Author's response to reviews

Title: Sonographic Optic Nerve Sheath Diameter as a Surrogate Measure for Intracranial Pressure in Anesthetized Patients in the Trendelenburg Position

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Author's response to reviews: see over
Dear Editor,

We refer to MS: 6358756215045898

Research article

“Effect of transient steep Trendelenburg position on optic nerve sheath diameter as a surrogate for intracranial pressure under general anesthesia: a prospective observational study”

We would like to thank the editor and the reviewers for the thoughtful review. We have attempted to comprehensively address each point raised by the reviewers and have made appropriate changes to the text.

Yours sincerely,

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Reviewer 1

Major compulsory revisions

1. Page 4, Paragraph 1 (lines 2-9): Please describe the difference between the head-down position mentioned by references 1 and 2 and the Trendelenburg position. Also, the authors state that the effect of the Trendelenburg position on ICP has not been evaluated, although this topic was addressed in several papers including references 20 (Kim et al 2014), 21 (Kalmar et al, 2010), and 24 (Park et al 2009). A quick literature review returned many more reports on patient positioning and ICP that should be acknowledged.

Thank you for your comment.

(1) We described the difference between the Trendelenburg position and the head down position in Introduction section, now it reads, “in that the head is straight along the axis of the body in the Trendelenburg position, whereas the head is extended back and the body remains straight in the head-down position.”

(2) As you pointed out, we have added in the Introduction section. Now it reads, “In addition, the combined effect of a prolonged Trendelenburg position and pneumoperitoneum has been reported to increase ICP [3].”

Also, we have revised in the Discussion section. Now it reads, “In contrast to our current results, it has been reported that the ONSD measured 10 min after pneumoperitoneum combined with the Trendelenburg position did not increase under general anesthesia with sevoflurane [22]. Increased cerebral blood flow might be compensated for by cerebrospinal fluid translocation to the vascular component during the 10-min interval between the position change and the measurement of the
ONSD. However, our present study measured the ONSD 3 min after pneumoperitoneum combined with the Trendelenburg position. This duration might be too short for the patient to develop compensation mechanisms. Interestingly, another study assessed the ONSD during laparoscopic prostatectomy, and found an increased ONSD 10 min after pneumoperitoneum combined with the Trendelenburg position [3]. This previous study used desflurane, which induced a greater increase in cerebral blood flow than sevoflurane [23], for anesthetic maintenance. Differences in the anesthetic drug might contribute, at least in part, to the conflicting results.

The effect of ETCO$_2$ on ICP did not accentuate the increase in the ONSD observed in the steep Trendelenburg position because the ETCO$_2$ level decreased during study period. Our present result suggests the importance of careful control of ETCO$_2$ in anesthetized patients in the Trendelenburg position. However, the previous report might be confusing for clinicians when adjusting the ETCO$_2$ during robot-assisted laparoscopic radical prostatectomy, because it showed an unexplained small difference between the ETCO$_2$ and the PaCO$_2$ over the whole period when the Trendelenburg position combined with pneumoperitoneum was adopted [3], unlike the results of our present analyses and previous studies [24-26].

We found that the rSO$_2$ was unchanged at all of the predetermined time points under general anesthesia. The rSO$_2$, which reflects a regional balance between cerebral oxygen supply and demand, has been studied to identify the effects of various positions on cerebral blood flow under diverse positions during laparoscopic surgery, yielding conflicting results [27-30]. The inconsistencies among studies may be partly due to the characteristics of near-infrared spectroscopy, which mainly reflects the venous compartment (artery:vein = 25%:75%), and its lack of accuracy for reflecting cerebral blood flow compared with jugular bulb oxygen saturation [31].”

2. **Page 5, Lines 14-16:** Why was an inspired sevoflurane concentration of 2-4% chosen as your standard anesthetic? Why not use a concentration closer to 1 minimum alveolar concentration? Is there a risk that such high dose of volatile anesthetic would increase ICP?
Also, was the intended remifentanil dose “2-5 ng/mL.” or some other dose?

Thank you for your comment. We agree with your opinion. In our patients, anesthesia was maintained with 2-3 vol% sevoflurane to minimize the effect of volatile anesthetics on ICP. We are sorry to our typographic error. We have revised the sevoflurane concentration to 2-3 vol%.

