

Peer review file

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Reviewer A

- Comment 1: As the authors revealed in the discussion, magnesium may potentiate the effect of muscle relaxants. I suggest the authors to describe their induction protocol in the method, including dosage of the muscle relaxants and opioids they used for the whole procedure. Furthermore, reversal agents using sugammadex 4 mg/kg is for deep blocks. Were quantitative monitoring of neuromuscular blockade such as train of four (TOF) used to guide dosage of sugammadex before tracheal extubation and confirmation of adequate reversal of neuromuscular block? An excessive dosage of sugammadex is not only a waste of cost but also is associated with its side effects such as bradycardia.

- Reply 1: We agree reviewer's comments. Unfortunately, we didn't monitor NM blockade. This the one of our weak point of trial.

We clarify the anesthetic regimen (including muscle relaxant dosage and opioids) in the method section and describe the 'pointed-out problem' in the limitation part.

- Change in the Text:

Page 6 line 17-20; "Anesthesia was induced ~ with 100% oxygen was done for 90 seconds (s).
Page 7 line 11-13; "Anesthesia was maintained using sevoflurane ~ 0.3 mg/kg/hr rocuronium was continuously administered intravenously to maintain muscular blockade."

Page 13 line 16-19: " Fourth, muscle relaxation was not monitored ~ in the magnesium infusion group."

Reviewer B

- Comment 1: ASA I and II status for lung surgery is uncommon.

- Reply 1: To generalize our study result, we think that it is reasonable and ethical to conduct the trial in the healthy patients. Thus, we conducted the trial only in the ASA PS I or II. As reviewer mentioned, ASA I and II patients for lung surgery is uncommon and result in recruitment of patients was very difficult. This is why our trial have to be conducted with long study period (from September 4, 2017 to November 14, 2019).

- Comment 2: Please elaborate on the ADMS device.

- Reply 2: We elaborated on the ADMS device and Unicon index.

- Change in the Text:

Page 7 line 7-11: To monitor depth of anesthesia ~ maintain acceptable correlation with the BIS (19,20).

- Comment 3: Did magnesium group have any neuromuscular blockade difference?

How might this confound your findings? Was it opioid related, volatile anesthesia related or a NMB issue? If it was a NMB issue, could it be related to the magnesium, which can prolong NMB?

Table 3 may suggest an effect. Page 10-line 21-22 states that no effects are seen related to delayed awakening, but could it be that those patients were excluded? Perhaps address this in the limitations portion of the manuscript.

- Reply 3: Unfortunately, we didn't monitor NM blockade. This the one of our weak point of

trial. But, the awakening time and number of delayed awakened patient were comparable between two groups We speculated that opioid may influenced the delayed awakening. We describe this concerns in the limitation part.

- Change in the Text:

Page 13 line 16-19: "Fourth, muscle relaxation was not monitored ~ in the magnesium infusion group."

- Comment 3-2: "The patients, who had not regained consciousness by 20 min after sevoflurane had been stopped, were withdrawn from the interventions and excluded from analysis." Could you elaborate on the reasoning for this decision?

- Reply 3-2: We decided the time limit for awakening based on the previous study (ref # 10) that median time for awakening time was about 8.4 min (IQR:7.8–10.0). We speculated that about 2 times of median awakening time (20 min) is sufficient for study time limit. The patients who had not gained consciousness for 20 min, were withdrawn from the intervention (remifentanil and study drugs were stopped) and excluded from analysis.

We clarified in the Text.

- Change in the Text:

Page 7 line 21: were withdrawn from the interventions ‘(remifentanil and study drugs were stopped)’ and excluded from analysis.

- Comment 4: Consider adding more information about the potential benefit related to post pain benefit that would make it more worthwhile to go to the trouble to employ this technique.

- Reply 4: The role of magnesium for perioperative analgesia already has been investigated by many authors. Thus, in this trial, we focused on the another beneficial effect (antitussive) of magnesium. Sorry for missing it

- Comment 5: In the results portion, the time unit of seconds should likely be spelled out in its first use.

