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Reviewer A

The authors assessed intraoperative changes in the Perfusion Index (PI) of bilateral upper extremities following thoracic paravertebral block (PVB) and intertransverse process block (ITPB) in patients undergoing lung resection surgery. The study found that PVB resulted in a notable unilateral increase in upper extremity PI, whereas ITPB led to a more inconsistent and lesser degree of increase. The research underscores the utility of monitoring PI values as an indicator of upper extremity sympathetic blockade, while cautioning about potential confounders that may affect observations during surgery. Overall, the manuscript is well-written and easy to follow.

Thank you for the comprehensive review and invaluable comments. We have addressed each comment point by point, and all corresponding changes in the manuscript are now highlighted in red.

Major Suggestions

Comment 1: The authors should discuss the potential for selection bias due to the non-randomized design of the study and its possible impact on the results. Clarification is needed on who decided the group allocation and the criteria for assigning patients to either the PVB or ITPB group.

Reply 1: Thank you for addressing this important matter. As you correctly noted, the study was conducted in a non-randomized fashion. The initial study comprised observational research involving two distinct groups (PVB vs. control) within different surgical contexts (thoracic vs. urologic procedures). Subsequently, the second study focused on a single group (ITPB in thoracic procedures). Consequently, group allocation was not manipulated arbitrarily but rather determined sequentially based on the conduction period of the study.

As indicated by the sample size determination, these studies were not originally designed for group comparisons based on a predefined hypothesis seeking differences between groups. Instead, our aim was to observe intraoperative changes in PI with (PVB or ITPB) or without (control) corresponding blockades within each group. While significant differences in intraoperative PI values between groups were observed, we acknowledge the necessity for future studies to validate these findings with clearly defined hypotheses for group comparisons. Although the results provided as group

comparisons lack a prior hypothesis or power calculation, providing the results stratified by groups with noted statistical differences is meaningful for hypothesis generation, rather than simply providing null descriptive statistics. However, we still acknowledge that this group comparison needs future validation with proper sample size calculation and randomization.

Given that the present study represents a combination of pilot studies, addressing this issue conclusively at this stage is not feasible. This point has been explicitly addressed in the discussion section.

Changes in the text 1: Following paragraph has been added as the third paragraph of the discussion,

" It is important to note that the current study was a combined study of two pilot studies aimed at observing intraoperative changes in PI with (PVB or ITPB) or without (control) regional blockades within each group. As these studies were not designed with a prior hypothesis specific to group comparison and power calculation, the result should be conceived as a hypothesis and framework generating measure rather than a confirmatory result. The study was conducted in a non-randomized fashion sequentially, with the first pilot study for PVB and control, followed by the second pilot study for ITPB. Future studies with proper sample size and randomization are needed to validate the results of the current study."

Also, the conclusion was revised to further clarify this issue as follows,

“In conclusion, the study suggests that PVB results in a noticeable unilateral increase in upper extremity PI, whereas ITPB tends to induce a more inconsistent and lesser degree of increase. While monitoring PI values can serve as an indicator of upper extremity sympathetic blockade, it is essential to acknowledge potential confounders during surgery that may impact these observations. It is important to emphasize that the present study serves as a preliminary exploration, and further research, particularly through randomized trials, is needed to validate these findings conclusively.”

Comment 2: Given the mention of potential confounders in interpreting the data, it would be beneficial for the authors to elaborate on how the findings of this study can be applied in clinical practice. What are the clinical implications and applications of this research?

Reply 2: The findings of the current study have two significant clinical implications. Firstly, there is a clinical need to verify sympathectomy intraoperatively following surgical sympathectomy (e.g., for hyperhidrosis) or regional blockade (e.g., PVB or ITPB). Observing changes in PI can help determine whether the planned sympathectomy was achieved or if additional ablation or blockade is necessary. This intraoperative verification allows for timely adjustments before emergence from anesthesia. Additionally, intraoperative PI measures can potentially facilitate the

comparison of efficacy among emerging thoracic regional techniques, such as erector spinae, retrolaminar, and costotransverse foramen blocks.

Secondly, as highlighted in the current study, systemic and hemodynamic alterations, along with surgical stimulation, may interfere with the observation of PI changes. While modifications with contralateral side and baseline can mitigate such confounding, they seem not to completely eliminate noise, as evidenced by the findings in the control group. Therefore, careful control of hemodynamics and surgical stimuli is advisable to accurately determine changes in PI values before and after regional blockade or surgical sympathectomy. This finding would be helpful for designing future studies.