In addition, the infusion rate 2-5 ng/ml for continuous infusion of remifentanil was usually sufficient to achieve hemodynamic stability during anesthetic maintenance in our patients.

3. Page 6, Line 26: Please clarify which comparisons were performed using an ‘ANOVA with rank”? The data presented in table 2 are all continuous variables and it’s not clear where or why a nonparametric analysis would be required. (major compulsory revision)

Thank you for your comment. One-way repeated measures ANOVA was used to evaluated to evaluate the effect of several different positions under general anesthesia on the change in the ONSD, SBP, DBP, MBP, HR, $P_{\text{peak}}$, $P_{\text{plat}}$, and rSO$_2$. And, One-way repeated measures ANOVA on rank were used to evaluate the effect of several different positions under general anesthesia on the change in the BT and ETCO$_2$. We have revised the content in Methods section. We also have revised Table 2 and expressed as median (interquartile range) for non-parametric variables.

Now it reads, “One-way repeated measures analysis of variance (ANOVA) was used to evaluate the effect of several different positions under general anesthesia on the change in the ONSD, SBP, DBP, MBP, HR, $P_{\text{peak}}$, $P_{\text{plat}}$, and rSO$_2$. If any interaction was significant, post hoc analysis was performed using the Holm–Sidak method. One-way repeated measures ANOVA on rank was used to evaluate the effect of the different positions under general anesthesia on the change in the BT and ETCO$_2$. If any interaction was significant, post hoc analysis was performed using Tukey's test.” (In
4. Page 9, Lines 4-11: The currently worded sentence suggests that the link between ONSD and ICP is fully described and validated, but the evidence supporting that statement has not yet been established in your manuscript. Please describe in some detail how to extrapolate the ICP from the ONSD, including a critical review of the strength of the evidence. At this point in the manuscript, it would be helpful to mention that an ONSD of 5 mm approximates an ICP of 20 cm H$_2$O, as discussed at Page 9, lines 24-26, and please be very thorough to explain how that assumption is determined. Because the relationship between ONSD and ICP is a critical assumption for this work, the data supporting the association needs to be thoroughly reviewed. (major compulsory revision)

Thank you for your comment. We agree with your opinion. We have added the content regarding the corresponding cut-off value for ONSD of 5 mm to ICP of 20 cmH$_2$O in Discussion section, now it reads, “Several previous studies reported that the ONSD cut-off value of 5 mm was sensitive and specific for the identification of computed tomographic findings suggestive of increased ICP [6, 13]. Importantly, the ONSD cut-off value of 5 mm was found to be able to distinguish an ICP > 20 mmHg measured by ventriculostomy, showing an area under a receiver operator characteristics curve of 0.93 with a sensitivity of 88% and specificity of 93% in patients with clinical or radiologic signs of increased ICP [14].”

We have also described this issue in the Introduction section, now it reads, “An increased optic nerve sheath diameter (ONSD) detected by ocular sonography is associated with clinical signs of high ICP in adults with traumatic brain injury and in children with hydrocephalus or liver failure [9-13]. Moreover, the ONSD has been correlated with ICP invasively measured by an intraparenchymal
catheter inserted into the frontal lobe in sedated patients receiving neurocritical care, including patients with severe traumatic brain injury [14]. Rapid and safe sonographic measurement of ONSD may enable patients to be screened for increased ICP.”

5. Page 10, Lines 10-15: This section ends with a recommendation for caution against prolonged steep Trendelenburg due to ICP concerns. This report does not offer evidence to suggest an association between Trendelenburg position and pathologic ICP, and so it is premature to warn strongly against positioning. If may be appropriate to comment that steep Trendelenburg positioning might be harmful, however the language should reflect the uncertainty of the association and the lack of clinical endpoints. (major compulsory revision)

Thank you for your comment. We have revised the sentence in Abstract section, now it reads, “Use of the isolated steep Trendelenburg position, for even a short duration, increased the sonographic ONSD, providing a better understanding of the effect of only a transient steep Trendelenburg position on ONSD as a surrogate measure for ICP.”

We also have revised the sentence in Conclusion section, now it reads, “The sonographic ONSD as a surrogate measure for ICP increases when patients are placed in the isolated steep Trendelenburg position even for a short duration. Monitoring of the sonographic ONSD may provide useful information on changes in ICP when the steep Trendelenburg position is inevitably performed.”

