PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Effect of Remimazolam Besylate versus Propofol on Haemodynamic Profiles in Patients Undergoing Thyroid Surgery with Recurrent Laryngeal Nerve Monitoring: A Protocol for a Randomised Controlled Trial

Authors

Lu, Dianyu; Zeng, qingmei; Zhang, Anyu; WEI, WEI; Huang, Haiyan; Chen, Weiquan; Li, Jinfei; Yao, Yonghua; Gu, Yu

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Applegate II, Richard**
Affiliation	**Loma Linda University School of Medicine, Anesthesiology**
Date	**05-Jul-2024**
COI	**I have no competing interests**

The authors present their protocol for comparing 2 drugs in an important surgical case type. The design is good and the report is complete.

Major concern

Methods page 9 starting line 7 - randomization is stated as generated by a website, then stated as the nurse anesthetist randomly assigning patients to the study groups.

• It is essential to understand whether the block allocation randomization will be followed.

• If the nurse anesthetist is assigning patients to study groups then please clarify that this will be done prior to meeting the patient or obtaining consent.

Measurement of hypotension page 16 starting line 55 to page 17 line 8: the authors state MAP will be recorded at nine time points

• The administration of vasoactive agents will also be recorded

• Please clarify that as implied in Table 1, MAP will be monitored throughout

• Please verify that the count of MAP deviations requiring intervention will be recorded and reported

• Suggest adding comparison of the number of MAP deviations requiring intervention as a secondary outcome

Exclusion criteria: page 8 line 42 - please clarify the reason for excluding patients on hormone therapy as this could be seen to bias patient selection away from women with childbearing potential or who are taking post-menopausal hormone replacement therapy.

Minor concerns

Page 3 lines 29 to 31: suggest "This is not a double-blind study as the different appearance of propofol and remimazolam besylate make it impracticable to blind the attending anesthesiologists."

Page 4 line 40 suggest "... often causes hemodynamic instability..." to be consistent with line 56 "... often requires vasopressor support"

Table 1 "Informed consent"

Page 8 line 2, exclusion criteria: suggest "Patients undergoing other surgery..."

Page 9 line 6 suggest "Randomization and blinding"

Page 9 line 37 suggest "blinding"

Page 10 line 54 to 56 - suggest consistent grammar "The tube will be securely taped once it is properly placed in the trachea"

Page 14 line 50 suggest "...activity, not only produces..."

Page 17 line 29 suggest "...and will provide appropriate..."

Reviewer	**2**
Name	**Peng, Ke**
Affiliation	**Soochow University**
Date	**08-Jul-2024**
COI	**None.**

The authors present a protocol for a single-center, single-blind, randomized, controlled trial to investigate the hemodynamic effects of remimazolam in patients undergoing thyroid surgery with recurrent laryngeal nerve monitoring. Here are my comments.

Major:

1. P5L52, “…, and whether remimazolam can achieve sedation similar to the classical intravenous anesthetic propofol in procedures requiring relatively deep anesthesia.”; P11L7, “…, aiming for a BIS value between 40 and 60.”; P21L17, “Some investigators have observed

no other clinical signs of inadequate anesthesia during TIVA with remimazolam when the BIS value is between 60 and 80, which is comparable to a BIS value of 60 under propofol anesthesia, …"

How is "the similar sedation" defined? Using BIS value or body responses? However, as the authors stated remimazolam with the BIS values between 60 and 80 was comparable to propofol with a BIS value of 60. What BIS target should be used for remimazolam and propofol respectively?

2. P6L19, by checking ChiCTR2300076583 at chictr.org.cn, the study execute time is from November 2023 to November 2024. However, here the authors stated "Study activities are expected to start in July 2024 and be completed in December 2025." Please explain this discrepancy.

3. P12L35, "After drug induction, the initial dose of propofol, remimazolam and remifentanil will be administered before endotracheal tube insertion, and the maintenance dose will be infused until skin closure." What were the initial doses of these drugs?

