Author’s response to reviews

Title: Adding dexmedetomidine to morphine-based analgesia reduces early postoperative nausea in patients undergoing gynecological laparoscopic surgery: A randomized controlled trial

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Author’s response to reviews:

Response letter

Q: Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Response: We thank all the reviewers for their constructive criticism and suggestions. We have addressed all the points raised by the reviewer, as summarized below.

Editor Comments:

Q: My personal comment is that you chose a primary endpoint that was somewhat ambitious, then your sample size is rather good. You failed to reach the primary endpoint, but your results provide a good estimate of the effect. The proper statement for the results in the abstract is “Although the two groups were statistically not different, either for the primary outcome, i.e. the total incidence of PONV (41% vs 52% respectively in the Dex and Crtl group), of for PONV score, time to first onset of PONV, or the need for rescue antiemetics within the first postoperative 24-hrs, the incidence of nausea and total PONV during the first 2-hrs period was lower in the Group Dex (10%) than in the Group Ctrl (25%, P=0.031).” Also mention the tolerance outcomes (even if no difference; there is a trend for more bradycardia with Dex).

Response: We are very appreciated with this important suggestion by the reviewer and re-written this part in the manuscript.
Q: Please merge Tables 1 and 2, as they both relate to outcomes not influenced by randomisation. In this part, delete the P values.

Q: Show the percentages always with 1 digit after dot.

Response: As suggested by the reviewer, we have merged Tables 1 and 2 and showed the percentages with 1 digit after dot. We keep the p value in the table, according to the article format requirements of the magazine.

Bhiken Ishwarlal Naik (Reviewer 2)

Major concerns

Q: Can the authors explain why they chose such a large effect size (50% reduction in the incidence of PONV)? This effect size has not been reproduced consistently in other studies. What would the sample size be if you chose a smaller effect size? Are you running the risk of a type II error with such a large effect size and smaller sample?

Response: As we know, strategies recommended to reduce baseline risk include: (1) The avoidance of general anesthesia by the use of regional anesthesia; (2) Preferential use of propofol infusions; (3) Avoidance of nitrous oxide; (4) Avoidance of volatile anesthetics; (5) Minimization of perioperative opioids; and (6) Adequate hydration.

In high risk population, a combination of propofol and air/oxygen (total IV anesthesia [TIVA]) could reduce PONV risk by approximately 25%. The recommended pharmacologic antiemetics for PONV prophylaxis in adults include the 5-hydroxytryptamine (5-HT3) receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, corticosteroids, butyrophenones, antihistamines, and anticholinergics. While PONV prevention is recommended, ondansetron 4 mg, droperidol 1.25 mg, and dexamethasone 4 mg were equally effective, and each independently reduced PONV risk by approximately 25%.

According to our previous study, we estimated an incidence of PONV of 50% in the control group. We assumed that dexmedetomidine could decrease the incidence of PONV by approximately 25% and effect size of 50% (from 50 to 25%) was chosen to detect whether there is a trend towards lower incidence of postoperative nausea and vomiting in the dexmedetomidine group. We are running the risk of a type I error.

Q: What was the rationale for the bolus dose at the end of surgery? You explain in the Discussion that this was likely the reason for the beneficial effects seen in the first 2 hours, but you provide no cogent reason why this bolus was performed.

Response: When dexmedetomidine is used as the sedative, a loading dose initiated over 10 minutes followed by a continuous infusion is recommended. So we administered a bolus dose at
the end of surgery as the loading dose to make sure dexmedetomidine was effective when the PCA began after surgery.

Minor concerns

1. Page 4, ln 8: change to 'first 24 hours postoperatively'
Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

2. Page 5, ln 1-2: please re-phrase this sentence. Currently does not make sense.
Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

3. Page 6, ln 39: change comma to 'coma'
Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

4. Page 6, ln 41: remove the extra &gt;
Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

5. Page 8, ln 7-8: add mmHg for the CO2 partial pressure for the US reader
Response: We have made correction according to the comments.

6. Page 9, ln 12: was tropisteron the only ant-emetic given. What happened to patients who still had PONV after this agent?
Response: We are very appreciated with this important suggestion by the reviewer. If rescued tropisetron failed to relieve the symptom, metoclopramide would be administered. In fact, no patients need additional metoclopramide in our trial.

7. Page 9, ln 26-31: There is a difference between a visual analogue scale and a numerical rating scale. You have used a numerical rating scale for this study. Please change to NRS and be consistent throughout the manuscript
Response: According to the referee’s suggestion, we have checked throughout the manuscript. In Page 8, In 46-49: We used “visual analogue scale (VAS)” to assess pain scores and In Page 9, In 5-12: we used “a four-point scale (0=none, 1=mild, 2=moderate, 3=severe)” to rate the degree of nausea. Therefore, we are very sorry that we didn’t revise the manuscript again.

8. Page 12, In 2: add the word 'who' after 'patients'

Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.


Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

10. Page 16, In 7: change patiens to patients

Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

11. In table 1 is the Risk score for PONV the Apfel score? If it is, please list it as that.

Response: We followed this suggestion and change to the manuscript was indicated in the text by highlighting.

Daniela Ghisi, MD (Reviewer 3): Summary

The topic discussed and the choice of the primary endpoint (PONV reduction in the first 24 hours) appears to be relevant from the clinical point of view, representing post-operative nausea and vomiting, a stigma for gynecological surgery. We emphasize that only myomectomy and laparoscopy-assisted vaginal hysterectomy surgeries are part of the included population.