6. Page 11, Lines 5-7: Only one study limitation is mentioned. Please account for additional sources of error. For example, could the induction agent or maintenance anesthetic affect ONSD separately from Trendelenburg position? How variable were the surgical conditions and intraoperative findings? Does blood loss or fluid management affect ONSD?
Does surgical positioning complicate the measurement? It will be very important to address the uncertainty concerning how well ONSD approximates ICP. (major compulsory revision)

Thank you for your comment. As you pointed out, we have added in the Limitation section. Now it reads, “Our study had the following limitations. First, we studied a fixed degree of incline when establishing the Trendelenburg position. Further analysis of whether there is a graded association between the degree of incline during the Trendelenburg position and the change in the ONSD is needed. Second, our investigations were conducted under general anesthesia without excluding the effect of anesthetics on ONSD. Therefore, the change in the ONSD when the position was changed under general anesthesia can differ from that in awake patients, who were previously found not to show significant changes in the ONSD when placed in the Trendelenburg position [32]. An attenuated ability to maintain homeostasis in cerebral blood flow during general anesthesia using volatile anesthetics would be a plausible explanation, because volatile anesthetics have a dose-dependent cerebral vasodilatory effect [33]. Third, there are no general consensus over optimal cut-off values of ONSD, despite of use of ONSD cut-off value of 5 mm to detect increased ICP > 20 mmHg in the present study [6, 7, 13-15]. Furthermore, the accuracy of ONSD in detecting elevated ICP remains controversial [7, 17, 34]. Therefore, the present study does not definitively prove that there is an elevated ICP with steep Trendelenburg positioning, but does indicate that there is a likely rise in ICP which may reach critical levels in some patients.”

7. Page 12, Lines 2-6: Please re-visit the conclusion. Given that there is still uncertainty about how well ONSD approximates ICP, please temper your recommendation for caution against the Trendelenburg position until it is known that a clinically meaningful change in ICP does occur, and that ONSD can detect the change. (major compulsory revision)
Thank you for your comment. We have revised the sentence as you pointed out, now it reads, “The sonographic ONSD as a surrogate measure for ICP increases when patients are placed in the isolated steep Trendelenburg position even for a short duration. Monitoring of the sonographic ONSD may provide useful information on changes in ICP when the steep Trendelenburg position is inevitably performed.”

8. Finally, please address similar findings published by other groups. A literature review finds 3 prior studies that compare ONSD during robotic laparoscopic prostatectomy. Verdonck et al (PLoS One. 2014 Nov 4;9(11):e111916) report no difference in ONSD diameter, while Whiteley et al (J Neurosurg Anesthesiol. 2014 Aug 7. [Epub ahead of print]) and Kim et al (J Endourol. 2014 Jul;28(7):801-6) (an article that was cited in the References) would seem to confirm the findings presented here. Please be sure to explain the similarities and differences between this study and these others. (major compulsory revision)

Thank you for your comment. We have described the similarity and difference between previous studies and our study in Discussion section.

Now it reads, “It has been reported that the ONSD is increased after pneumoperitoneum desufflation and before a neutral level is resumed at the end of surgery [21]. This previous finding might support our results. However, the PaCO$_2$ is expected to increase at the end of surgery, although this increase was not shown in the previous study, and this increased PaCO$_2$ might affect the ONSD. Therefore, the effect of the isolated Trendelenburg position on ONSD may not have been exclusively evaluated.

In contrast to our current results, it has been reported that the ONSD measured 10 min after pneumoperitoneum combined with the Trendelenburg position did not increase under general anesthesia with sevoflurane [22]. Increased cerebral blood flow might be compensated for by
cerebrospinal fluid translocation to the vascular component during the 10-min interval between the position change and the measurement of the ONSD. However, our present study measured the ONSD 3 min after pneumoperitoneum combined with the Trendelenburg position. This duration might be too short for the patient to develop compensation mechanisms. Interestingly, another study assessed the ONSD during laparoscopic prostatectomy, and found an increased ONSD 10 min after pneumoperitoneum combined with the Trendelenburg position [3]. This previous study used desflurane, which induced a greater increase in cerebral blood flow than sevoflurane [23], for anesthetic maintenance. Differences in the anesthetic drug might contribute, at least in part, to the conflicting results.