4. P15L21, "Preoperative data collection" (1) Please elaborate the way to evaluate the cardiac function. (2) Considering the aim of this study, are the comorbidities and medication history only about cardiovascular system? (3) There may be missing data especially in laboratory tests, I think the authors should clarify the way to deal with missing data in "Statistical methods" section.

5. P15L54, "Adverse events during anesthesia". This item should not include hypotension, hypertension, bradycardia and tachycardia, which are already listed above.

6. P16L40, (1) Considering the aim of this study, I think the secondary outcomes should include more hemodynamic index, such as the number of hypotension or hypertension episodes, and the cumulative duration of hypotension or hypertension. (2) Flumazenil will only be used in the remimazolam group, so it is not appropriate to be one of secondary outcomes.

7. P16L55, "We will record the MAP on the monitor at nine time points…" To show the hemodynamic effects in more detail, I recommend monitoring more frequently at the beginning. Will HR be recorded?

8. P27-29, the figures are invisible. Please check.

Minor:

1. P4L35, "…regimen has minimal impact on EGM responses". The "EGM" is misspelled. I think it should be "EMG".

2. Please remove unnecessary abbreviations which appear only once, such as "GABAA" (P5L19), "ICU" (P8L27) and "PBW" (P10L42).

3. P7L15, Table 1: several rows are not aligned.

4. P8L8, “Aged 18- 60 years old.” This is not in line with the registration and abstract where the age is between 18 and 65 years old.

5. P16L3, “Postoperative data collection” are not exactly consistent with “Postoperative follow-up” section (P12L16). Please check.

6. P16L36, “The primary outcome is the proportion of patients who experience hypotension, defined as MAP≥30% below preoperative baseline, …”

(1) I think a better statement should be “The primary outcome is the occurrence of hypotension…” (2) MAP at T0 (before induction) is set as the baseline value. Why not using MAP at wards as the baseline value?

7. P17L38, “Based on previous studies and our recently completed data, …” Please add citations here.

Reviewer	**3**
Name	**Hung, Kuo-Chuan**
Affiliation	**Chi Mei Medical Center**
Date	**08-Jul-2024**
COI	**none**

The study protocol is well-written and conducted reasonably; I have no further comments on this protocol.

VERSION 1 - AUTHOR RESPONSE

Point by point response to reviewer 1#

Dear Dr. Richard Applegate II

We sincerely appreciate your recognition and suggestions on the protocol, which will play an extremely important guiding role in the following research. Hereby, I will provide detailed explanations of your comments.

Major concern

1-Methods page 9 starting line 7 - randomization is stated as generated by a website, then stated as the nurse anesthetist randomly assigning patients to the study groups.

• It is essential to understand whether the block allocation randomization will be followed.

• If the nurse anesthetist is assigning patients to study groups then please clarify that

this will be done prior to meeting the patient or obtaining consent.

Response: Sorry for my unclear expression. We have revised this section according to your instructions and also referenced the literature. We expect that we have accurately understood your suggestions and that the revisions are in line with your comments. If the revisions do not meet your suggestions or do not fully address the issue, we look forward to your further guidance to improve our protocols. Thank you very much!

The details of the revisions are as follows (P8L3-9):

Prior to the start of the study, a randomization code will be generated in a block size of four on the website http://www.Randomization.com and securely stored in a sealed opaque envelope by the nurse anaesthetist who will allocate patients according to the randomisation schedule. After obtaining written informed consent, the nurse anaesthetist will randomly assign patients to either the propofol group (P group) or the remimazolam group (R group) in a 1:1 ratio according to the randomisation schedule before entering the operating room.

2-Measurement of hypotension page 16 starting line 55 to page 17 line 8: the authors state MAP will be recorded at nine time points

• The administration of vasoactive agents will also be recorded

Response: We sincerely appreciate your suggestions and sorry for our unclear expression! As an important secondary outcome, the administration of vasoactive agents, including the specific doses of different vasoactive agents given as single or continuous infusions and the total duration of administration, etc., will be recorded in detail. For details, P14L25-26 and P16L8-10.