- Reply 5: The suggested change has been made in the abstract.

- Change in the Text:

Page 2 line 15: 2, cough persistence < 5 ‘seconds’; 3, cough persistence ≥ 5 ‘seconds’

- Comment 6: page 3-line 5-Consider the following "...during emergence from anesthesia and tracheal extubation."

- Reply 6: This effect is not proven in background level. Before this study, antitussive effect of magnesium have been proven in asthma and opioid induced cough. We think that correction is inappropriate.

- Comment 7: Page 6-line 6-should be "opened their eyes"

- Reply 7: The suggested change has been made.

- Change in the Text:

Page 7 line 19: ‘their’ eyes

- Comment 8: Page 6-line 21-"large sound " is an awkward phrasing. Perhaps consider loud noise or a noise stimulus or a loud verbal stimulus. Whichever is most appropriate.

- Reply 8: The suggested change has been made.

-Change in the Text:

Page 8 line 11: 1: response to ‘loud verbal stimulus’ or physical contact

- Comment 9: Page 8-line 3-the word "were" does not fit and the sentence needs reworked.

- Reply 9: The suggested change has been made.

- Change in the Text:

Page 10 line 3-4: Finally, 130 patients completed all the assessments. (Figure 1).

- Comment 10: page 8- line 13-Et Sev should likely be spelled out for better clarity for the first use and a better acronym should be considered (ETSevo??).

- Reply 10: First use of acronym EtSev is spelled out in the page 8 line 7. The suggested change (ETSevo) has been made.

- Change in the Text:

Page 8 line 7: the end-tidal sevoflurane '(ETSevo)'

- Comment 11: page 8-line 18-I suggest the following wording change to increase clarity: As one would expect, the plasma-ionized magnesium levels measured at the completion of surgery were higher in the magnesium infusion group as compared to the control group.

- Reply 11: The suggested change has been made.

- Change in the Text:

Page 10 line 18-19: As one ~ compared to the control group

- Comment 12: page 9-line 3 evaluate should be plural

- Reply 12: The suggested change has been made.

- Change in the Text:

Page 11 line 4: 'evaluates' the effect

- Comment 13: page 9-line 9-should be "...has a beneficial effect..."

- Reply 13: The suggested change has been made.

- Change in the Text:

Page 11 line 9: has 'a' beneficial effect

- Comment 14: page 10-line 16-change to "dose related" instead of "related to doses"

- Reply 14: The suggested change has been made.

- Change in the Text:

Page 12 line 18: magnesium are 'dose related'

- Comment 15: Page 13-line 19- sentence needs a period

- Reply 15: The suggested change has been made.

- Change in the Text:

Page 15 line:

Reviewer C

- Comment 1: The choices of DLTs, including size, left or right?

- Reply1: The detailed description of tube size, operational side were revised in Method and Table 1. But, we didn't record that the left or right sided tube were used. I am sorry for unsatisfactory data.

- Change in the Text:

Page 6 line 21-22: Tracheal intubation was performed in all patients with a 35-Fr. DLT for women and 37-Fr. DLT for men.

Table 1:

- Comment 2: The number of attempts of insertion of DLTs, including replacing DLTs for cuff laceration. More manipulation brings more stimulation.

- Reply 2: We revised the table 1 according to the reviewer's recommendation. There were no differences between groups.

- Change in the Text:

Page line: Table 1

- Comment 3: With or without intraoperative adjustment of DLTs by fibroscope bronchoscopy? Was FOB confirmation of the position of DLTs the standard management? FOB was stimulating, too.

- Reply 3: We clarified and re-described the induction regimen in the Method section. The comparison of number of correction was done and added to Table 1. There were no differences between groups.

- Change in the Text:

Page 6 line 22-23: The correct positioning of DLT was confirmed with fiberoptic bronchoscopy. If repositioning was necessary, the DLT was guided into position via bronchoscope.

Table 1

- Comment 4: Do you monitor the cuff pressure intraoperatively?

