Author’s response to reviews

Title: Effects of Different Doses of Magnesium Sulfate on Pneumoperitoneum-related Hemodynamic Changes in Patients Undergoing Gastrointestinal Laparoscopy: a randomized, double-blind, controlled trial

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Dear Editor:

“Effects of Different Doses of Magnesium Sulfate on Pneumoperitoneum-related Hemodynamic Changes in Patients Undergoing Gastrointestinal Laparoscopy”, which we wish to be considered for publication in “BMC Anesthesiology”. The paper was coauthored by Wei Tan, Dong-chen Qian, Meng-meng Zheng, and Xuan Lu, Yuan Han.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in BMC Anesthesiology.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions. Further, We believe that our study makes a significant contribution to the literature because this is the first study to evaluate the direct effects of magnesium sulfate on cardiac output and systemic vascular resistance using FloTrac/Vigileo Monitoring System, and this paper will be of interest to the readership of your journal because the clinical application of magnesium sulfate for maintaining perioperative hemodynamic stability and reducing postoperative pain could be of great significance especially in elderly patients with cardiovascular diseases, and there is scope for further research on the topic as well.
Reviewer #1:

1. Page 5, row 18 The primary outcome of the study is the difference in SVR between different groups, so it may be advisable to use the best hemodynamic monitoring devices to detect data at its best. How did the authors choose FloTrac/Vigileo among available devices? Since every patient has a central venous catheter in place (page 6, row 30), was transpulmonary thermodilution considered? What about other arterial waveform analyzers?

We greatly appreciated the reviewer’s positive comments on our manuscript. Thanks for mentioning this valuable point. Firstly, I agree with you that SVR also can be monitored by several other indirect and direct measurements. And previous studies had used indirect or direct arterial pressure as a measure to indicate the peripheral circulatory resistance.(Jee D, Br J Anaesth, 2009). Compared to NIBP, both the thermodilution method and FloTrac / Vigileo can monitor SVR, but since the thermometry measurement requires pulmonary artery catheterization, the trauma and risk are greater than FloTrac / Vigileo. Besides, the use of the thermodilution method does not provide continuously monitor changes in SVR. In contrast, by using of FloTrac / Vigileo system, not only SVR can be obtained easily, but also many other hemodynamic parameters such as, CO, CVP and MAP can be continuously measured. Therefore, FloTrac / Vigileo can be used in the design test by considering the patient's risk /benefit ratio. (Please see the details in line 42-44, Page 13 and Line 1-9, Page 14)

2. Page 7, row 27 Authors declare that anesthesia was maintained with propofol and remifentanil infusion in a very precise infusion rate range (4-6mg/kg/h and 0.25-0.35 mcg/kg/min, respectively); patients were monitored with pEEG, in a way to maintain bispectral index between 45-60. Were medication infusion rates varied even outer from given range? How did the investigators choose to vary propofol or remifentanil?

Thanks for mentioning this important point. In fact, we thought about this problem very carefully before the trial design. We agree that it is better to discuss more details. Firstly, at the time of induction, we administered midazolam and sufentanil, which have long-lasting sedative and analgesic effects, thus intraoperative propofol and remifentanil infusion rate were relatively low in maintenance dose. Secondly, during the surgery, we adjusted the pumping rate of propofol and remifentanil based on BIS, heart rate and blood pressure, our study controlled for BIS value. When the BIS value was above 60 or below 45, propofol infusion rate would be adjusted by 0.5mg/ kg/h each time. If the BIS value was maintained between 45-60, but the blood pressure fluctuates more than 20% of the basal level, remifentanil infusion rate would be adjusted by 0.02ug/kg/min each time. (Please see the details in line 1-3, Page 7 and Line 9-19, Page 7)

3. Page 7, row 41 Muscle relaxation was monitored by mean of Train of Four ratio, with cis-atracurium
boluses (0.05 mg/kg) aimed to maintain TOF<25%. At the end of the surgery, block was reverted with a atropine/neostigmine mixture at a standard dosage (0.02mg/kg and 0.04 mg/kg, respectively), and patient extubated without declaring a TOF ratio in the paper. Since "time to extubation" has been evaluated among the three groups, it may be advisable to report these data. Moreover, since a profound muscle block during pneumoperitoneum has been reported to improve post-operative analgesia, it may advisable to report data around intra-operative TOF ratio in the different groups, too.