• Please clarify that as implied in Table 1, MAP will be monitored throughout

Response: We sincerely apologise for any confusion or inaccuracy that may have been caused by our symbols in Table 1. As part of standard clinical anaesthesia procedures, the patient's vital signs, including blood pressure and heart rate, are continuously monitored throughout the surgical procedure. To ensure comprehensive and detailed data collection for subsequent statistical analysis, we will carefully select specific time points to record these critical parameters. To avoid any misunderstanding, we have made the necessary adjustments to the symbols that indicate continuous monitoring to more accurately indicate that these vital signs are being recorded at selected time points. For details, P6 Table 1.

• Please verify that the count of MAP deviations requiring intervention will be recorded and reported

• Suggest adding comparison of the number of MAP deviations requiring intervention as a secondary outcome

Response: We sincerely appreciate your valuable suggestions, which are of great practical importance and value in improving our study. In accordance with your instructions, we have added the recording of the count of MAP deviations requiring intervention and listed the comparison of these deviations as a secondary outcome of our research. The modification to the study protocol has been approved by the Medical Ethics Committee (2024 Research Ethics Amendment No. 3) and the information has also been updated in the Chinese Clinical Trial Registry. For details, P15L25-27.

3-Exclusion criteria: page 8 line 42 - please clarify the reason for excluding patients on hormone therapy as this could be seen to bias patient selection away from women with childbearing potential or who are taking post-menopausal hormone replacement therapy.

Response: We sincerely appreciate your insightful and valuable comment. Indeed, we have not fully considered the potential selection bias that could result from excluding individuals who are pregnant or menopausal. We think your comments are very important to ensure the accuracy of the results. Therefore, after carefully considering your comments, we have removed hormones from the exclusion criteria, and have obtained ethical approval for this change. For details, P7L21.

Minor concerns

1-Page 3 lines 29 to 31: suggest "This is not a double-blind study as the different appearance of propofol and remimazolam besylate make it impracticable to blind the attending anesthesiologists."

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P2L18-19. Following the editor's suggestion to use British English, we have written anaesthetist instead of anesthesiologists, and as we are not native English speakers, please do not hesitate to contact us if the use is inappropriate and we will continue to make improvements.

2-Page 4 line 40 suggest "... often causes hemodynamic instability..." to be consistent with line 56 "... often requires vasopressor support"

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P3L29.

3-Table 1 "Informed consent"

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P6 Table1.

4-Page 8 line 2, exclusion criteria: suggest "Patients undergoing other surgery..."

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P7-12.

5-Page 9 line 6 suggest "Randomization and blinding"

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P8L2.

6-Page 9 line 37 suggest "blinding"

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P8L20.

7-Page 10 line 54 to 56 - suggest consistent grammar "The tube will be securely taped once it is properly placed in the trachea"

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P10L1-2.

8-Page 14 line 50 suggest "...activity, not only produces..."

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P13L24-25.

9-Page 17 line 29 suggest "...and will provide appropriate..."

Response: Thank you for your suggestion! We have revised it according to your suggestion. For details, P16L20-21.

Point by point response to reviewer 2#

Dear Dr. Ke Peng

We sincerely appreciate your recognition and suggestions on the protocol, which will play an extremely important guiding role in the following research. Hereby, I will provide detailed explanations of your comments.

Major:

1- P5L52, "…, and whether remimazolam can achieve sedation similar to the classical intravenous anesthetic propofol in procedures requiring relatively deep anesthesia."; P11L7, "…, aiming for a BIS value between 40 and 60."; P21L17, "Some investigators have observed no other clinical signs of inadequate anesthesia during TIVA with remimazolam when the BIS value is between 60 and 80, which is comparable to a BIS value of 60 under propofol anesthesia, …"

How is "the similar sedation" defined? Using BIS value or body responses? However, as the authors stated remimazolam with the BIS values between 60 and 80 was comparable to propofol with a BIS value of 60. What BIS target should be used for remimazolam and propofol respectively?