Changes in the text 2: Following paragraphs were elaborated to clearly deliver the abovementioned issues further.

"To account for systemic factors prone to fluctuations induced by general anesthesia and surgical stimuli, such as sympathetic tone, hemodynamics, and temperature—factors that, in turn, affect the PI(19,21)—we implemented bilateral monitoring of PI. By observing changes in the adjusted value, PI-O/PI-CL, we could discern whether the increase in PI values was induced systematically or regionally (i.e., by the blockade). Unfortunately, however, hidden confounders seem to remain, leading to fluctuations in PI-O/PI-CL even in the absence of a blockade, as observed in the control group. Potential confounding factors may include imbalanced changes in perfusion or temperature of an extremity. This issue should be addressed in future studies with more meticulous PI monitoring and carful patient positioning. *Additionally, it is advisable to carefully control for hemodynamics and surgical stimuli to accurately determine changes in PI values before and after regional blockade or surgical sympathectomy.*"

"There has been a growing interest in paravertebral proxies and their underlying mechanisms that convey analgesic effects on the chest wall(1-9). Theoretically, the anterior spread of local anesthetic should occur through channels such as the costotransverse foramen to provide this analgesic effect, as supported by various cadaveric and anatomical studies(7-9). However, there is still limited evidence available from real clinical contexts. Therefore, the present study aimed to develop a clinically useful tool for the noninvasive detection of sympathetic blocks in an operating environment. This tool not only offers a way to better understand newly developed regional techniques but also addresses the scarcity of evidence in clinical settings. Furthermore, it may provide real-time intraoperative feedback for a successful surgical sympathectomy(22). *Additional measures can be considered before emergence from anesthesia if expected changes are not observed after surgical sympathectomy or regional blockade.*"

The clinical implication of the current finding was also discussed in the following part,

"In a previous study that reported an increase in upper extremity PI after PVB, an additional experimental setting was necessary(20). In that study, the blockade was administered before anesthesia and the surgical stimulus, with a distinct observation period of 30 minutes. Although this setup could offer more controlled data, it deviates from everyday clinical practice. In the current study, our aim was to establish a more practical approach for evaluating sympathetic blockade after paravertebral or its proxies, one that can be readily applied in clinical settings."

Minor Suggestions

Comment 3: Could the authors elaborate on the term "normalized" mentioned in the abstract? Specifically, how was normalization achieved in the context of this study?

Reply 3: The term "normalized" was meant to indicate "scaled". To convey this meaning clearly, the statement has been revised as follows.

Changes in the text 3:

"The PI value of the operating side (PI-O) was *divided by* the contralateral side (PI-CL), and the relative change to baseline was assessed (relative PI-O/PI-CL), with a 50% increase considered meaningful."

Comment 4: It is important for each figure to be self-explanatory. Regarding Figure 2, could the authors clarify what 'time 0' signifies? Additionally, why does the timeline not start at 0 for the PVB and ITPB cases, and what does the blue box represent?

Reply 4: We apologize for the confusion. In Figure 2, the time indicated signifies the actual time from the beginning of the record, hence the start of monitoring. To address potential confusion, we have revised all baseline times (immediately after position change, thus, beginning of the blockade) to be labeled as time 0. The sky-blue shaded area in the figure now represents the procedure time, ranging from the position change to the end of the block.

Changes in the text 4: The time frames indicated in Figure 2 and supplementary material have been adjusted accordingly. Additionally, the legend for Figure 2 has been revised as follows,

"The starting point (time 0) of the figure indicates position change and the sky-blue shaded area indicates procedure time *(from position change to block end).*"

Reviewer B

Thank you for the comprehensive review and invaluable comments. We have addressed each comment point by point, and all corresponding changes in the manuscript are now highlighted in red.

Comment 1: I have some doubts on methodology. It looks like 2 different case series on the same topic. I wonder how You discuss about sample sizeing like a RCT. My advise is to extensively revise methodology.

Reply 1: Thank you for addressing this important matter. As you correctly noted, the study was conducted in a non-randomized fashion. The initial study comprised observational research involving two distinct groups (PVB vs. control) within different surgical contexts (thoracic vs. urologic procedures). Subsequently, the second study focused on a single group (ITPB in thoracic procedures).

