for your important suggestion. We fully agree with the comment that a screening and possibly a forward search on previous meta-analyses should be part of the data collection process. We read the previous meta-analyses carefully and found that the study of Liang et al. included children and adults undergoing multiple methods of anesthesia and administration of DEX and the study of Jin et al. also included the children population. Different from the previous studies, we included the population was only the adults undergoing the general anesthesia and dexmedetomidine was administered intravenously, additionally, we excluded the RCTs that DEX compared with opioids agents. The number of included studies in our meta-analysis is lower than that of these two meta-analyses due to our more stringent selection criteria.

2. P5, L9: The search terms seem to be redundant (e.g. “nausea” should include all hits from “postoperative nausea”). Also, there should be brackets around (“nausea and vomiting”) although this is also redundant. I’m also a bit confused about the search strings in Supplement 2. The Embase search seems to be filtered by (“postoperative AND nausea AND vomiting”) and the Cochrane search by (“postoperative nausea and vomiting”). This is both more restrictive and different from the search strategy presented in the methods section. Please clarify.

Response: We fully agree with the comment that we the search terms in article were redundant and removed it in the revised manuscript. We are very sorry for our incorrect writing in the Embase search and we corrected it in the Supplement 2.

3. The analysis seems competently done. Personally, I wouldn’t make the use of random or fixed effect models conditional on the significance test for  $I^2$  – and would use a random effects model throughout – but such model selection procedures are widespread and I don’t think it makes a difference here.

Response: Many thanks for your positive comment.

4. Table 1: I would think the included studies should be properly cited and included in the reference list. (See also Item #17 from PRISMA Checklist)

Response: Thank you for your suggestion. We added the reference in Table 1.

5. Table 1: Suggest to replace “Number” by “Sample size” and “Nausea and vomiting” by “Nausea and/or vomiting”.

Response: Thank you for your comment. We revised these words in Table 1.

6. Figure captions: All captions are a bit too brief to stand alone. For example: A funnel plot of what?

Response: Thank you for your comment. We described all captions in detail in the revised manuscript.

7. Figure 2: I guess it should read: “1724 duplicates removed”. Also, I think there is a box missing for the studies excluded at the abstract screening stage. It would be good to break down exclusion by specific criteria. Finally, suggest to replace “endpoint” by “outcome”.

Response: Thank you for your comment. We revised the flow diagram in the current manuscript. Please see Figure 2.

8. Figure 3: Suggest to replace “Experimental” by “Treatment” or “DEX treatment”.

Response: Thank you for your comment. We revised all the Figures in the current manuscript.

9. Figure 8: I was looking for the axis labels, but now I see there are very small, but they are there. This could be made a bit more obvious.

Response: Thank you for your comment. We enlarged the axis labels in the revised manuscript. Please see Figure 8.

#### **VERSION 2 – REVIEW**

<b>REVIEWER</b>	Kateryna Bielka Bogomolets National Medical University, Anesthesiology and intensive care
<b>REVIEW RETURNED</b>	12-Jan-2023
<b>GENERAL COMMENTS</b>	This version of the manuscript is much more better. It could be accepted to publication.