Thanks you for your valuable suggestion. We totally agree that muscle block during pneumoperitoneum may be linked to post-operative analgesia. In the text, the description of 'with cis-atracurium boluses (0.05 mg/kg) aimed to maintain TOF<25' is incorrect. This was designed when we were planning the experiment in the early stage. But in actual anesthesia maintenance, cisatracurium (0.1-0.12mg/kg/h) was administered intravenously. Indeed, the TOF value during the operation was maintained as 0. We really apologized for this mistake. We add the TOF ratios in each time points in Table 8. In addition, in this trial, we routinely sent the patients to the PACU, and the staffs worked in PACU monitored and removed the tracheal tube when the TOF ratio <25%. I am so sorry that we did not record the corresponding TOF ratio for postoperative extubation. This is also a shortcoming of this test. (Please see the details in line 27-33, Page 7)

4. Page 7, row 54 Post-operative pain, assessed by mean of VAS at 5 min and at 20 min post extubation is considered a secondary outcome, but no information is provided around analgesia given. Is it multimodal (locoregional and/or systemic)? What kind of medications and dosages are infused? Thanks for bringing up such an important and meaningful question. In this trial, patients were not given regional analgesia and PCA analgesic pumps were used after the patient leaving PACU. We evaluated the VAS score 5 min and 20min after extubation. When the score >5, we used fentanyl 0.05 mg iv for analgesia. There is no difference in dosage of fentanyl between groups. The determine of using PCA analgesic pumps or not depend on the patient’s willing. I am very sorry that the specific steps for postoperative analgesia have not been explained in detail in the article. The dosage of postoperative fentanyl is now added in the text. (Please see the details in line 15-22, Page 9 and table 10)

5. Page 8, row 1 Authors provide detailed information around management of possible intra operative complication. They define hypotension as MAP<60mmHg and state that investigators react with fluid boluses and vasoconstrictor, without taking in account data coming from pEEG, maybe suggestion possibility of hypotension due to oversedation. Please clarify this point.

Thanks for helping us correct the inappropriate description. We really apologized for this mistake and complete the description in the article. During the operation, we maintained the BIS value between 45 and 60, When above 60 or below 45, propofol infusion rate was adjusted by 0.5mg/ kg/h each time. If the BIS value maintained between 45-60, but the blood pressure dropped more than 20% of the basal level, remifentanil infusion rate would be adjusted by 0.02ug/kg/min each time. After adjusting, if MAP was still less than 60 mmHg, vasoactive drugs will be infused. (Please see the details in line 37-44, Page 7)

6. Page 9, row 24 Authors state they routinely use, as intraoperative fluids, sodium ringer lactate and hydroxyethyl starch, even in the case of stable hemodynamic condition and not overt bleeding patients. Please clarify this point.

I am very sorry that there is no detailed description of the intraoperative fluid infusion, and we will add the description in our article. The principle of rehydration in our study: to avoid potential severe hypotension as a result of anesthesia induction, all patients received 8-10 ml/kg compound electrolyte solution before the induction of anesthesia. Intraoperatively, the intravenous infusion of lactate ringer
solution or compound electrolyte solution was 6 ml/kg/h. (Please see the details in line 1-6, Page 9)

7. Page 11, row 37 Since the primary outcome from this study is the difference in SVR between different groups, it may be useful to consider baseline patients' medication history, especially in case of essential hypertension. Chronic beta-blockade, calcium antagonists or ACE inhibitors may interfere with hemodynamic response to pneumoperitoneum. Thanks for highlighting this question. Even we have excluded high blood pressure, low blood pressure and heart failure patients in our trials, there were still a few patients who have the medication history of chronic beta-blockade, calcium antagonists or ACE inhibitors. The descriptions of these medications have been added in Table 2.