Response: Sorry for our unclear expression! Our intention was to convey that remimazolam comparable to propofol in sedation. To expound on this issue more accurately and in greater detail, we have rewritten the corresponding paragraphs. For details, P5L6 and P20L3-12.

Regarding the assessment of the sedative effects of remimazolam and propofol, we have reviewed the literature and provide detailed explanations of your comments as follows:

In clinical practice or research, various sedation-related rating scales, such as the Richmond Agitation-Sedation Scale (RASS), the Ramsay scale and the Moderate Alertness/Sedation Assessment (MOAA/S) scale, as well as the patient's physiological indicators, such as blood pressure and heart rate, and the patient's response to stimuli, pupillary light reflex and body movements, etc., are commonly used to assess the level of sedation. However, in general anaesthesia the situation is more complex, as the above assessment methods may be invalid. In such cases, the Bispectral Index (BIS) monitor becomes an invaluable tool, providing an objective and quantitative measure of the depth of sedation by analysing the patient's electroencephalogram.

Multiple studies have compared the sedative effects of remimazolam and propofol employing the aforesaid methodology and have found that the sedative effects of remimazolam are comparable to those of propofol. For example:

① Based on their previous studies showing that remimazolam was comparable to propofol in maintaining light-to-moderate sedation in ICU patients[1, 2], Tang and colleagues further compared remimazolam with propofol for deep sedation, defined as a RASS score of − 4 or − 5, in critically ill patients[3]. The results showed that the percentage of time within the target sedation range without rescue sedation was similar between the two groups, as well as clinical outcomes and adverse events.

② Chang et al. conducted a comprehensive meta-analysis including a total of twelve randomised controlled trials (RCTs) to evaluate and compare the sedation efficacy and safety profile of remimazolam versus propofol. The pooled results showed that there was no significant difference in sedation success rates, time to loss of consciousness, or recovery and discharge times between the two groups treated with either remimazolam or propofol[4].

③ During cervical conization, no significant differences were observed in the overall alfentanil dosages administered, bradycardia, bodily movement, or time to losing consciousness between remimazolam or propofol[5].

1. Tang Y, Yang X, Shu H, Yu Y, Xu J, Pan S, Zou X, Yuan S and Shang Y. Remimazolam besylate for sedation of postoperative patients in intensive care units: a phase I, open label, dose-finding study. Chin Med J (Engl). 2022;135:2134-2136.

2. Tang Y, Yang X, Yu Y, Shu H, Yuan Y, Liu H, Zou X, Yuan S and Shang Y. Remimazolam besylate versus propofol for long-term sedation during invasive mechanical ventilation: a pilot study. Critical care (London, England). 2022;26:279.

3. Tang Y, Gao X, Xu J, Ren L, Qi H, Li R, Shu H, Zou X, Yuan S, Yang X and Shang Y. Remimazolam besylate versus propofol for deep sedation in critically ill patients: a randomized pilot study. Critical care (London, England). 2023;27:474.

4. Chang Y, Huang Y-T, Chi K-Y and Huang Y-T. Remimazolam versus propofol for procedural sedation: a meta-analysis of randomized controlled trials. PeerJ. 2023;11:e15495.

5. Wang L, Wang Y, Ma L, Wang Y, Mu X, Huang Z, Zheng Z and Nie H. Cardiopulmonary Adverse Events of Remimazolam versus Propofol During Cervical Conization: A Randomized Controlled Trial. Drug design, development and therapy. 2023;17:1233-1243.

Based on a comprehensive review of the existing literature, we are of the opinion that remimazolam exhibits sedative effects that are comparable to those of propofol.