As indicated by the sample size determination, these studies were not originally designed for group comparisons based on a predefined hypothesis seeking differences between groups. Instead, our aim was to observe intraoperative changes in PI with (PVB or ITPB) or without (control) corresponding blockades within each group. While significant differences in intraoperative PI values between groups were observed, we acknowledge the necessity for future studies to validate these findings with clearly defined hypotheses for group comparisons. Although the results provided as group comparisons lack a prior hypothesis or power calculation, providing the results stratified by groups with noted statistical differences is meaningful for hypothesis generation, rather than simply providing null descriptive statistics. However, we still acknowledge that this group comparison needs future validation with proper sample size calculation and randomization.

Revising methodology, fundamentally, requires reconducting the study, and addressing this issue conclusively at this stage is not feasible. Thus, we decided to more clearly indicate in the manuscript that the current study is a pilot study.

Changes in the text 1: Following paragraph has been added as the third paragraph of the discussion,

"It is important to note that the current study was a combined study of two pilot studies aimed at observing intraoperative changes in PI with (PVB or ITPB) or without (control) regional blockades within each group. As these studies were not designed with a prior hypothesis specific to group comparison and power calculation, the result should be conceived as a hypothesis and framework generating measure rather than a confirmatory result. The study was conducted in a non-randomized fashion sequentially, with the first pilot study for PVB and control, followed by the second pilot study for

ITPB. Future studies with proper sample size and randomization are needed to validate the results of the current study."

Also, the conclusion was revised to further clarify this issue as follows,
"In conclusion, the study suggests that PVB results in a noticeable unilateral increase in upper extremity PI, whereas ITPB tends to induce a more inconsistent and lesser degree of increase. While monitoring PI values can serve as an indicator of upper extremity sympathetic blockade, it is essential to acknowledge potential confounders during surgery that may impact these observations. *It is important to emphasize that the present study serves as a preliminary exploration, and further research, particularly through randomized trials, is needed to validate these findings conclusively.*"

Comment 2: Morover there are only few data on block effectiveness and QT evaluation.
Reply 2: As you pointed out, a more comprehensive evaluation of block effectiveness, including assessments such as temperature and/or sweating changes in the upper extremity, postoperative pain scores, analgesic requirements, and dermatomal coverage of the chest wall, was not included in the current study. This limitation cannot be addressed at the current stage and is acknowledged as follows,
"This study presents several limitations. Firstly, the efficacy of blockade was solely assessed based on sonographic endpoints, such as the downward movement of the pleura or bulging of the intertransverse tissue complex during injection. Future studies would benefit from a more comprehensive evaluation, including detailed assessments of dermatomal coverage and postoperative pain scores."

Comment 3: Another specific issue is related to protocol variation (line 111).
Reply 3: Thank you for the comment. Although the protocol had been changed after the commencement of the study, since the initial enrollments before the protocol change occurred only in the control group, this change has no impact on the protocol variation in the study groups (PVB and ITPB). To clarify this issue, the following statement has been added to the manuscript.
Changes in the text 3: "The protocol had been updated on December 16, 2022 (after enrollment of 4 subjects in the control group) from a dual injection protocol (T4-5 and T6-7) due to the request from the surgical department to cover wider level of dermatomes. *Since this protocol change occurred only after enrolling subjects in the control group, there were no variations in the protocol for the study groups.*"

Reviewer C

The manuscript is very well and thoroughly written and English is excellent.
I only have a few remarks for some corrections.

Thank you for the comprehensive review and invaluable comments. We have addressed each comment point by point, and all corresponding changes in the manuscript are now highlighted in red.

Comment 1: Please enter a space between the word and the following brackets which is including the reference. This concerns lines 36, 39, 42,44,48, 105, 206, 208, 213, 215, 221, 223, 225, 232, 233.
Reply 1: Thank you for the suggestion. All the concerning parts were revised accordingly.
Changes in the text 1: All the concerning parts were revised accordingly.

Comment 2: Line 39, please correct for: "This kind of approaches can relieve technical difficulty and decrease risks associated with the …."
Reply 2: Thank you for the suggestion. The concerning part was revised accordingly.
Changes in the text 2: "This kind of approaches can relieve technical difficulty and *decrease* risks associated with the paravertebral blockade (PVB)."

Comment 3: Line 66, please correct for: "…or urologic procedure performed with general anesthesia (control group)."
Reply 3: Thank you for the suggestion. The concerning part was revised accordingly.
Changes in the text 3: "… urologic procedure performed with general anesthesia (control group)."

