Author’s response to reviews

Title: Preoperative versus postoperative ultrasound-guided rectus sheath block for improving pain, sleep quality and cytokine levels in patients with open midline incisions undergoing transabdominal gynecological surgery: A randomized-controlled trial

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Author’s response to reviews:

Dr. Guangde Tu
Editor-in-Chief
BMC Anesthesiology

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Dear Dr. Klein:

Thank you for your kind letter and helpful advice regarding our manuscript. We have carefully revised the manuscript in accordance with the reviewers’ comments. The revised manuscript includes new line and page numbers. Below are our point-by-point responses to reviewers’ comments.

Best Regards.

Yours Sincerely,

Wen-fei Tan
Reviewer reports:

(Reviewer 1): The authors have submitted a RCT regarding the use of RSB for open gynecological procedures.

I have the following comments/ questions for the authors.

In paragraph 3 of the introduction the authors talk about comparing location of injection and timing. I do not think the discussion about location of injection is relevant to this manuscript and should be removed.

Response: Thank you for your advice. We have now removed this section.

The authors also state that "However, little information is available about the effect of RSB on sleep quality and the inflammatory response during the immediate postoperative period." But as this study has not control group( no RSB with local infiltration) the author cannot compare these findings to a group without a rectus sheath block and so cannot comment on this question they raise.

Response: The reviewer is correct. Our main point is highlighted by the last sentence: “In particular, there is no information about whether preoperative block or postoperative block will benefit patients.”

The authors have not stated their objectives clearly. The introduction ends with "We hypothesized that performing RSB after surgery would result in a longer duration of analgesic effects and have a subtle influence on sleep time after surgery” > Please state what is primary and what are secondary hypotheses. Also state what is the null hypothesis ( no difference) and alternate hypothesis. The above statement is a combination of both with not a well-defined null hypothesis or a set of objectives.

Response: The reviewer is correct. Thank you for the advice. The primary and secondary hypotheses are stated in the paragraphs below. The null hypothesis is that there is no difference between performing RSB before and after surgery.

Another set of objectives are stated in the methods "The objective of the trial was to evaluate the postoperative pain, sleep quality and changes in cytokine levels of patients undergoing gynecological surgery with RSB performed preoperatively versus postoperatively." You have listed a different list of primary and secondary objectives in study outcomes. Please remove all other objectives or hypothesis references and be consistent with the hypothesis. Is the primary objective the hypothesis as well?
Response: The reviewer is correct. Thank you for the advice. We have removed all other objectives and references to the hypothesis.

What surgical procedure were included? Please list them.

Response: Thank you for your advice. We have now listed the procedures in the inclusion criteria.

For the power calculation please provide the effect size (ES) as you have used it for the sample size calculation. Also the sample size was 32 per group (64 total) but the final evaluable was 61 was this study underpowered. Please report the power for this sample size. Why did the authors not add more subjects after the loss to follow-up events or account for some loss to follow-up (about 10%) is seen in many RCTs.

Response: The effect size (ES) was 0.712. We did not randomize 10% of the patients in each group in the real trial to ensure that we have an adequate sample size due to the limitations in funding. Thank you very much for reminding us. Group sample sizes of 30 and 31 achieve 85% power to detect a difference of 17.6 between the null hypothesis and the alternative hypothesis. The group means were 211.5, and the alternative hypothesis was that the mean of group 2 would be 229.1 with known group standard deviations of 35.3 and 42.1 and a significance level (alpha) of 0.05000 using a one-sided two-sample t-test with PASS11 software (NCSS LLC, Utah, USA).

For the VAS scores and oxycodone use in the 2 time intervals why are medians and IQR reported. Please present means and 95% CI for all the variables. Also please report the difference in means and CI for the difference in means for the primary and secondary objectives for all continuous variables.

Response: The VAS scores and oxycodone use in the 2 time intervals are reported as medians and IQR because the results are not normally distributed. Thank you for your advice. We reported the difference in means and CI for the difference in means for the primary and secondary objectives for all continuous variables.

For the inflammatory markers can you provide details on the clinical significance of the differences in levels for IL-6 found between the 2 groups. Also the marker discussed in the discussion is IL-6; what is the clinical significance of the other 3 markers? The IL-1 and INF seem different at baseline between the 2 groups, what is the implication of that?