For the question "However, as the authors stated remimazolam with the BIS values between 60 and 80 was comparable to propofol with a BIS value of 60. What BIS target should be used for remimazolam and propofol respectively?", I will provide detailed explanations as follows:

Response: Although some studies have suggested that a BIS >60 may not mean inadequate sedation in remimazolam anaesthesia[1, 2], there is no universally recommended reference, so the majority of clinical trials still set the target sedation level at a BIS of 40-60. To ensure consistency in the assessment of this particular cohort of patients, we have referred to the majority of protocols in the literature and, following the currently accepted and widely used BIS criteria for maintenance of sedation, have also set the BIS between 40-60. Certainly we should acknowledge this limitation and have listed it in the limitations section of the article. We will continue to refine this limitation in future studies. For details, P20L9-12.

1. Kim KM, Bang J-Y, Choi B-M, Noh G-J. Assessment of explicit and implicit memories during remimazolam anaesthesia using the process dissociation procedure: A prospective cohort study. Eur J Anaesthesiol. 2023;40(11):833-840.

2. Doi M, Hirata N, Suzuki T, Morisaki H, Morimatsu H, Sakamoto A. Safety and efficacy of remimazolam in induction and maintenance of general anesthesia in high-risk surgical patients (ASA Class III): results of a multicenter, randomized, double-blind, parallel-group comparative trial. J Anesth. 2020;34(4):491-501.

We expect that we have accurately understood your suggestions and that the revisions are in line with your comments. If the revisions do not meet your suggestions or do not fully address the issue, we look forward to your continued guidance so that we can further improve the protocol. Your help is greatly appreciated!

2-P6L19, by checking ChiCTR2300076583 at chictr.org.cn, the study execute time is from November 2023 to November 2024. However, here the authors stated "Study activities are expected to start in July 2024 and be completed in December 2025." Please explain this discrepancy.

Response: Sorry for our ambiguous expression! Owing to an oversight, we mistakenly wrote that the study would be conducted from November 2023 to November 2024 when registration on chictr.org.cn. Nevertheless, our initial protocol was expected the study to start in September 2023 and be completed in December 2025. The delay in the start date is due to adjustments in the clinical work of the investigators and the scheduling of thyroid neuromonitoring surgeries

at our centre. We sincerely apologise for the above inaccuracies and misrepresentations, and have made corrections.

Considering the reviewers' suggestion to improve the study by increasing the observation time points and adjusting certain secondary outcomes, we have decided to modify the study protocol according to the comments, and therefore the study conduct time needs to be adjusted accordingly. We expect the study to be conducted from September 2024 to September 2027. The above modification of the study protocol has been approved by the Medical Ethics Committee (2024 Research Ethics Amendment No. 3) and the information has also been updated in the Chinese Clinical Trial Registry.

Details of the specific revisions can be found at P5L19-20.

3-P12L35, "After drug induction, the initial dose of propofol, remimazolam and remifentanil will be administered before endotracheal tube insertion, and the maintenance dose will be infused until skin closure." What were the initial doses of these drugs?

Response: Sorry for our unclear expression! We set initial doses of remimazolam at 1mg/kg.h and initial doses of propofol at TCI (target-controlled infusion) 2μg/ml and remifentanil at TCI 2 ng/ml. As the TCI parameters for propofol and remifentanil are set according to the individual's condition, it is impossible to estimate their exact doses.

We appreciate your reminder and have rewritten this section to better describe our experimental design. For details, P11L12.

4-P15L21, "Preoperative data collection" (1) Please elaborate the way to evaluate the cardiac function. (2) Considering the aim of this study, are the comorbidities and medication history only about cardiovascular system? (3) There may be missing data especially in laboratory tests, I think the authors should clarify the way to deal with missing data in "Statistical methods" section.