Comment 4: Line 161: what do you mean by the first and the second study?
Reply 4: This was a combined study of two pilot studies, first for PVB and control and second for ITPB. You can also find statements indicating this issue in following parts and the patient flow diagram (Figure 1).
"This was a joined work of two pilot studies, one for 1) PVB; and the other for 2) ITPB, both conducted at a university affiliated hospital (Chungnam National University Hospital, Daejeon, Korea) from 1) November 2022 to January 2023; and 2) June to August 2023."

"The first pilot study (PVB) was designed as a two arm non-randomized controlled trial. The study group was set to observe PI change after PVB intraoperatively. As the

surgical position, lateral decubitus position, per se could affect the PI values in both hands, a control group was set which also adopts same surgical position intraoperatively. To meet the needs for a control group that matches the surgical position and anesthesia type of the study group, urologic procedures such as nephrectomy, radiofrequency ablation of renal mass were included.

The second pilot study (ITPB) was designed as a single arm observational study which resembles the PVB group of the prior pilot study."

Comment 5: Line 176 - 179: do you mean that these fluctuations occur after 15 minutes of initiation of surgery?

Reply 5: As you can see in the supplementary material, there were some fluctuations in the relative PI-O/PI-CL even without any blockade during the surgery (control group), indicating a possible influence on PI balance by surgical stimulation and/or hemodynamic alterations. Therefore, we focused on the period from the beginning of the blockade (time 0) to 5 minutes post-blockade (thus including the procedure time + 5 minutes) to determine significant changes in relative PI-O/PI-CL primarily due to the blockade. This time period is free from surgical stimulus and hemodynamically stable because it encompasses the block procedure and surgical draping (5 minutes post-blockade).

Changes in the text 5: The corresponding statement has been revised as follows,

"Consequently, we considered only the periods from the procedure's commencement to *5 minutes after the end of blockade* (during surgical draping) as valid for assessing PI changes resulting from the blockade."

Comment 6: Line 337, table 2: how can we interpret your numbers which you descibe for the fluid intake ? For example, the numbers in the control group ((350.0,1200.0). What does 350.0 mean and what is 1200.0 ? Are you quoting the lower and the upper ranges ? Could the differences in fluid intake between groups bias the outcome of the perfusion index?

Reply 6: As mentioned in the footnote of the table, it indicates median, first, and third quartile numbers, thus the numbers in the bracket indicate interquartile range. Some possibility exists that fluid requirement per se, or intake can influence on hemodynamic and thus on intraoperative PI. However, most cases involved in this study did not require large amounts of fluid intake, as indicated by the duration of surgery and total fluid intake. As group imbalance and possible influence on the outcome may be a concern to the readers, p-values have been introduced to Table 2. Additionally, to provide a clearer quantification of intraoperative fluid intake, the values were transformed into 'ml/hr' in the revised table.

Changes in the text 6: The table has been revised accordingly.

Comment 7: Line 344- 345 Figure 1. Patient flow diagram: Please explain why you have two flow diagrams for inclusion and exclusion of patients

Reply 7: As previously mentioned, this was a combined study of two pilot studies, first for PVB and control and second for ITPB.

Reviewer D

I have read with great interest this manuscript. The investigators looked at the perfusion index to evaluate the effect of two different paraspinal blocks want to sympathetic system. This work is interest and I congratulate the investigators. However, there are several methodological weaknesses that make the quality of this work low.

Thank you for the comprehensive review and invaluable comments. We have addressed each comment point by point, and all corresponding changes in the manuscript are now highlighted in red.

Comment 1: First, there is no research hypothesis. It is not clear what the authors hypothesize or theorize regarding the effect of the blocks on the perfusion index.

Reply 1: Thank you for the comment. We stated our hypothesis in the introduction as follows.

Changes in the text 1: "Perfusion index (PI) is a parameter that derived from a photoplethysmogram signal and reflects the pulsatile versus non-pulsatile component of the signal. This index has been used as a surrogate marker of sympathetic blockade (12-16). *This pilot study hypothesized that thoracic PVB and intertransverse process block (ITPB) would increase PI of upper extremity.* The aims of this study were twofold: 1) to evaluate intraoperative changes in PI after these blockades; 2) to set up a framework for the analysis of intraoperative PI changes after these blockades."

Comment 2: The method section does not mention a placebo group. While the authors used a control group, a placebo group would have been scientifically more appropriate.