- Reply 4: We clarified the monitoring of cuff pressure in the Method section

- Change in the Text:

Page 6 line 23- page 7 line 1: Cuff pressure was set to 20 to 25 mmH₂O with a hand pressure gauge.

- Comment 5: As there were more male (although non-significantly) with significant higher body height in control group, how do you present the comparably perioperative stimulation from DLTs? Comparable requirements of anesthetics and analgesics?

- Reply 5: As reviewer's opinion, cough reflex is more in male. Although there were more male in Group C (43 vs. 37), there was no significant difference between groups ($p=0.367$). We decided the dose of study drugs, based on the body weight. We think that these are not the confounding factor.

Anesthetic requirement (MAC hour) during surgery was not recorded in this trial. The concern of anesthetic requirement was already described in the limitation part (13 page line 8-12).

Sorry for our incomplete data.

Reviewer D

- Comment 1: There are multiple grammar and language problems, too many to point out individually. This manuscript needs to be reviewed by a native speaker before resubmission.

- Reply 1: Before submission, we had gotten the advice from the professional English language editing agency (Editage: www.editage.co.kr). Let me attach the certificate of English Language editing. In revised manuscript, some corrections were done according to the reviewers' recommendations. If it is inappropriate, we can get additional correction from editing agency.

- Comment 2: A p-value of 0.077 in the overall incidence of coughing clearly points to an underpowered study. Claiming that there is absolutely no difference between the groups is a type-II error and wrong conclusion.

- Reply 2: We agree the reviewer's opinion. In regards to cough incidence, it is underpowered study. Posthoc power analysis revealed 50.1 %. We described this concerns in the limitation part.

- Change in the Text:

Page 13 line 19-22: 'Fifth, a p-value of 0.077 ~ error and wrong conclusion'

- Comment 3: Page 3, lines 23, 24: the fact that low dose remifentanyl was used is neither in the title nor in the abstract. Remifentanyl was given throughout the anesthetic. This could have had agonistic, but also antagonistic effects. The latter was not taken into account or even discussed.

- Reply 3: We redescribed the infusion of low dose remifentanyl in the Abstract. The remifentanyl issue was already described in the Third limitation (13 page line 10-14); "because all patients in our study were receiving remifentanyl with magnesium at the time of anesthesia recovery, it is difficult to draw conclusions regarding the inhibitory effects of magnesium on emergence cough when magnesium is administered alone. Thus, we cannot rule out the effects of interactions, such as the additive or synergistic effects of magnesium and remifentanyl."

- Change in the Text:

Page 2 line 9-10: In combination with a low dose of remifentanyl,

- Comment 4: Endtidal sevoflurane concentration over time (MAC hours) was not recorded. If it was not fixed, one cannot conclude that the primary findings are only due to the intervention and not due to other confounders

- Reply 4: We agreed the reviewer's comment. As mentioned in the limitation part, we did not record the ETSevo concentration during the surgery. It is weak point of the study. But, anesthesia was maintained using sevoflurane and remifentanyl to maintain blood pressure and heart rate within 20% of baseline value, and to maintain a Unicon index of 40 to 60 during surgery. We clarified the anesthetic maintain method, in the Method part.

- Change in the Text:

Page 7 line 11-13: Anesthesia was maintained ~ of 40 to 60 during surgery.

- Comment 5: The Unicon score during surgery was not provided.

- Reply 5: We did not record the Unicon index during surgery. We just recorded the Unicon index during awakening. But we titrate the anesthetic level during surgery to Unicon index of 40 to 60. We clarified it, in the Method part

- Change in the Text:

Page 7 line 11-13: Anesthesia was maintained ~ of 40 to 60 during surgery.

- Comment 6: Table 4: the differences in hemodynamics are fascinating; please provide preoperative and intraoperative values as well to be able to see relative changes over time with magnesium infusions.

How about patient satisfaction, was this ever assessed?

- Reply 6: Unfortunately, we did not record preop. and intraop. HR and patient safety. We couldn't analyze and describe the value. Sorry for our incomplete data.

