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Peer Review File

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Reviewer A

Comment:

First of all, I am very sorry for the late review. I read the work by Miyoshi and colleagues entitled: "Impact of fentanyl on acute and chronic pain and its side effects when used with epidural analgesia after thoracic surgery in multimodal analgesia: A retrospective cohort study.". The authors presented a retrospective cohort study demonstrating that the addition of fentanyl to epidural anesthesia reduced acute pain and increased the incidence of hypotension and pruritus but did not affect that of post-thoracotomy pain syndrome in multimodal analgesia management. Although the paper may contain some interesting findings, I do not think that these findings are original or clinically meaningful. The improvement of pain and possible side effects caused by epidural opioids are well-known facts. It is difficult to confirm how much pain improvement by epidural FTN or the incidence of complications is clinically important to patients with this study alone. One interesting finding in this article is that there is no difference in PTPS incidence in both groups. However, PTPS should be assessed in consideration of surgical procedures as well as postoperative pain management, so I think it is a difficult topic to judge retrospectively.

Reply:

Thank you for your careful peer review and helpful comments. We are thankful for the time and energy you expended. As you point out, the side effects of epidural opioids have been investigated for a long time. And part of our research results did not deviate significantly from the results expected from past studies. As a new perspective, we examined the effects and side effects of epidural fentanyl in patients undergoing multimodal analgesia with NSAIDs. And, there are not many studies on thoracic surgery. We believe that these perspectives are novel. Regarding PTPS, as shown in the method, we limited the target patients to video-assisted thoracoscopic surgery and confirmed that there was no change in the composition of the surgery team and the pain management protocol of the ward. However, we think it is necessary to consider more detailed surgical contents as you point out. Unfortunately, our study is retrospective and cannot examine the details of surgery. This is the limit of our research. We believe that some of our findings are useful.

Changes in the text: There are no corresponding changes to the comments.

Reviewer B

Comment:

Authors presented a retrospective study comparing patients who received epidural anesthesia with fentanyl (F) in 2014 to 2016 to patients who had epidural anesthesia without fentanyl between 2016 and 2017. Some details were left out which precludes the reader to make some judgements about the study results. Please see my more specific comments below.

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Reply: Thank you very much for peer review of our manuscript and providing important comments. We are thankful for the time and energy you expended. We carefully read the comments of you and made corrections. We hope you will be satisfied with the revised manuscript and responses.

Comment 1: At the end of the introduction section on page 5, please also state study hypothesis.
Reply 1: Thank you for your advice. We add a research hypothesis at the end of the introduction.
Changes in the text: We followed your advice and added the hypothesis. (see Page 5, line 87-89)

Comment 2: According to page 7 line 119 – 121 (P7L119-121), patients in 2 groups were enrolled at different time points. Please elaborate in the Discussion section if there were any differences on the patient care in general at that time interval. Also mention this in the limitations section.
Reply 2: As you point out, we need to add an explanation for study period bias. There were no changes in the main member of surgeons during the study period. (We describe it in the Methods, Page 6, Line 104-105) In addition, we determine postoperative pain management policies through consultation between surgery and anesthesiology. There were no changes other than the epidural anesthesia menu during this period.
Changes in the text: We have added these to the Methods section (see Page 6, line 106-108) and Limitations (see Page 14, line 262-264).

Comment 3: P8L153: Please add a sentence regarding the decision of using parametric vs a non-parametric test. Such as conducting a test of normality or assessing the quantile- quantile plots.
Reply 3: We apologize for the inadequate evaluation of the distribution of the data. We used the t-test to analyze height, weight and age. However, when these data were confirmed by the Shapiro-Wilk test, they were found to have a non-normal distribution. Therefore, we have changed the analysis of all quantitative variables data to the Mann-Whitney U test. Due to this change, we have removed the "t-test" from the statistical analysis section.
Since we only analyze the data using the Mann-Whitney U test, we don't think it is necessary to describe how to determine parametric and nonparametric. However, we can add a description if needed.
Changes in the text:
We have removed the "t-test" from the statistical analysis section. (see Page 9, line 169)
We have changed some of the parameter values in Table 1. (see Page 21, line 379, Table 1)

Comment 4: In the Statistical Analysis section, please mention how the study sample size was selected.
Reply 4: We apologize for not mentioning how the sample size and study period were determined. We calculated the sample size by G*power3.1.0 software based on the pilot data. We have added a description about the sample size to the Statistical Analysis section.

