

Effects of Pneumoperitoneum and Trendelenburg position on intracranial pressure assessed using different non-invasive methods

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ABSTRACT

Introduction: The laparoscopic approach is becoming increasingly frequent for many different surgical procedures. However, the combination of pneumoperitoneum and Trendelenburg positioning associated with this approach may increase patient's risk for elevated intracranial pressure (ICP). Because the gold standard for the measurement of ICP is invasive, little is known about the effect of these common procedures on intracranial pressure.

Methods: We prospectively studied 40 patients without any history of cerebral disease, undergoing laparoscopic procedures. Three different methods were used for non-invasively estimating ICP: ultrasonography of the optic nerve sheath diameter (ONSD); Transcranial Doppler-based (TCD) pulsatility index (ICP_{PI}) and a method based on the diastolic component of the TCD cerebral blood flow velocity (ICP_{FVd}). ONSD and TCD were performed immediately after induction of general anaesthesia, after pneumoperitoneum insufflation, after Trendelenburg position and again at the end of the procedure.

Results: ONSD, ICP_{FVd} and ICP_{PI} significantly increased after the combination of pneumoperitoneum insufflation and Trendelenburg position. ICP_{FVd} showed an area under curve (AUC) of 0.80 [95% CI of 0.70-0.90] to distinguish the stage associated with the application of pneumoperitoneum and Trendelenburg position; ONSD and ICP_{PI} showed an AUC of 0.75 [95% CI of 0.65-0.86] and 0.70 [95% CI of 0.58 to 0.81], respectively.

Conclusions: The concomitance of pneumoperitoneum and Trendelenburg position can increase intracranial pressure as estimated with non-invasive methods. In high-risk patients undergoing laparoscopic procedures, non-invasive ICP monitoring through a combination of ONSD ultrasonography and TCD-derived ICP_{FVd} could be a valid option to assess the risk of increased intracranial pressure.

Keywords: Pneumoperitoneum; intracranial pressure; Trendelenburg position; Transcranial Doppler; optic nerve sheet diameter.

INTRODUCTION

Laparoscopic surgery has become a rapidly growing alternative technique to conventional open surgery for many types of surgical procedures because of its minimal invasiveness, reduced risk of haemorrhage, lower post-operative pain, and a consequent earlier discharge¹⁻³. An adequate surgical exposure requires the application of a carbon dioxide (CO₂) pneumoperitoneum (PP) and often a concomitant steep head-down position (up to 45 degrees, Trendelenburg position).

PP and the consequent increased intra-abdominal pressure can have many systemic physiological consequences including decreased venous return, hypercapnia and respiratory acidosis due to absorption of CO₂ across the peritoneal surface^{4,5}. Haemodynamic and respiratory effects are generally mild and well tolerated⁶.

The effects of PP and Trendelenburg position on intracranial pressure (ICP) are poorly documented, but there is growing evidence that demonstrates positive correlation between intraabdominal pressure and ICP^{7,8}. In an animal model, ICP increased significantly during raised intra-abdominal pressure (15mmHg) combined with Trendelenburg position⁹.

The effect of PP and Trendelenburg position on ICP cannot be easily determined intraoperatively¹⁰ as invasive ICP monitoring is contraindicated in this group of patients because of the possible complications¹¹. Therefore, in particular for patients at risk of developing intracranial hypertension during laparoscopic surgery, a non-invasive method to monitor ICP would be desirable¹².

The aim of this study was to assess the extent of hypothetical ICP changes resulting from PP and Trendelenburg position by applying ultrasonographic measurement of the optic nerve sheath diameter (ONSD) and Transcranial Doppler (TCD)-derived methods in patients with no head injury undergoing laparoscopic surgery; we furthermore discuss and compare the use of each method in this setting.

METHODS

The study was approved by the institutional ethics committee on the 10th April 2015, (Registration Number 029REG2015) and written informed consent was obtained from all participants. Forty-three American Society of Anaesthesiologists (ASA) class I to II adult patients undergoing abdominal laparoscopic surgery requiring pneumoperitoneum and Trendelenburg position were initially enrolled between May 2015 and October 2015 at Galliera Hospital, Genova, Italy.

Patients younger than 18 years, with pre-existing ophthalmic diseases, a history of ophthalmic surgery or affected by any kind of neurological disease were excluded. In three cases, an appropriate temporal window for TCD measurement could not be found, and such patients were excluded from the cohort.