The study aims at demonstrating how an intra-operative bolus of dexmedetomidine (0.4 mcg/kg) followed by the association of dexmedetomidine at a concentration of 1 mcg/ml in PCA with morphine 0.5 mg/ml administered in an infusion modality baseline of 1 ml/hour and boluses of 2 ml with an 8-minute lock-out may reduce the incidence of post-operative vomiting compared to morphine PCA alone without intra-operative bolus of dexmedetomidine in patients undergoing gynecological surgery with TIVA general anesthesia with the use of dexamethasone as prophylaxis for PONV.
The use of dexmedetomidine has the dual purpose of improving post-operative recovery and decreasing PONV incidence. The primary endpoint is not statistically significant since the reduction of PONV in the first 24 hours is only 21% compared to an expected 50%. The study confirms that the use of a dexmedetomidine intra-operative bolus allows to reduce PONV in the early post-operative period (first two hours). The reduction in the occurrence of PONV and the consumption of opioids, as well reported by the author, must be well weighed compared to the increase of bradycardia and sedation (dose-dependent dexmedetomidine side effect).

Response: Thank you very much for your careful and thoughtful comments. As we know, postoperative pain is mainly related to the surgical trauma. In our previous study, patients after laparoscopic ovarian and salpingectomy had less pain and half of them didn’t need intravenous patient-controlled analgesia.

To determine the effect of dexmedetomidine on morphine-based patient-controlled analgesia (PCA), we only chose patient who scheduled for elective laparoscopic myomectomy or laparoscopy-assisted vaginal hysterectomy in this trial.

Major Issues

Q: In the paragraph of the abstract concerning the methods it would be interesting to find the use of dexmedetomidine intra-operative bolus and not only the setting of the PCA (line 17, page 2).

Response: We are sorry that our previous abstract was not accurate enough. We have revised this part in the draft.

Q: In the paragraph of the abstract and the article concerning conclusions the authors presume that the addition of dexmedetomidine to morphine PCA is able to reduce the onset of early PONV. We believe that it is not possible to conclude that reduction in PONV results from the use of dexmedetomidine in PCA or the intra-operative bolus. Furthermore, as this is a secondary endpoint and the use of multiple tests is not reported in the statistical methods, we consider this result not justifiable from a statistical point of view.

Response: We administered a bolus dose at the end of surgery as the loading dose to make sure dexmedetomidine was effective when the PCA began after surgery. So we revised the conclusion to “adding dexmedetomidine to morphine-based PCA with a loading dose” to make sure our intervention more clear.

We strongly agree with the comments of the reviewers and revised the result and conclusion of the manuscript.

Q: Line 54 on page 12 points out how the reduced consumption of opiates and, therefore, of dexmedetomidine may have influenced the outcome of the study. Considering that the consumption of morphine is equal in the two groups, how could incidence for PONV decrease
without increasing the concentration and, therefore, the total volume administered of dexmedetomidine? What considerations regarding possible side effects?

Response: In our study, we found that morphine consumption during the 0-2h was not significantly different between the two groups, but the incidence of nausea was lower in the Group Dex. We attributed this to the loading dose of dexmedetomidine before the end of the surgery, since its terminal half-life is about 2h. Similar result also could be seen in our previous research (Eur J Anesthesiol 2016; 33: 761–6).

In our study, the percentage that experienced bradycardia and over sedation in PACU was significantly higher in the Group Dex. The side effects may be directly related to the dose of dexmedetomidine. So if we increase the concentration of dexmedetomidine, the potential increased risk of bradycardia and over sedation should be considered.

Minor Issues

Q: In the calculation of the sample size an incidence reduction of PONV of 50% is estimated: it would be interesting to understand from which article this data is extrapolated because it's crucial in the statistical failure of the study.

Response: As we know, strategies recommended to reduce baseline risk include: (1) The avoidance of general anesthesia by the use of regional anesthesia; (2) Preferential use of propofol infusions; (3) Avoidance of nitrous oxide; (4) Avoidance of volatile anesthetics; (5) Minimization of perioperative opioids; and (6) Adequate hydration.

In high risk population, a combination of propofol and air/oxygen (total IV anesthesia [TIVA]) could reduce PONV risk by approximately 25%. The recommended pharmacologic antiemetics for PONV prophylaxis in adults include the 5-hydroxytryptamine (5-HT3) receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, corticosteroids, butyrophenones, antihistamines, and anticholinergics. While PONV prevention is recommended, ondansetron 4 mg, droperidol 1.25 mg, and dexamethasone 4 mg were equally effective, and each independently reduced PONV risk by approximately 25%.

According to our previous study, we estimated an incidence of PONV of 50% in the control group. We assumed that dexmedetomidine could decrease the incidence of PONV by approximately 25% and effect size of 50% (from 50 to 25%) was chosen to detect whether there is a trend towards lower incidence of postoperative nausea and vomiting in the dexmedetomidine group. We are running the risk of a type I error.

In our previous research (Eur J Anesthesiol 2016; 33: 761–6), we assumed that dexmedetomidine could decrease the incidence of PONV by approximately 25% and effect size of 50%.

Q: Drug preparation for the different study groups is entrusted to a study coordinator and not to an external service.
Response: Drug preparation for the different study groups is entrusted to a study coordinator who was not involved in randomisation and drug administration, anesthesia and perioperative care and follow-up.