(1) Response: Sorry for our unclear expression! We will evaluate the cardiac function according to 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery, and 2014 ESC/ESA Guidelines on non-cardiac surgery cardiovascular assessment and management[1, 2]. Routine evaluations including: New York Heart Association classification, functional capacity using metabolic equivalents, the 12-lead electrocardiogram.

Special tests: In patients with a history of previous cardiovascular disease or complaints of suspected cardiac disease, the following tests may be added to evaluate whether the patient meets the exclusion criteria, including cardiovascular disease assessment of left ventricular function, coronary angiography, biomarkers cardiac troponin T and I, B-type natriuretic peptideand N-terminal proBNP, if necessary. We appreciate your reminder and have rewritten this section to better describe our experimental design. For details, P14L13-16.

1. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, Ford I, Gonzalez-Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Lüscher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Sousa-Uva M, Voudris V and Funck-Brentano C. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014;35:2383-2431.

2. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF and Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e278-e333.

(2) Response: We appreciate your detailed and rigorous questions! Although the main objective of this study is to compare the effect of remimazolam on haemodynamic profiles, the interference of patients' coexisting other systemic diseases and their relevant medication history on the main outcome of the study could not be excluded. Therefore, we will record each patient's co-morbidity and relevant medication history in detail, and further perform statistical analysis at the end of the study to obtain a relatively accurate result.

(3) Response: Sorry for our unclear expression! We appreciate your reminder and have rewritten this section to better describe our statistical approach with the following additions: When dealing with missing data using imputation methods, for continuous quantitative data, the mean or median can be used for imputation, and for discrete quantitative data, the mode can be employed for imputation. For details, P17L16-19.

5-P15L54, "Adverse events during anesthesia". This item should not include hypotension, hypertension, bradycardia and tachycardia, which are already listed above.

Response: We appreciate your reminder and have rewritten this section. For details, P15L2-3.

6-P16L40, (1) Considering the aim of this study, I think the secondary outcomes should include more hemodynamic index, such as the number of hypotension or hypertension

episodes, and the cumulative duration of hypotension or hypertension. (2) Flumazenil will only be used in the remimazolam group, so it is not appropriate to be one of secondary outcomes.

Response: We appreciate your professional and valuable comments on the study protocol, which will be extremely important in guiding the proper conduct of the study, and to ensure the accuracy and completeness of the trial results. We added the number of hypotension or hypertension episodes, and the cumulative duration of hypotension or hypertension to the secondary outcome and deleted flumazenil consumption according to the comment. For details, see P15L26-27.

The above modification of the study protocol has been approved by the Medical Ethics Committee (2024 Research Ethics Amendment No. 3) and the information has also been updated in the Chinese Clinical Trial Registry.

We expect that we have accurately understood your suggestions and that the revisions are in line with your comments. If the revisions do not meet your suggestions or do not fully address the issue, we look forward to your continued guidance so that we can further improve the protocol. Thank you very much!

7. P16L55, "We will record the MAP on the monitor at nine time points…" To show the hemodynamic effects in more detail, I recommend monitoring more frequently at the beginning. Will HR be recorded?

Response: We appreciate your constructive and rigorous comments on the study design, and your suggestions for monitoring more frequently at the beginning are important for obtaining more accurate and improved study results! We have revised the study design to include recording vital signs at the time points of 15 minutes after intubation and 15 minutes after the beginning of surgery. For details, P16L3-6.

The above modification of the study protocol has been approved by the Medical Ethics Committee (2024 Research Ethics Amendment No. 3) and the information has also been updated in the Chinese Clinical Trial Registry.

Sorry for our unclear expression! We will record vital signs, including HR and BP, SpO2 and BIS value, at a total of eleven time points. We appreciate your reminder and have rewritten this section. For details, P16L2.

We expect that we have accurately understood your suggestions and that the revisions are in

line with your comments. If the revisions do not meet your suggestions or do not fully address the issue, we look forward to your continued guidance so that we can further improve the protocol. Your help is greatly appreciated!

8-P27-29, the figures are invisible. Please check.

