Peer Review File

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Response to the Review Comments A:

Comment 1: My principal concern is that the authors have specified clearly the primary outcome, time until ready for PACU discharge L149. The authors' power analysis was based on a 30% difference in the duration of PACU stay. Yet, the authors have not shown that L192 difference was clinically important, where clinical importance was defined by the power analysis. Total time of many patients in PACU depends on the sum of individual times. Therefore, it is indeed the ratio of means that matters. Calculate 95% confidence interval for % mean reduction, matching the planned analysis. If the logarithms are not normally distributed in the two groups, the authors can use: Ledolter J, Dexter F. Analysis of interventions influencing or reducing patient waiting while stratifying by surgical procedure. Anesthesia & Analgesia 112:950-957, 2011. There is only 1-strata unlike in that paper, but it applies fully. If the logarithms are reasonably close to normally distributed, then the authors can use: Ledolter J, Dexter F, Epstein RH. Analysis of variance of communication latencies in anesthesia: Comparing means

of multiple log-normal distributions. Anesthesia & Analgesia 113:888-896, 2011. The authors have 2-groups unlike in that paper, but it applies fully. Show whether a 30% difference or not. Include the CI for primary outcome in abstract and in Results.

Reply 1: Thanks for our reviewer's excellent comments. In some previous studies [1. Jo YY, Lee D, Jung WS, Cho NR, Kwak HJ. Comparison of intravenous dexmedetomidine and midazolam for bispectral index-guided sedation during spinal anesthesia. Med Sci Monit 22:3544-3551, 2016. 2. Elsersy HE, Metyas MC, Elfeky HA, Hassan AA. Intraoperative magnesium sulphate decreases agitation and pain in patients undergoing functional endoscopic surgery: a randomised double-blind study. Eur J Anaesthesiol 34:658-664, 2017. 3. Eskander JP, Rapoport Y, Cornett E, Gennuso S, Franklin M, Kaye AD, Fox CJ. Does promethazine shorten the length of stay in the post anesthesia care unit? J Perioper Pract 28:194-198, 2018], the authors concluded that the mean length of PACU stay was decreased by 26.1-38.2%, which was statistically significant. So, in our study, we defined a 30% difference in the duration of PACU stay as clinical significance. According to the pilot experiment with a sample size of 10 patients in each group, we obtained the mean difference between two groups: 7.9 min. Based on the intention-to-treat principle, power of analysis calculation ($\alpha = 0.05$ and $1 - \beta = 0.8$) showed that 38 patients were required to detect a difference in mean standard deviation (SD) of length of PACU stay. To allow for a 10% patients dropout, 50 patients should be enrolled in each group. In our study, we eventually enrolled 99 patients, which was sufficient for definite results. **Changes in the text:** According to our reviewer's advice, we expressed the data of length of PACU stay as mean with 95%

confidence interval (CI). Compared with propofol, remifentanil administered during analepsia showed a reduction in the length of PACU stay (62 min [60.75 – 69.29 min] vs. 49 min [46.47 - 51.06 min], *P*< 0.001). We have included the CI for primary outcome in abstract and in Results section of the text (see Page 2, line 41-42; Page 10, line 195).

Comment 2: L192 and elsewhere, please report the actual P-value unless P < 0.0001. The authors have multiple comparisons but did not make adjustment for that. It seems unnecessary provided the authors provide to the readers the information that they could do so on their own in the future. That is not so, for example, from L192.

Reply 2: We appreciate our reviewer's excellent comments. According to the suggestion, we have reported the actual P-value. During our multiple comparisons, P-values were calibrated to determine whether they were statistically significant in abstract and in Results section of the revised manuscript.

Changes in the text: As advised, we have reported the actual P-value unless P < 0.0001 in abstract and in the section of Results (see Page 2, line 42, 44; Page 3, line 45-46; Page 10, line 195, 197-198, 200).

Comment 3: L1 Add to title or first sentence of abstract that there is tracheal extubation in the PACU.

Reply 3: Thanks for the recommendation of the reviewer. As suggested, we have added to the title and the first sentence of abstract to illustrate that tracheal extubation is often

performed in PACU in the revised version.

Changes in the text: We have added “injected during analepsia” to the title (see Page 1, line 1). We have added “To guarantee efficient operating room activity, tracheal extubation is often performed in post-anesthesia care unit (PACU).” in the abstract of the revised manuscript (see Page 2, line 22-23).