Reply 2: Thank you for the comment. We agree that the approach you suggested would be more scientifically robust. However, it was not clinically feasible for us, as providing multimodal analgesia employing regional blockade is the widely accepted standard. Thus, omitting a blockade for the research process could be considered unethical. To address this issue, we included a urologic procedure group as a control group, which currently lacks routine regional blockade for analgesia. We have added a statement addressing this limitation in the manuscript.

Furthermore, as this study observed objective changes in PI values, it is hardly expected that a placebo or a sham block could make a considerable difference in the results.

Changes in the text 2: "Fourthly, we were unable to include a true control group in thoracic procedures. Since incorporating a regional blockade as part of multimodal analgesia is a widely accepted standard, omitting a blockade for a research purpose was clinically unfeasible. Instead, we included a urologic procedure group as a control

group, which currently lacks routine regional blockade for analgesia."

Comment 3: Patients were not randomized. Therefore, significant bias in the results is expected. More so if there was no blinding assessment of the data.

Reply 3: Thank you for addressing this important matter. As you correctly noted, the study was conducted in a non-randomized fashion. The initial study comprised observational research involving two distinct groups (PVB vs. control) within different surgical contexts (thoracic vs. urologic procedures). Subsequently, the second study focused on a single group (ITPB in thoracic procedures).

As indicated by the sample size determination, these studies were not originally designed for group comparisons based on a predefined hypothesis seeking differences between groups. Instead, our aim was to observe intraoperative changes in PI with (PVB or ITPB) or without (control) corresponding blockades within each group. While significant differences in intraoperative PI values between groups were observed, we acknowledge the necessity for future studies to validate these findings with clearly defined hypotheses for group comparisons. This issue of non-randomized trial is further addressed in the discussion as follows.

Given the PI values are objective measurements, bias due to blinding issues should be minimal.

Changes in the text 3: Following statements were added to the discussion,

"It is important to note that the current study was a combined study of two pilot studies aimed at observing intraoperative changes in PI with (PVB or ITPB) or without (control) regional blockades within each group. As these studies were not designed with a prior hypothesis specific to group comparison and power calculations, the result should be conceived as a hypothesis and framework generating measure rather than a confirmatory result. The study was conducted in a non-randomized fashion sequentially, with the first pilot study for PVB and control, followed by the second pilot study for ITPB. Future studies with proper sample size calculation for group comparison with randomization are needed to validate the results of the current study."

Comment 4: It is not clear why the authors conducted to pilot studies.

Reply 4: As previously mentioned, our primary hypothesis was that thoracic PVB and intertransverse process block (ITPB) would increase PI of upper extremity. After this hypothesis, we clearly stated our aim for this pilot study as follows,

"The aims of this study were twofold: 1) to evaluate intraoperative changes in PI after these blockades; 2) to set up a framework for the analysis of intraoperative PI changes after these blockades."

This framework is crucial because utilizing the photoplethysmogram signal (i.e., PI), which is readily and widely used in clinical practice, allows for easier intraoperative

assessment of sympathetic blockade.

There is a clinical necessity to verify sympathectomy intraoperatively following surgical sympathectomy (e.g., for hyperhidrosis) or regional blockade (e.g., PVB or ITPB). Observing changes in PI can aid in determining whether the planned sympathectomy was achieved or if additional ablation or blockade is necessary. This intraoperative verification enables timely adjustments before emergence from anesthesia. Additionally, intraoperative PI measures have the potential to facilitate the comparison of efficacy among emerging thoracic regional techniques, such as erector spinae, retrolaminar, and costotransverse foramen blocks.

Based on the findings of the current study, a future study can be appropriately designed with considerations of the data and caveats found in this study. The clinical implications of the findings of the current study and the need for well-designed randomized trials in the future have been further elaborated in the text.

These points were also stated in the introduction as follows:

"There has been an enthusiasm around paraspinal blocks (1-5). These blocks include erector spinae plane block, intertransverse process block, and retrolaminar block, and commonly aims paravertebral spreading of local anesthetic without directly introducing the needle into the paravertebral space (6). This kind of approaches can relieve technical difficulty and decrease risks associated with the paravertebral blockade (PVB).

Previous cadaveric studies have demonstrated the spread of dye into the paravertebral space following paraspinal blocks (7-9). However, despite these findings, there is a lack of clinical data on the efficacy of these blocks in achieving sympathetic blockade. It is important to consider that cadaveric studies may have limitations and may not accurately reflect results in living patients (10,11). This highlights the need for a clinically feasible tool to evaluate sympathetic blockade."