The effect of ETCO$_2$ on ICP did not accentuate the increase in the ONSD observed in the steep Trendelenburg position because the ETCO$_2$ level decreased during study period. Our present result suggests the importance of careful control of ETCO$_2$ in anesthetized patients in the Trendelenburg position. However, the previous report might be confusing for clinicians when adjusting the ETCO$_2$ during robot-assisted laparoscopic radical prostatectomy, because it showed an unexplained small difference between the ETCO$_2$ and the PaCO$_2$ over the whole period when the Trendelenburg position combined with pneumoperitoneum was adopted [3], unlike the results of our present analyses and previous studies [24-26].”

Minor essential revisions

9. The title, “Effect of transient steep Trendelenburg position on optic nerve sheath diameter as a surrogate for intracranial pressure under general anesthesia: a prospective observational study”, does not describe the use of ultrasonography, nor succinctly describe the research thesis. As a substitution, the authors may consider the title, “Sonographic optic nerve sheath diameter as a surrogate measure for intracranial pressure in anesthetized patients in the Trendelenburg position”. (minor essential revision)
Thank you for your comment. As you suggested, we have revised.

10. Page 5, Lines 11-13: The standardized ventilator protocol used tidal volumes of 8 mL/kg. Please comment on whether this is per kg of ideal body weight or actual body weight, as actual body weight may have delivered a higher tidal volume than intended. (minor essential revision)

Thank you for your comment. We used tidal volumes of 8 ml/kg of ideal body weight. We have added this content.

11. Page 8, Lines 2-3: Table 1 mentions that 12 of 21 patients experienced baseline hypertension. Untreated hypertension can impact cerebral vascular autoregulation and therefore ICP. Please comment on the range of perioperative blood pressure control. Does this subgroup of patients behave differently than those without hypertension? Also, because intrathoracic pressure and lung compliance may have an effect on venous return from the head and therefore ICP, please add the number of patients presenting with chronic obstructive pulmonary disease. (minor essential revision)

Thank you for your comment. As you suggested, we have added in Result section.

Now it reads, “There was no significant difference in MBP between patients with and without hypertension [109.0 ± 7.7 (range: 94.7–117.7) mmHg vs. 104.8 ± 9.3 (range: 94.7–117.3) mmHg, respectively; \(P = 0.135\)]. There was no patient with chronic obstructive pulmonary disease.” and
“When patients with or without preoperative hypertension were separately considered, similar results were shown (with: 4.5 ± 0.5 mm at T_SUP vs. 5.1 ± 0.3 mm at T_TREN, \( P < 0.001 \); without: 4.5 ± 0.4 mm at T_SUP vs. 5.0 ± 0.3 mm at T_TREN, \( P = 0.003 \)).”

12. Page 8, Lines 4-11: Table 2 summarizes this information very well. For simplicity, please consider omitting this paragraph and simply referring to the table. However, Table 2 does show that the peak and plateau airway pressures are elevated in Trendelenburg position (with and without pneumoperitoneum), which might be expected. What is the association between airway pressure and ONSD? (minor essential revision)

Thank you for your comment.

(1) We revised the description in Result section, now it reads,

“The ONSD at T_TREN significantly increased compared with that at T_SUP (5.1 ± 0.3 mm vs. 4.5 ± 0.4 mm; Fig. 1). When patients with or without preoperative hypertension were separately considered, similar results were shown (with: 4.5 ± 0.5 mm at T_SUP vs. 5.1 ± 0.3 mm at T_TREN, \( P < 0.001 \); without: 4.5 ± 0.4 mm at T_SUP vs. 5.0 ± 0.3 mm at T_TREN, \( P = 0.003 \)).

In addition, the ONSD at T+P increased compared with that at T_SUP. At T_END, the ONSD was similar to that at T_SUP.”

(2) The Trendelenburg position may disturb cerebral venous drainage by inducing higher intrathoracic pressure as shown in our study, and subsequently increase ICP. We described this content in Discussion section, now it reads, “The Trendelenburg position may disturb cerebral venous drainage by increasing the impedance of the lungs to inflation [19]. Therefore, when the lungs are ventilated with the same tidal volume used for the supine position, the Trendelenburg position may
lead to higher intrathoracic pressure and subsequently increase the ICP by the transmission of intrathoracic pressure to the intracranial space [20]. Indeed, our current results indicated increased airway pressure during the Trendelenburg position.”