Changes in the text:

We have added the sentence to the beginning of Statistical Analysis section. "The sample size was calculated using G*Power 3.1.0 (Heinrich Heine University Düsseldorf), and the number of patients required to detect a difference in resting VAS was calculated to be 130 per group with an α error of 0.05 and 1-β error of 0.8. Since the number of thoracic surgery cases was about 100 per year, a 2-year study period was set for each group." (see Page 9, line 164-167)

Comment 5: According to P9L163, 142 patients in group F and 140 patients in group N were included. Please clarify if all the patients who were eligible were included in the study and by chance authors ended up having almost equal number of subjects in each group, or was there any patient selection process? If the latter, please provide more details.

Reply 5: First of all, we determined the study period based on the calculated sample size. We apologize for not fully explaining how the cases were collected. The numbers of cases in both groups are very close because we are comparing the same procedure over similar study periods. In addition, we do not select patients by any criteria other than this selection criterion, as we show in the Methods section regarding patient selection for study. We have already revised the text in relation to Comment 4 regarding these matters, so we have not revised the text for Comment 5.

Changes in the text: There is no corresponding changes to the comment.

Comment 6: In the Statistical Analysis section, please clarify what was the primary outcome variable of the study.

Reply 6: Thank you for your advice. As you point out, we didn't show what we analyzed.

Changes in the text: We added the primary outcome variable of the study at the beginning of the statistical analysis section. "We used univariate analysis to compare the study factors between the two groups with and without fentanyl for PCEA." (see Page 9, line 168-169)

Comment 7: Authors compared multiple outcomes at multiple time points between the two groups, but used type I error rate of 0.05 as significance criterion. Not making any adjustment for multiple comparisons inflates the overall type I error rate of the study. Please maintain an overall alpha level (chance of type I error) of 0.05 by using an adjustment method for multiple testing. If not, please mention this in the limitations section.

Reply 7: As you point out, we had to consider type I error rate for the data in Table 2. In the revised text, we performed Bonferroni correction for the pain VAS score (both resting pain and movement pain), the number of bolus administration, and the use of adjuvant analgesics to adjust the multiplicity. With these corrections, we have corrected the p-values.

Changes in the text:

We have added to the Statistics section that we have made corrections to Bonferroni correction. (see Page 9, line 171-173)

We have changed the p-value in Table 2. (see Page 22, line 386, Table 2)

Comment 8: P9L163 – 164: The sentence is not clear.

Reply 8: As you point out, this sentence is ambiguous. This sentence means that all patients

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needed adjuvant analgesics during the observation period up to 3 days after surgery.
Changes in the text: We have modified our text as "All patients required adjuvant analgesics during the observation period up to 3 days postoperatively." (see Page 10, line 181-182)

Comment 9: P9L172: According to Table 2, group F had a LESS (not more) bolus requests than group N did. Please be consistent.
Reply 9: Thank you for your advice. This is our mistake.
Changes in the text: We have modified our text as advised (see Page 10, line 190)

Comment 10: P13L238: please indicate retrospective study design here.
Reply 10: Thank you for your advice.
Changes in the text: We have modified our text as advised (see Page 14, line 256)

Comment 11: P13L239: please say "multivariable" (multiple independent variables) instead of "multivariate" (multiple responses per subject).
Reply 11: Thank you for your advice.
Changes in the text: We have modified our text as advised (see Page 14, line 257)

Comment 12: Tables 1, 2 and 3: It is not clear which test was used for which comparison.
Reply 12: Thank you for your advice. We did not state which statistical test was used. As you point out, we need to add statistical tests we used. We used the Mann-Whitney U test for quantitative variables and the Chi square test for categorical variables.
Changes in the text: We added which statistical test was used to table legend each table. (see Table1, Page 21, line 380-382, Table 2, Page 23, Line 389-391, table3, Page 24, line 399-400, table4, Page 25, line 405)