Comment 4: L66 and L219, and elsewhere, when referring to workflow from OR into PACU, rely on studies of such workflow. The principal one that will mitigate the authors' statements probably is: Marcon E, Dexter F. An observational study of surgeons’ sequencing of cases and its impact on postanesthesia care unit and holding area staffing requirements at hospitals. Anesthesia & Analgesia 105:119-126, 2007. See the references. The authors' implications depend on the selection of PACU staffing and on case sequencing in operating rooms. This in no way mitigates the value of the authors' work, just interpretation economically.

Reply 4: We appreciate our reviewer’s excellent comments. It is true that duration of PACU depends on PACU staffing and case sequencing. To observe the effect of propofol/remifentanil on the length of PACU stay, we only recruited the patients undergoing laparoscopic surgery for endometrial cancer surgery by the same surgeon group.

Changes in the text: None.

Comment 5: L131 refers to Figure 1 showing extubation in the PACU. State this and

refer to your very clear Figure 1 around L91.

Reply 5: Thanks for the recommendation of the reviewer. It was our negligence that we didn't state the work flow clearly. In our center, to guarantee efficient operating room activity, the intubated patients are routinely transferred into the PACU, waiting for fully recovery and extubation. We have done some modification in the Methods section of the text, Figure 1 and the legend of Figure 1.

Changes in the text: To better state the work flow in the PACU including anesthetic intervention, time to extubation and time to discharge, we have done some modification in the Methods section of the text, Figure 1 and the legend of Figure 1 (see Page 7, line 129-131; Page 21, line 399-403).

Comments 6: Figure 3 page 20 add explanation for the feature of the Box and Whisker plot on the left (e.g., hinges?). There are multiple versions.

Reply 6: Thanks for our reviewer's excellent comments. In Figure 3, the Box and Whisker plot on the left represent range interquartile and the outliers respectively.

Changes in the text: As advised, we added the relevant description in the legend of Figure 3 (see Page 21, line 412-413).

Response to the Review Comments B:

Comment 1: Title: Please explain when exactly remifentanil was administered

Reply 1: Thanks for our reviewer's excellent comments. Laparoscopic procedures are

the main surgical treatment in patients with endometrial cancer. Deep muscle relaxant is often required to maintain sufficient abdominal capacity at a low pneumoperitoneum pressure, consequently decreasing side effects of laparoscopy and leading to enhanced recovery after surgery. However, due to the short interval between the laparoscopic procedure and the last stitch, many patients may suffer from relative deep relaxant effects in spite of neuromuscular block monitoring. Therefore, to guarantee the efficiency of operation room, the patients were routinely transferred to PACU for emergence and extubation. During the period of PACU stay, sputum aspiration was performed, if the patient moved unconsciously or the hemodynamic parameters increased more than 30% of the baseline, without meeting the criteria of extubation, 1μg/kg remifentanil was injected to deepen the sedation and reduce the agitation.

Changes in the text: As suggested, we have modified the title (see Page 1, line 1).

Comment 2: Abstract: Please state clearly WHEN the bolus of propofol/remifentanil was administered 'If the hemodynamic parameters fluctuated more than 30% of the baseline, or patients moved unconsciously...' What does this mean exactly? Was for example hypertension treated with propofol/ remifentanil? Was an agitated patient (moved unconsciously…) sedated with the same?

Reply 2: Thanks for our reviewer's excellent comments. When the patients entered the PACU, endotracheal suctioning was performed. Many of the patients may suffer from hemodynamic fluctuation or conscious body movement caused by light anesthesia and relative deep relaxation (without reaching the criteria of extubation). We would inject

propofol/remifentanil to deepen the sedation and reduce the agitation, other than to treat hypertension simply.

Changes in the text: To state clearly when and why the bolus of propofol/remifentanil was administered, we have modified the abstract (see Page 2, line 22-23, 29-31, 32-33).

Comment 3: Introduction 'However, many patients may suffer from residual muscle relaxant effects when transferred to post-anesthesia care unit (PACU)… In such clinical settings, rescue anesthetic, such as propofol, is often used to smooth extubation and optimize emergence': Residual muscle relaxation can be avoided by systematically using neuromuscular monitoring (TOFF ratio) as is advised by many anesthesia societies. In parallel, neostigmine/ suggamadex can be used for reversal… This avoids the problem of propofol bolus altogether…