13. **Page 9, Lines 2-3**: The results report that there was a detectable change after 3 minutes of Trendelenburg position, not “immediately” as currently worded. Please correct this statement. (minor essential revision)

Thank you for your comment. We revised the word of ‘immediately’ to ‘3’.

14. **Page 9, Line 26 to Page 10, Line 5**: Thank you for addressing the relationship between ventilatory mechanics, venous return, and ICP. Please separate this topic into its own paragraph, which can include your discussion of ETCO2. Please also address the relationship between airway pressures and ONSD in your discussion. (minor essential revision)

Thank you for your comment. As you suggested, we have revised in Discussion section, now it reads, “The Trendelenburg position may disturb cerebral venous drainage by increasing the impedance of the lungs to inflation [19]. Therefore, when the lungs are ventilated with the same tidal volume used for the supine position, the Trendelenburg position may lead to higher intrathoracic pressure and subsequently increase the ICP by the transmission of intrathoracic pressure to the intracranial space [20]. Indeed, our current results indicated increased airway pressure during the Trendelenburg position.” (In the Discussion section)

“The effect of ETCO₂ on ICP did not accentuate the increase in the ONSD observed in the steep Trendelenburg position because the ETCO₂ level decreased during study period. Our present result
suggests the importance of careful control of ETCO₂ in anesthetized patients in the Trendelenburg position. However, the previous report might be confusing for clinicians when adjusting the ETCO₂ during robot-assisted laparoscopic radical prostatectomy, because it showed an unexplained small difference between the ETCO₂ and the PaCO₂ over the whole period when the Trendelenburg position combined with pneumoperitoneum was adopted [3], unlike the results of our present analyses and previous studies [24-26].” (In the Discussion section)

15. Page 5, Lines 5-6: Please move the sentence “Twenty-one patients scheduled for robot-assisted laparoscopic radical prostatectomy were enrolled and evaluated” to the Results section.

(discretionary revision)

Thank you for your comment. We move the sentence, as you pointed out.

16. Page 9, Lines 13-23: Please provide some range on ICP values that might be clinically significant for these otherwise healthy patients. By how much should ICP change when the patient is placed in Trendelenburg? What is the association between the angle of inversion and ICP? Is this change clinically relevant in most patients? How about patients with impaired cerebrovascular autoregulation? (discretionary revision)

Thank you for your comment. As you pointed out, we have added, now it reads, “However, the position has been considered to increase ICP, which has a normal range of 7–15 mmHg in supine healthy adults [18]. This increase was seen in previous studies that found that the head-down position increased ICP above 20 mmHg in neurologic patients [1].”
We are sorry not to investigate the association between the angle of inversion and ICP. We described this point a limitation in Discussion section. In addition, we excluded the patients with cerebrovascular disease in the present study.

We would like to thank you for your kind comments.
Reviewer 2

Major Compulsory Revisions: None

Minor Essential Revisions: Please add a sentence in the discussion to the effect that the accuracy of optic nerve sheath diameter in detecting elevated intracranial pressure is a source of debate and the threshold values have not been determined. As a result this study does not definitively prove there is an elevated ICP with steep Trendelenburg positioning but does indicate that there is a likely rise in ICP which may reach critical levels in some patients.

Thank you for your opinion. As you suggested, we have added.

Now it reads, “Third, there are no general consensus over optimal cut-off values of ONSD, despite of use of ONSD cut-off value of 5 mm to detect increased ICP > 20 mmHg in the present study [6, 7, 13-15]. Furthermore, the accuracy of ONSD in detecting elevated ICP remains controversial [7, 17, 34]. Therefore, the present study does not definitively prove that there is an elevated ICP with steep Trendelenburg positioning, but does indicate that there is a likely rise in ICP which may reach critical levels in some patients.”

Discretionary Revisions: None
Reviewer 3

Discretionary Revisions

1. The authors should reference the INVOS 5100 as "INVOS 5100 cerebral/somatic oximeter (Coviden Inc., Dublin, Ireland).

   Thank you for your comment. We have revised it.

2. The sentence "No patients required a blood transfusion" can be removed.

   Thank you for your comment. We removed the sentence as you pointed out.

3. The references do not need to be boldfaced. This is a likely product of the authors' reference software.

   Thank you for your comment. We revised the boldface type in Reference.

Minor Essential Revisions

NONE

Major Compulsory Revisions

NONE