8. Page 13, row 13 Authors state that patients from group H needed less a lower remifentanil infusion rate compared to patient from L and S group. This sentence may need to be supported with explanation on the way adopted in the study to manage remifentanil infusion rate among different investigators and patients. Thanks for highlighting these questions, it did help us in describing the methods more precisely. More detail in Materials and Method section have been added. We recorded the pumping rate of remifentanil every ten minutes to calculate the average pumping rate of it within one hour after the pneumoperitoneum. If the BIS value was maintained between 45-60, but the blood pressure fluctuates more than 20% of the basal level, remifentanil infusion rate would be adjusted by 0.02ug/kg/min each time. (Please see the details in line 9-19, Page 7 )

Reviewer #2:

1. Methods Page 6 Line 12. Please define cardiac dysfunction vs poor left ventricular function as exclusion criteria. Was Grade 1 diastolic dysfunction an exclusion criteria? Please be more clear about inclusion and exclusion criteria. Thanks for helping us to correct the inappropriate description. We really apologized for this mistake. The cardiac dysfunction we excluded in the test refered to patients with NYHA grade III and IV. Cardiac dysfunction included poor left ventricular function and diastolic dysfunction, so we have deleted “poor left ventricular function” in the text. The inclusion and exclusion criteria have been corrected in the article. Patients with American Society of Anesthesiologists grade I and II patients were enrolled in this study. Patients with hypermagnesemia, known allergy to magnesium sulfate, unstable blood pressure (hypertension or hypotension), cardiac dysfunction (NYHA grade III and IV), morbid obesity, and severe hepatic, renal or endocrine were excluded from the study. (Please see the details in line 31-36, Page 5)

2. Page 7 Line 43. Please substitute myokymia with TOF ratio. Thank you for helping us correct our mistakes. We appreciated your kind suggestion and we have now substitute myokymia with TOF ratio. (Please see the details in line 33, Page 7 )

3. Page 10. Why did the authors choose a spot evaluation for hemodynamic parameters (at predefined time intervals), despite the FloTrac system records data at a much shorter interval? Would it be possible an analysis at more frequent intervals? Statistical analysis Thanks you for your valuable suggestion. As you maintioned, if we analyse at more frequent intervals
in hemodynamic parameters, the collected data can be more accurate. A 10 min spot evaluation was feasible, convenient for further analysis, and can reflect the main experimental results. Besides, most previous magnesium-related studies used spot evaluated data as the main method for data collection. (Jee D, Br J Anaesth, 2009). However, the workload of continuous acquisition could be more complicated. Thus, we predefined 10 min as the time intervals.

4. Page 11 Line 4. Please test variables for distribution and express data as means or medians as appropriate and not only as means.
We appreciated your kind suggestion and totally agree with your point of view. In the statistical analysis, the data conforming to the normal distribution were expressed by the means ± standard deviation, and the data of the non-normal distribution were represented by the median and the interquartile range. We have corrected the inappropriate description. (Please see the details in line 1-5, Page 11 and table 1)

5. Line 8. Consider the chance of non parametric statistical tests for not normally distributed data. In this context statistical results might be flawed. Reformulate results according to distribution and non parametric comparison between not normally distributed variables if appropriate.
Thank you for helping us in enhancing and improving the quantity of our statistical data’s description, we have reformulated results according to distribution and non parametric comparison between not normally distributed variables. We chose the Kruskal-Wallis test to analyze not normally distributed variables. (Please see the details in line 9, Page 11 )

6. Results Page 13 Line 57. What do the authors mean with 'recently'? In the last 15 years, there's been a huge proliferation of less invasive tools for hemodynamic monitoring. Please reformulate the sentence.
Thank you so much for your suggestions. We are sorry about the misusage of language, and we have corrected the inappropriate description. (Please see the details in line 38-40, Page 13 )

7. Page 14. Please state FloTrac monitoring system limits. Authors consider the lack of calibration as a strength. It can be actually argued that the absence of calibration can be seen as a limit of the system rather than a strength. Please reformulate the sentence.
Thanks for helping us correct the inappropriate description. We totally agree with your point of view and apologized for this mistake. The absence of calibration is indeed a limit of FloTrac monitoring system and we have corrected in the article. (Please see the details in line 42-44, Page 13 and Line 1-9, Page 14)