Reply 3: Thanks for our reviewer's excellent comments. It is true that residual muscle relaxation can be avoided by systematically using neuromuscular monitoring (TOF ratio) as advised by many anesthesia societies. Clinically, deep muscle relaxant is often required to maintain sufficient abdominal capacity at a low pneumoperitoneum pressure, consequently decreasing side effects of laparoscopy and leading to enhanced recovery after surgery. However, due to the short interval between the laparoscopic procedure and the last stitch, many patients may suffer from relative deep relaxant effects (TOF< 0.7, without reaching the time of neostigmine use) in spite of neuromuscular block monitoring. Actually, 87 of 200 patients recruited in our study were successfully extubated without need of intervention agents. Ultimately, a total of 99 patients who

didn't meet the extubation criteria were to receive propofol/remifentanil. Although, neostigmine can be used for reversal of muscle relaxation, but it is best used only if TOF reaches 0.7. Sugammadex is very expensive in China, which is not suitable for routine use.

Changes in the text: To clearly illustrate our purpose, we made some modification in the sections of Introduction and Methods (see Page 4, line 58-62; Page 7, line 125).

Comment 4: 'This prospective clinical trial compared the effects of remifentanil and propofol, used during emergence, on length of PACU stay for patients undergoing laparoscopic surgery for endometrial cancer.' I am confused about the reason why this trial was conducted. I am not convinced about the necessity of giving remifentanil/propofol in the PACU for the reasons mentioned in the introduction. (If the patient was agitated because he/she/they was/were in pain, was propofol still given (eg pain was not treated?)?)

Reply 4: Thanks for our reviewer's excellent comments. In our center, to guarantee the efficiency of operation room, the patients are immediately transferred to PACU when the surgery ends. What's more, deep muscle relaxant is often required to maintain sufficient abdominal capacity at a low pneumoperitoneum pressure, consequently decreasing side effects of laparoscopy and leading to enhanced recovery after surgery. However, due to the short interval between the laparoscopic procedure and the last stitch, many patients may suffer from relative deep relaxation in spite of neuromuscular block monitoring. Therefore, some rescue anesthetics are required to smooth the

extubation. Although pain may be the cause of agitation, the endotracheal tube might be the main reason for hemodynamic fluctuation and unconscious body moving. That's the reason why this trial was conducted. The postoperative VAS score was low, which indirectly indicated that the hemodynamic fluctuation and body movement was induced by pain.

Changes in the text: To clearly illustrate our purpose, we made some modification in the sections of Introduction and Methods (see Page 4, line 58-62; Page 7, line 125).

Comment 5: Anesthesia methods: invasive blood pressure (IBP): was an arterial line systematically put in for ASA I-II patients??

Reply 5: Thanks for our reviewer's excellent comments. In our trial, the surgery was performed in the steep Trendelenburg position, which may have a great impact on the hemodynamic parameters. For this reason, we routinely performed invasive blood pressure for these patients to keep circulation constant.

Changes in the text: None.

Comment 6: Regarding muscle relaxation: no neuromuscular monitoring was used?

Reply 6: Thanks for our reviewer's excellent comments. We used neuromuscular monitoring. However, due to the short interval between the laparoscopic procedure and the last stitch, many patients may suffer from relative deep relaxant effects in spite of neuromuscular block monitoring. In our trial, we enrolled the patients who had not yet reached the timing of neostigmine use.

Changes in the text: To clearly illustrate our methods, we described our Methods more in detail (see Page 7, line 125).

Comment 7: Were remifentanil and propofol administered using TCI models?

Reply 7: Thanks for our reviewer's excellent comments. In our study, remifentanil/ propofol were bloused other than administered using TCI models.

Changes in the text: None.

Comment 8: Regarding intra-operative analgesia strategy: fentanyl/ remifentanil/flurbiprofen + TAP block… Was acetaminophen administered?

Reply 8: Thanks for our reviewer's excellent comments. In our center, we don't have acetaminophen for injection.

Changes in the text: None.

Comment 9: Toff ratio was measured after extubation in the PACU? (What about patients with difficult airway criteria: were these also extubated knowing the possible risk of re-intubation in case of residual NMB). Why wasn't TOFF ratio mentioned in the overall patient monitoring?

Reply 9: Thanks for our reviewer's excellent comments. TOF, as the guide of antagonism and extubation, was continuously measured till extubation. What's more, we are dedicating to find a suitable way to make extubation more smoothly and safely. That's why we conduct this trial. In our study, the patients with difficult airway criteria

were excluded from our study. It is our negligence not to mention the TOF ratio in the section of Methods, we have added relative contents in the text.