- Comment 7: The trial was registered only in Korea. Please register at clinicaltrials.gov as

well.

- Reply 7: CRIS is the internationally certified public clinical registration site. Any researcher in the world can review my trial in English. We do not need to register in more than one registration system unless it is required, such as legal requirements. The WHO International Clinical Testing and Registration Platform (ICTRP) recommends that clinical research conducted in the country should be registered in the country's clinical research registration system in order to reduce the burden of duplicate registration for researchers and to enable citizens to know the clinical research information carried out in their own countries. In addition, Declaration of Helsinki states that every research study involving human subjects must be registered in a publicly accessible database BEFORE recruitment of the first subject. If we register at clinicaltrials.gov now, I'm afraid that the registration was made AFTER recruitment of the first subject.

- Comment 8: The title is misleading as magnesium was not given during emergence and it was an infusion during the entire anesthetic; please change.

- Reply 8: The suggested change has been made.

-Change in the Text:

Page 1 line 1: Antitussive effect of 'a' magnesium 'infusion' during

- Comment 9: Page 2, line 6: of a magnesium infusion

- Reply 9: The suggested change has been made.

- Change in the Text:

Page 2 line 6: of 'a' magnesium 'infusion'

- Comment 10: Page 2, line 8, and page 5, line 5: what surgery?

- Reply 10: The suggested change has been made.

- Change in the Text:

Page 2 line 7: underwent 'thoracic surgery requiring' one-lung ventilation (OLV)

- Comment 11: Page 2, line 10: how much and for how long?

- Reply 11: The suggested change has been made.

- Change in the Text:

Page 2 line 11: (infusion of 15 mg/kg/hr after a single bolus of 30 mg/kg)

- Comment 12: Page 2, line 11: Statistics are missing

- Reply 12: Because, there was limited space for abstract, we couldn't mention the statistic in the abstract. Instead, we described the statistical analysis in the method part. I'm sorry for missing it.

- Comment 13: Please use key word that are not in the title increase success of search.

- Reply 13: The suggested change has been made.

- Change in the Text:

Page 2 line 22: Complications, cough, magnesium, 'one lung ventilation,' thoracic surgery

- Comment 14: on a previous study

- Reply 14: The suggested change has been made.

- Change in the Text:

Page 8 line 20: based on a 'previous' study

- Comment 15: one-or two-tailed?

- Reply 15: It is two-tailed. The suggested change has been made.

- Change in the Text:

Page 9 line 7: All statistical analyses were 'two-sided' and

- Comment 16: for what reason?

-Reply 16: Fig. 1 described the reason. I'm afraid it could be duplicated mention with Fig. 1.

- Comment 17: postoperative pain been assessed in this study (table 3) and no difference was found; when was it assessed and how do the authors speculate that there was no difference?

- Reply 17: As mentioned the Text (8 page line 12-13), 'pain score were assessed 30 min after post anesthesia care unit admission'. The magnesium infusion was stopped after the patient awakening. this is may be the reason why no difference was found in postoperative pain.

- Comment 18: what doses?

- Reply18: It is the infused Mg dose. The suggested change has been made.

- Change in the Text:

Page 12 line 18: These side effects of magnesium are 'dose related' (33).

- Comment 19: Table 1: the different types of surgery need to be mentioned in the Methods section or at least referred to.

- Reply19: Table 1 showed that there were no difference the type of surgery between two groups (p=0.807). We speculated the type of surgery didn't influence the result.

- Comment 20: Table 3, degree of sedation: what do these numbers mean?

- Reply 20: The suggested change has been made. Detailed description of 'degree of sedation' was added in the footnote of Table 3

- Change in the Text:

Page line: Table 3 'Degree of sedation,0 = no response to stimulus, 1 = response to loud verbal stimulus or physical contact, 2 = response to general voice, 3 = clear consciousness.'

Reviewer E

-Comment 1: This reviewer interpreted that all the methods and results were clearly presented in this manuscript.

- Reply 1: Thank you for your review comments