Response: We appreciate your reminder and sorry for the oversight, we've re-uploaded the image!

Minor:

1-P4L35, "…regimen has minimal impact on EGM responses". The "EGM" is misspelled. I think it should be "EMG".

Response: Thank you for your reminder and sorry for my typos! I have revised it. For details, P3L26.

2-Please remove unnecessary abbreviations which appear only once, such as "GABAA" (P5L19), "ICU" (P8L27) and "PBW" (P10L42).

Response: Thank you for your reminder! I have revised it.

3-P7L15, Table 1: several rows are not aligned.

Response: Thank you for your reminder! I have revised it.

4-P8L8, "Aged 18- 60 years old." This is not in line with the registration and abstract where the age is between 18 and 65 years old.

Response: Thank you for your reminder and sorry for my typos! I have revised it. For details, P7L3.

5-P16L3, "Postoperative data collection" are not exactly consistent with "Postoperative follow-up" section (P12L16). Please check.

Response: Thank you for your reminder and sorry for our unclear expression! We would like to explain that postoperative follow-up is mainly the collection of patients' complications on the second day after surgery, and that postoperative data collection includes data collection from the end of surgery until full recovery from anaesthesia, as well as the second day follow-up, so the two are not exactly the same. For a more accurate description we have made a revision as detailed at P15L11.

6-P16L36, "The primary outcome is the proportion of patients who experience hypotension, defined as MAP≥30% below preoperative baseline, …"

(1) I think a better statement should be "The primary outcome is the occurrence of hypotension…" (2) MAP at T0 (before induction) is set as the baseline value. Why not using MAP at wards as the baseline value?

Response: Thank you for your comments! (1)I have revised it according to your suggestions. For details, P15L20 (2) Initially, we considered that recording blood pressure from the monitor at all time points would be more conducive to comparisons between data, but we carefully considered your suggestion and felt that blood pressure on the ward was more representative of patients' daily levels, so we revised MAP at wards as the baseline value, which was approved by the ethics committee. For details, P16L3.

7-P17L38, "Based on previous studies and our recently completed data, …" Please add citations here.

Response: Thank you for your reminder and sorry for my omission! I have rewritten this section. For details, P16L28.

Point by point response to reviewer 3#

Dear Dr. Kuo-Chuan Hung

We sincerely appreciate your endorsement of the agreement and we will continue to work hard.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Applegate II, Richard**
Affiliation	**Loma Linda University School of Medicine, Anesthesiology**
Date	**06-Sep-2024**
COI	**I have no competing interests**

The authors have satisfactorily addressed my concerns

One minor suggestion on page 8, line 6 consider "...nurse anaesthetist will assign patients to either ... according to the randomisation schedule"

Reviewer	**2**
Name	**Peng, Ke**
Affiliation	**Soochow University**
Date	**25-Sep-2024**
COI	**None.**

Thank you for revising this paper. I think it is greatly improved.

VERSION 2 - AUTHOR RESPONSE

Point by point response to reviewer 1#

Dear Dr. Richard Applegate II

We sincerely appreciate your suggestions on the protocol.

Minor concerns

1-One minor suggestion on page 8, line 6 consider "...nurse anaesthetist will assign patients to either ... according to the randomisation schedule"

Response: Thank you for your reminder! We have revised it according to your suggestion. For details, P8L7.

Point by point response to reviewer 2#

Dear Dr. Ke Peng

We sincerely appreciate your endorsement of the agreement and we will continue to work hard.

VERSION 3 - REVIEW

Reviewer	**1**
Name	**Applegate II, Richard**
Affiliation	**Loma Linda University School of Medicine, Anesthesiology**
Date	**24-Oct-2024**

COI

The authors have adequately addressed my concerns

Reviewer	**2**
Name	**Peng, Ke**
Affiliation	**Soochow University**
Date	**09-Oct-2024**
COI	

Now it is suitable for publication.