8. Page 15 Line 35. Please reformulate the sentence about remifentanil. Despite being associated with opioid induced hyperalgesia, remifentanil is still one of the most widespread and used opioids in the intraoperative time due to some unique features; in this sense, its use is far from being limited.
Thank you very much for correcting the introduction of the analgesic effect of remifentanil. I am very sorry about this error. Remifentanil is one of the most widely used opioid analgesics in clinical practice. Elimination of short half-life, no accumulation, and less impact on hemodynamics. In this trial, we also used conventional propofol combined with remifentanil for intraoperative maintenance. We found that adjuvant analgesia with magnesium sulfate can significantly reduce the dose of remifentanil . (Please see the details in line 23-25, Page 15 )
9. Line 51. What the author means by 'pneumoconiosis' hypertension? The study is about hemodynamic variables during pneumoperitoneum induction.
We feel so sorry about the mistakes and appreciated your kind suggestion. we have now deleted the 'pneumoconiosis' hypertension, and tried to use pneumoperitoneum associated hypertension. (Please see the details in line 33, Page 15)

10. Please provide data about CVP values. CVP is required by FlocTrac monitoring system in order to calculate SVR, and expressing SVR values without CVP might be limiting.
Thanks you for your valuable suggestion. The data about CVP values have been added in the article. (Please see the details in line 30-37, Page 12)

11. Table 2,3,4,5,6,7 What is the p-value on the right side of tables referring to? Is within group variation? Please specify. Please provide 95% CI together with p value.
I am sorry that I did not clearly explain the p value in the text. The P0-value refers to the difference within group variation, P-value refers to the differences between groups variation. When the difference between the groups was statistically significant, we compared each of the two groups(P1 refers to the significance of difference between group S and group L; P2 refers to the significance of difference between group S and group H; P3 refers to the significance of difference between group L and group H ). We are thankful to you for reminding us of adding the 95 % CI in the literature. However, considering the data type is various and and the data quantity is big, if all the data are added 95% confidence interval, the data and the table may be too large and the statistics are more complicated, so we only add 95% confidence interval to some important data. (Please see table4 - 8)

12. Discussion The authors emphasize Magnesium Sulfate effects on hemodynamic improvements in terms of SVR, MAP and CO. It is notable how CO improvement, while being statistically significant, is only marginal and confined to T2 and T3 intervals. Please provide a comment on how this small and transient parametric improvement might translate into clinical benefit?
Thanks for your questions. During PNO for operative laparoscopy, impairment of hemodynamic status occurs mainly at the beginning of peritoneal insufflation. Based on our statistic data, T2-T4 are the most severe periods of hemodynamic fluctuations, and it was also the most effective time period for magnesium sulfate to inhibit post-pneumoconiosis hypertension, which is consistent with other clinical trials have been reported that systolic and diastolic arterial pressures were lower at 10, 20, and 30 min post-pneumoperitoneum after the usage of 50 mg/kg of magnesium sulfate in the magnesium group (Jee D, Br J Anaesth, 2009). CO decreases after pneumoperitoneum, the body sympathetic excitement compensatory raises SVR to maintain arterial blood pressure, then the increases in SVR further decreases the CO, forming a vicious circle. However, The effects of pneumoperitoneum on hemodynamics can be catastrophic among patients with ischemic heart disease or other sever complications. As the blood vessels progressively harden and cardiovascular compensatory function declines, their ability to adapt to changes in circulating blood volume is severely reduced. Therefore, although the improvement of CO is limited to the T2 and T3 time points, the advantage of this transient improvement is very beneficial for patients with poor cardiac diastolic function. (Please see the details in line 19-23, Page14 and Line 28-37, Page 14)

13. The authors often emphasize FloTrac/Vigileo role in their manuscript. We would like to highlight how FloTrac is only one of the less-invasive hemodynamic monitoring systems available nowadays and
It did not prove more reliable or accurate than others. In addition, the study is about Magnesium sulfate and not about FloTrac. As a result, we would like the authors to stay focused on the true nature of the study and not to stress too much attention on the monitoring device.

We appreciated your kind suggestion and totally agree with your point of view. We have now deleted the excessive description regarding the FloTrac / Vigileo monitors in the article, and it seems to be much clearer than before and to be understood easily. (Please see the details in line 1-10, Page 14)