Changes in the text 4: Paragraphs discussing these issue were further elaborated as follows,

"To account for systemic factors prone to fluctuations induced by general anesthesia and surgical stimuli, such as sympathetic tone, hemodynamics, and temperature—factors that, in turn, affect the PI(19,21)—we implemented bilateral monitoring of PI. By observing changes in the adjusted value, PI-O/PI-CL, we could discern whether the increase in PI values was induced systematically or regionally (i.e., by the blockade). Unfortunately, however, hidden confounders seem to remain, leading to fluctuations in PI-O/PI-CL even in the absence of a blockade, as observed in the control group. Potential confounding factors may include imbalanced changes in perfusion or temperature of an extremity. This issue should be addressed in future studies with more meticulous PI monitoring and carful patient positioning. *Additionally, it is advisable to carefully control for hemodynamics and surgical stimuli to accurately determine changes in PI values before and after regional blockade or surgical sympathectomy.*"

"There has been a growing interest in paravertebral proxies and their underlying mechanisms that convey analgesic effects on the chest wall(1-9). Theoretically, the anterior spread of local anesthetic should occur through channels such as the costotransverse foramen to provide this analgesic effect, as supported by various cadaveric and anatomical studies(7-9). However, there is still limited evidence available from real clinical contexts. Therefore, the present study aimed to develop a clinically useful tool for the noninvasive detection of sympathetic blocks in an operating environment. This tool not only offers a way to better understand newly developed regional techniques but also addresses the scarcity of evidence in clinical settings. Furthermore, it may provide real-time intraoperative feedback for a successful surgical sympathectomy(22). *Additional measures can be considered if expected changes are not observed after surgical sympathectomy or regional blockade before emergence from anesthesia.*"

The clinical implication of the current finding was also discussed in the following part,

"In a previous study that reported an increase in upper extremity PI after PVB, an additional experimental setting was necessary(20). In that study, the blockade was administered before anesthesia and the surgical stimulus, with a distinct observation period of 30 minutes. Although this setup could offer more controlled data, it deviates from everyday clinical practice. In the current study, our aim was to establish a more practical approach for evaluating sympathetic blockade after paravertebral or its proxies, one that can be readily applied in clinical settings."

Comment 5: In the results there were two patients who their results were withdrawn because of unexpected blind changes in the surgical and block procedures. Perhaps the authors should have included junior patients.

Reply 5: The withdrawn cases were due to unexpected changes in the operating schedule, which were incompatible with the research schedule, and the inability to perform the blockade due to unexpectedly poor visualization during the block procedure. The statement regarding this issue was revised as follows.

Changes in the text 5: "Five subjects were withdrawn from the analysis due to data loss. Additionally, two subjects in the ITPB group were withdrawn, one due to unexpected change in the operating schedule (which was incompatible with the research schedule), and the other due to the inability to perform the planned blockade because of poor visualization during ultrasound scanning."

Comment 6: Table one shows that 40% of the patients in the ITPB group had diabetes

which is a known cardiovascular disease affecting the vascular system. On the other hand, 9% of the patients in the paravertebral group had diabetes. Fragility is a concern in this study

Reply 6: As mentioned previously, this was a pilot study that was not primarily based on a predefined hypothesis seeking differences between groups. Along with the non-randomized fashion, the results from the current study should be validated in future well-designed RCTs.

Nevertheless, to provide further insights into the baseline characteristics, we revised Table 2 to include p-values for group comparisons.

Changes in the text 6: Table 2 was revised accordingly.

Comment 7: Table 3 is incomplete. It lacks procedure change time and onset time in the control group. It is not clear how the data was analyzed.

Reply 7: As no procedure (block) was performed in the control group, there are no available values for the procedure and onset time. Thus, the p-values for the procedure time and onset time were based on two-group comparisons. The overall statistical tests employed in the analysis were clearly outlined in the method section.

Comment 8: Overall their results and discussion are well described however due to the many methodological issues they not relevant.

Reply 8: Thank you for the comment. The manuscript has been revised accordingly, addressing the methodological issues with incorporating other comments.

Comment 9: Grammar can be improved.

Reply 9: Thank you for the comment. We are planning to undergo English editing as needed after finishing the overall revision process.

Comment 10: Figures are clear.

Reply 10: Thank you.