Author’s response to reviews

Title: The impact of dexmedetomidine added to ropivcaine for transversus abdominis plane block on stress response in laparoscopic surgery: a randomized controlled trial

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Author’s response to reviews:

Reply/Response Letter

Dear Dr. Abola,

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the editor’s and reviewers’ comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

I look forward to hearing from you soon.
With best wishes,

Yours sincerely,

Jianpin Lai

Director of Department of Nuclear Medicine, the People’s Hospital of China Three Gorges University & the First People’s Hospital of Yichang, Hubei, China.

We would like to express our sincere thanks to the editor and the reviewers for the constructive and positive comments.

Replies to Editor

Editor Comments

Methods

1. Methods: Why were these time points chosen to measure blood levels of stress hormones? Why was a measurement not included shortly after pneumoperitoneum?

Answer: In our study protocol we chose the following four observational time points: prior to induction (baseline), prior to pneumoperitoneum, prior to the end of pneumoperitoneum, and at the end of surgery. In fact, the time point of prior to induction means the period before patients receive nerve block in the operating-room. We can obtain the stress level at this time point as the baseline. Based on the results of our study (Table 2), the baseline stress levels were consistent across the groups. We have focused on the effect of pneumoperitoneum on stress response of body in our design. Therefore, we chose about 5 minutes before pneumoperitoneum as an observational time point to detect the stress level before pneumoperitoneum. About 1 hour later, pneumoperitoneum was terminated. Before termination, the stress level was detected again indicated as the changing after pneumoperitoneum. At the end of surgery, there were no surgical stimulus, and endotracheal tube was extubated. We have detected the stress level with no intervention and observed the recovery status.

If a measurement was included shortly after pneumoperitoneum, it would provide more perfect change trend of stress level induced by pneumoperitoneum. It perhaps was another limitation in our study. To our surprise, the results of our research were not affected by the limitation.
Discussion

1. Please comment on what affect laryngoscopy/intubation may have had the stress response and whether this is a potential confounder of your results.

Answer: Laryngoscopy/intubation may also produce the strong stress response during the general anesthesia. In our anesthesia protocol, lidocaine (1.5 mg/kg) and remifentanil (1-2 µg/kg) were single intravenously administrated to decrease the stress response 60 seconds before placement of laryngoscopy. In addition, all patients in each group have undergone the same anesthesia protocol with the same anesthesiologist. In my opinion, the potential effect induced by laryngoscopy or intubation on the results should be minimized.

2. Please comment on your thoughts on how dexmetomidine is blunting the stress response - does this blunt the response to pneumoperitoneum or to surgery and tissue injury?

Answer: The excitability of sympathetic-adrenal medullary system increases when the body is in a state of stress, which results in sympathetic nerve stimulation and catecholamine hormone secretion including norepinephrine and epinephrine. As a highly selective alpha-2 agonist, dexmedetomidine has potent sympatholytic, analgesic, and sedative properties, mediated through α2-adrenoceptors in the central and peripheral nervous systems, in autonomic ganglia at pre-and post-synaptic sites, and at the locus coeruleus, which contributes to inhibition of sympathetic nerve and decreasing release of catecholamines. In our study, the analgesic effect induced by TAP block with ropivacaine and dexmetomidine maybe also blunt the response to pneumoperitoneum or to surgery and tissue injury.

3. Why do you think you are seeing a decreased stress response? Is this from a systemic affect of DEX or are you potentiating the effect of your local anesthesia TAP block with DEX?

Answer: Compared with Control (no TAP block no DEX), Ropivacaine (no DEX), and Low DEX + ropivacaine groups, the levels of detected stress response indicators were reduced during and after surgery in Medium and High DEX + ropivacaine groups. Generally, the stress response can be controlled by enhancing the depth of anesthesia and the intensity of analgesia. In our study, we found that the consumption of propofol and remifentanil during the surgery were significantly low in Ropivacaine, Low, Medium, and High DEX + ropivacaine groups compare with the Control group. So we think that the stress response is decreased in the observation groups.

It is not clear whether the decreased stress response results from a systemic affect of DEX or the effect of local anesthesia TAP block with DEX. In my opinion, there is a combined role from a systemic effect of DEX and the local effect of TAP block with DEX.
4. Please comment on whether your time points for stress hormone blood draws can adequately measure the body's stress response during surgery?

Answer: The time point of prior to pneumoperitoneum reflects the effects of incision and laryngoscopy/intubation, even or the TAP block on stress response. The time point of prior to the end of pneumoperitoneum reflects the whole surgical effect including pneumoperitoneum and pain on stress response. The time point of at the end of surgery mainly shows the impact of pain and extubation on stress response. Therefore, the above time points for stress hormone blood drawn can adequately detect the body's stress response during surgery. In fact, there was a strong stress response during the surgery as showed in Table 2.

5. I would add a paragraph that highlights the strengths of your study: single surgeon for all patients, single anesthesiology for all TAP blocks, assessment of TAP block prior to induction of anesthesia, standardized protocol for anesthesia and intraoperative analgesics. Highlighting these allows you to further your argument that the differences you are seeing in stress hormones are related to your intervention.

Answer: I have added this paragraph in Method section: “In order to minimize the effect of non-research factors on results, the same surgeon team served for all patients, and the single anesthesiologist served for all TAP blocks and assessment of TAP block prior to induction of anesthesia. And there was a standardized protocol for anesthesia and intraoperative analgesics in this study.”(Method section, line 193-196, page 9)

Conclusion

1. Please consider adjusting the wording of your conclusion. Suggestion: The addition of dexmedetomidine at the dose of 0.5 mcg/kg into ropivacaine for ultrasound guided transversus abdominis plane block is the optimal dose to inhibit stress response with limited impact on or blood pressure and heart rate in patients undergoing laparoscopy gynecological surgery.