Response: The information on the inflammatory markers is shown below.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>GRO PRE</th>
<th>GRO POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>6.4 ± 0.1</td>
<td>6.4 ± 0.1</td>
</tr>
<tr>
<td>INF</td>
<td>9.9 ± 0.1</td>
<td>10.3 ± 0.3</td>
</tr>
<tr>
<td>TNF</td>
<td>5.7 ± 0.8</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>IL-6</td>
<td>5.1 ± 0.5</td>
<td>4.9 ± 0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative</th>
<th>GRO PRE</th>
<th>GRO POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>6.4 ± 0.1</td>
<td>6.5 ± 0.1</td>
</tr>
<tr>
<td>INF</td>
<td>10.0 ± 0.2</td>
<td>10.2 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>24h</td>
<td>48h</td>
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<tr>
<td>------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>TNF</td>
<td>5.9 ± 0.4</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>IL-6</td>
<td>6.1 ± 0.1</td>
<td>12.2 ± 5.2</td>
</tr>
<tr>
<td>IL-1</td>
<td>6.5 ± 0.1</td>
<td>6.4 ± 0.1</td>
</tr>
<tr>
<td>INF</td>
<td>10.0 ± 0.1</td>
<td>10.0 ± 0.2</td>
</tr>
<tr>
<td>TNF</td>
<td>5.7 ± 05</td>
<td>5.5 ± 0.7</td>
</tr>
<tr>
<td>IL-1</td>
<td>12.2 ± 5.2</td>
<td>12.2 ± 5.2</td>
</tr>
<tr>
<td>INF</td>
<td>10.0 ± 0.1</td>
<td>10.1 ± 0.1</td>
</tr>
<tr>
<td>TNF</td>
<td>5.7 ± 05</td>
<td>5.7 ± 0.9</td>
</tr>
<tr>
<td>IL-6</td>
<td>15.1 ± 1.6</td>
<td>19.1 ± 6.8</td>
</tr>
<tr>
<td>IL-1</td>
<td>6.6 ± 0.2</td>
<td>6.5 ± 0.1</td>
</tr>
<tr>
<td>INF</td>
<td>10.2 ± 02</td>
<td>10.1 ± 0.1</td>
</tr>
<tr>
<td>TNF</td>
<td>4.5 ± 0.9</td>
<td>4.7 ± 1.2</td>
</tr>
<tr>
<td>IL-6</td>
<td>19.1 ± 6.8</td>
<td>19.1 ± 6.8</td>
</tr>
</tbody>
</table>

In this trial, the preoperative RSB not only exhibited stable hemodynamics, as shown by the monitoring data, but also inhibited the upregulation of all cytokines tested, specifically IL-6. Clinically, the other 3 markers are all factors that influence sleep, but we will discuss these markers in future trials. IL-1 and INF are not different at baseline between the 2 groups.

The authors mentioned that the patient in the pilot study reported discomfort with the urethral catheter and suggested methods to alleviate this. Were these strategies deployed in the study patients. If urethral catheter was used did it stay in place for all patients for the first 48 hours postoperatively? Did any of the patients report discomfort from it? How did this effect the sleep and IL-6 levels?

Response: All of these strategies were used in the study patients. Urethral catheters stayed in place for all patients for the first 24 hours postoperatively without any complaints.

In the conclusions the authors have not mentioned the lack of difference in time to rescue, pain scores and opioid use which were the primary and secondary objectives listed. Please add these and discuss the importance of these findings that were observed between the 2 groups.

Response: The reviewer is correct. Thank you for the advice. We have now rewritten the conclusion.

(Reviewer 2): This study highlights a very interesting issue about timing of rectus sheath block. Nevertheless, does not offer a clear answer.

Post-operative sleep quality is a complex topic and the cytokines correlation it appears to be only one of the variables to take in consideration. The study has a couple of major limitations that need to be clarified:

- The title is too much generic. Please reformulate the title in order to indicate better the aim of the study.

Response: The reviewer is correct. Thank you for the advice. We have now rewritten the title.
- In Background paragraph of the abstract there is not a "background" of the study, but the aim of the study. Please rewrite this passage.

Response: The reviewer is correct. Thank you for the advice. We have now rewritten this section.

- I have an issue about masking. In order to explain the operator masking, could you please specify who else knew about the group allocation of the patient and who was in charge of "blind" drug/saline preparation?

Response: The reviewer is correct. All of the patients, the anesthesiologist performing the block, and the staff involved in postoperative data collection and analyses, were blinded to the group allocations. There was another anesthesiologist who knew about the group allocation of the patients and who was in charge of drug preparation.

- Please specify the timing of blood samples for inflammatory cytokines. In the text it is not clear if the baseline blood sample was taken before induction, after induction before RSB, after RSB before the surgical incision or after. "During operation" is too generic.

Response: Thank you for your advice. We have added “prior to induction” in the paper.

- Redundant methods notes in patient paragraph

Response: Thank you for your advice. We have deleted some of this information.

- PSQI was measured one day before the surgery reflecting the difference between good sleepers and poor sleepers, but have you considered also the preoperative night's sleep?

Response: PSQI (one month before surgery) was measured one day before the surgery, reflecting the difference between good sleepers and poor sleepers. There is no data of sleep quality during the night prior to the operation, and we will pay attention to this factor in future trials. Thank you.

- Do you have BIS data of the preoperative night?

Response: There is no BIS data of sleep quality for the preoperative night. We will pay attention to this factor in future trials. Thank you.

- Are OSAS patients excluded by this study?
Response: There were no OSAS patients excluded from this study.

- In "BIS-AUC and sleep…" paragraph, page 14, why do you mention a "Propofol group"? It was not mentioned in the anesthetic description. Please correct or clarify.

Response: Thank you very much. That description is indeed incorrect, and we have now corrected it.

- Does the sample size calculated on sleep effects of the pilot study differs substantially from the sample size calculated for this study?

Response: Group sample sizes of 30 and 31 achieve 85% power to detect a difference of 17.6 between the null hypothesis. The group means were 211.5, and the alternative hypothesis was that the mean of group 2 would be 229.1 with known group standard deviations of 35.3 and 42.1 and a significance level (alpha) of 0.05000 using a one-sided two-sample t-test with PASS11 software (NCSS LLC, Utah, USA). The sample size calculated on sleep effects of the pilot study is powerful.