Changes in the text: To clearly illustrate our methods, we described our methods more in detail in the section of Methods (see Page 7, line 125; Page 7, line 139).

Comment 10: I'm confused about the order: were patients extubated in the OR or PACU? Was the bolus given prior to extubation?

Reply 10: Thanks for our reviewer's excellent comments. It is our negligence not to illustrate our work flow clearly. In our center, at the end of the surgery, all the patients are routinely transferred to the PACU. The endotracheal tube is withdrawn in the PACU other than in the OR. At admission of the PACU, many of the patients are under the condition of relative deep muscle relaxation and light sedation, which may cause hemodynamic fluctuation and unconscious body moving. Hence, during the transition to extubation, the bolus of propofol/remifentanil was given.

Changes in the text: To clearly illustrate our work flow, we described our methods more in detail (see Page 7, line 134-137).

Comment 11: 1 mcg/kg of remifentanil is the usual INTUBATION dose... Why was such a high dose given at the end of the procedure?

Reply 11: Thanks for our reviewer's excellent comments. According to our clinical experience, only if injected with 1 mcg/kg of remifentanil, the patient can achieve sufficient depth of sedation. Meanwhile, we also found that this dosage would not cause significant circulation inhibition.

Changes in the text: None.

Comment 12: Results: 'In addition, 18 patients in group Rem and 20 patients in group Pro required repeated intervention with anesthetics' Please provide more details…

Reply 12: Thanks for our reviewer's excellent comments. Among the 38 patients, 15 patients in group Rem and 16 patients in group Pro required twice repeated intervention, and 3 patients in group Rem and 4 patients in group Pro required repeated intervention three times. There was no statistical difference, as shown in Table 2.

Changes in the text: As advised, we added relevant details in Results section and Table 2 (see Page 10, line 206-208).

Comment 13: Why wasn't a sedation score used (for example: Ramsey?)

Reply 13: Thanks for our reviewer's excellent comments, which have given us some indications for our subsequent trials. Actually, we didn't use Ramsay score to guide the extubation. However, the patients were all fully awake when extubated.

Changes in the text: None.

Comment 14: Opioid-induced hyperalgesia is mentioned in the discussion… It would be wrong to assume that this did not occur… The right testing was not done and pain was not evaluated in the ward (or this is not mentioned here…).

Reply 14: Thanks for our reviewer's excellent comments. In our study, we performed multimodal analgesia including preoperative bilateral transversus abdominis plane

(TAP) block under ultrasound guidance, intraoperative opioid use, and postoperative administration of flurbiprofen. Previous studies have revealed that the total amount of remifentanil is associated with the occurrence of opioid-induced hyperalgesia [Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology 2006; 104: 570–87. cFishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med 2009; 10: 829–39; BJA]. Just as our reviewer commented, opioid-induced hyperalgesia might last for a long time, and it would be inappropriate to assume that this did not occur since the pain was not evaluated in the ward. Subsequently, we should pay more attention to whether the use of remifentanil would induce hyperalgesia. We have modified the related description in Discussion and Limitation sections of the revised manuscript.

Changes in the text: To describe our results more accurately, we made some modification in Discussion and Limitation sections of the revised manuscript (see Page14, line 285).

Comment 15: How much rescue morphine/fentanyl was given in the pacu? Was there any difference between both groups?

Reply 15: Thanks for our reviewer's excellent comments. In our study, we performed multimodal analgesia including preoperative bilateral transversus abdominis plane (TAP) block under ultrasound guidance, intraoperative opioid use, and postoperative administration of flurbiprofen. During the PACU stay, if the patients complained of

more than moderate pain (VAS > 4), 50-100 μg fentanyl would be injected. Among the enrolled patients, only 5 patients in each group had required for extra analgesic rescue in the PACU. There was no statistical difference between the two groups.

Changes in the text: To describe our work flow more clearly, we have made some modification in the section of Methods of the text (see Page 7, line 129-131; Page 11, line 215-216).

Comment 16: Table 2 VAS is not the right term as it is mentioned here as no pain/moderate/mild/severe… This is not the actual VAS pain score…

Reply 16: Thanks for our reviewer's excellent comments. In our trial, when the endotracheal tube was withdrawn, we assessed the postoperative pain by verbal analog scale (VAS). We defined no pain for VAS 0, mild pain for VAS 1-3, moderate pain for 4-6, and severe pain for more than 7. We added the detailed description in Table 2.

Changes in the text: According to our reviewer's comments, we added the detailed description in the section of Methods and Table 2 (see Page 8, line 162-163).