Answer: The Abstract’s conclusion section has been rewritten as “The addition of dexmedetomidine at the dose of 0.5 µg/kg into ropivacaine for ultrasound-guided transversus abdominis plane block is the optimal dose to inhibit stress response with limited impact on blood pressure and heart rate in patients undergoing laparoscopy gynecological surgery.”(Abstract section, line 64-67, page 3-4)

The conclusion section of Discussion has also been rewritten as “In conclusion, the addition of dexmedetomidine as an adjunct at the dose of 0.5 µg/kg into ropivacaine for ultrasound-guided transversus abdominis plane block is the optimal dose to inhibit stress response with limited impact on blood pressure and heart rate in patients undergoing laparoscopy gynecological
surgery. Future studies are needed to evaluate the efficacy of addition of dexmedetomidine to peripheral nerve blockade for more involved and painful procedures such as open surgery or the other types of surgery.” (Discussion’s conclusion section, line 370-375, page 17-18)

Misc:
1. Please remove P values from Table 1 - patient characteristics. This is not necessary.
   Answer: P values from Table 1 - patient characteristics has been deleted. (Table 1 section)

2、Title: it is generally recommended that the findings of the study are not within the manuscript title. A possible suggested title would be "The impact of dexmedetomidine added to ropivicaine for transversus abdominis plane block on stress response in laparoscopic surgery: a randomized controlled trial."
   Answer: The manuscript title has been already changed to "The impact of dexmedetomidine added to ropivicaine for transversus abdominis plane block on stress response in laparoscopic surgery: a randomized controlled trial." (Title page section, line 2-3, page 1)

Replies to Jacek Smereka (Reviewer 1)
I suggest including the following articles in the discussion:

   Answer: This article has been included as reference 32 in the discussion section. (Discussion section, line 349, page 16)

   Answer: This article has been included as reference 31 in the discussion section. (Discussion section, line 350, page 16)
Replies to Rabie Soliman (Reviewer 2)

Methodology

1- There was group without DEX to TAP block and other with DEX to TAP block; The block itself induces a stress response during interventions

A- Do you measure baseline level of stress hormones before and after the block before induction of anesthesia? How to clarify how to solve this issues?

B- You did the block and then induction of anesthesia was started: the block to be effective you have to wait 20-30 minutes: You measured the levels before the pneumoperitoneal: Please you have to measure after laryngoscopy and intubation as there one of the most common cause of stress response during GA.

C- The highest peak of hormones during and few minutes after pneumoperitoneal: Why you did not levels during this times: Why you waited to take levels just before pneumoperitoneal: I think that is so necessary.

Answer: Please refer to Answer to the Editor’ comment: Methods 1; Discussion 1 and 4.

Results

1、There is no difference regarding the awareness duration in spite of the dose of propofol and remifentanil if highest in the control group, do you have an explanation?

Answer: Both propofol and remifentanil are short-acting medications. After they are discontinued, generally patients recover soon from the anesthesia even though with higher dosage during the surgery.

3、The bradycardia is higher with DEX: also the remifentanil induces bradycardia: there was no bradycardia in the control group in spite of the dose of propofol and remifentanil if highest in the control group, do you have an explanation?

Answer: Generally speaking, there is no significant effect on heart rate when both propofol and remifentanil are constantly infused at a relative low speed.

4、The DEX was given after intubation and one of the most common cause of stress response during GA is laryngoscopy and intubation you how to clarify how to solve this issues?
Answer: Please refer to Answer to the Editor’ comment: Methods 1. In addition, the DEX was given before intubation, not after intubation in our study.

5、The stress response during distension of the abdomen as a result of pneumoperitonium and CO2 absorption how DEX in local block affect this response? Please clarify.

Answer: Please refer to Answer to the Editor’ comment: Discussion 3.

6、If you are talking about the stress response of pneumoperitoneal:: You have to measure the levels before during after or every 30 minutes and not after 30 minutes after pneumoperitonium and before the end of pneumoperitoneal as you have to know the half life of most stress hormones is minutes?

Answer: Please refer to Answer to the Editor’ comment: Discussion 4.

7、Please you can modify your research to focus about the analgesic effect of DEX with TAP and not the stress as your data is insufficient about the stress response during pneumoperitonium.

Answer: A few comments have been added to discuss the stress response in the manuscript. (Discussion section, line 314-317, page 15; line 324-336, page 15-16)

7、Otherwise you have to give DEX IV to assess the stress response during pneumoperitonium.

Discussion

1、You are talking about the effect of DEX and local block::and not talking about the stress response, you did not determie whether the DEX was given IV or local?

Answer: In the manuscript, the effect of DEX and local block, and the stress response all of them have been already discussed, including DEX given IV or local.

2、What is written in discussion not related to the title {Dexmedetomidine added to ropivacaine for transversus abdominis plane block inhibits stress response in laparoscopic surgery: a randomized controlled trial. Please you have to re-write the discussion again according the title.

Answer: A few comments have been added to discuss the stress response in the manuscript. (Discussion section, line 314-317, page 15; line 324-336, page 15-16)

The other revision

The institution of authors including Zhaojun Qin, Chunyan Xiang, Tingting Liu, Leyun Zhan, Min Zhang, Jianpin Lai has two different names which have been revised in the manuscript. The new name is the People’s Hospital of China Three Gorges University & the First People’s Hospital of Yichang, Hubei, China.