On arrival in the surgical suite, standard monitoring was applied, including pulse-oximetry, electrocardiography, and non-invasive arterial blood pressure. Patients were not pre-medicated. After preoxygenation, general anaesthesia was induced with intravenous propofol (1.5 mg/kg), and fentanyl (1 µg/kg). To facilitate endotracheal intubation, cisatracurium besilate (0.15 mg/kg) was administered intravenously. Mechanical ventilation was performed with a tidal volume of 8 mL/kg and respiratory rate was adjusted to maintain an end-tidal carbon dioxide (ETCO₂) of 4.6 to 5.5 kPa during surgery. Anaesthesia was maintained with remifentanyl 0.05 to 0.2 µg/kg/min and 1 to 1.5 minimum alveolar concentration (MAC) of sevoflurane in 50% oxygen/air. Head-down Trendelenburg position was achieved by tilting the table to an angle range of 20-25 degrees (visually assessed), adjusted for surgical exposure and laparoscopic accessibility. CO₂ pneumoperitoneum was established using intraabdominal pressure between 10 to 15 mmHg.

Ultrasonographic measurements of ONSD and of the middle cerebral artery (MCA) flow velocity (FV) by Transcranial Colour Doppler were conducted by a single trained investigator (CR) as previously described (DC-T6, Mindray Medica, Schenzen, China)¹⁰ with a linear 7,5 MHz ultrasound probe (7L4a, Mindray Medica Dc-n3) and 2,5 MHz ultrasound probe (2P2, Mindray Medica Dc-n3), respectively (figure 1). In addition, the

duration of surgery, anaesthesia, intraoperative blood loss, and the volume of administered fluids were assessed. Mean arterial pressure (ABPm), ETCO₂, MCA flow velocities (systolic (FVs), mean (FVm), and diastolic (FVd)), and ONSD were recorded at the following time points:

B: baseline, after induction of anaesthesia;

PP: after pneumoperitoneum, 10 minutes after pneumoperitoneum insufflation;

TP+PP: 10 minutes after Trendelenburg position with pneumoperitoneum insufflation;

A: at the end of surgery, after pneumoperitoneum and in neutral position, still under general anaesthesia.

Pulsatility-index derived non-invasive ICP (ICP_{PI}) was calculated according to a linear regression model between ICP and PI, obtained from data described by Budohoski *et al.*¹³. PI was calculated according to Gosling's method¹⁴ (PI= (FVs-FVd)/FVm).

$$\text{ICP}_{PI} = 8.35 + 7.60 \cdot (\text{PI}) \text{ (mmHg)}$$

FVd-based non-invasive ICP (ICP_{FVd}) was derived from work of Czosnyka *et al.*¹⁵, in which the authors describe a method for non-invasive estimation of cerebral perfusion pressure (CPP) in traumatic brain injured patients:

$$\text{CPP} = \text{ABPm} \cdot (\text{FVd}/\text{FVm}) + 14 \text{ (mmHg)}$$

In this case, nICP (non-invasive ICP) was estimated as the difference between inflow (ABPm) and non-invasive cerebral perfusion pressure

$$\text{ICP}_{FVd} = \text{ABPm} - \text{CPP} \text{ (mmHg)}$$

The value of the ONSD-derived ICP (ICP_{ONSD}) was calculated according to an estimation formula based on the linear regression between invasive intraparenchymal ICP and ONSD, in a cohort of 23 neurocritical care patients (preliminary unpublished results):

$$ICP_{ONSD} = 4.5 \text{ ONSD} - 11.3 \text{ (mmHg)}$$

In the above formula, ONSD is expressed in mm

Statistical analysis

Continuous variables were expressed as median (interquartile range). Data were tested for normality using the Shapiro-Wilk Test. One-way repeated measures analyses of variance (parametric ANOVA and non-parametric Friedman Test), followed by Tukey Post-hoc test or paired Wilcoxon signed rank test with correction for multiplicity were applied to evaluate the differences in nICP estimation and physiological variables during different stages of the procedure, respectively for parametric and non-parametric data.

A Receiver Operator Characteristic (ROC) curve analysis was implemented to assess the performance of the tested nICP methods to distinguish between time points during the procedure, assuming that this corresponds with ICP (B versus PP, B versus PP+TP and PP versus PP+TP). As ROC is essentially a technique based on the comparison of two operating characteristics (true positive and false positive rates) as a criterion changes, it can be applied to evaluate the performance of an estimator to distinguish different conditions related to changes in certain parameters even in the absence of a gold standard for comparison. In our case, because the invasive ICP monitoring is not recommended for the procedure, we applied ROC analysis to assess the nICP methods' performance to discriminate different stages of the procedure that could potentially cause changes in ICP (i.e., PP and postural changes associated with TP). Comparisons between areas under ROC curves (AUC) were performed using DeLong's and Bootstrap tests to check for significant differences between two AUCs.

A sample size calculation was performed using power analysis based on differences between means (power analysis with a paired t-test), in which a power of 80%, significance level of 5% and medium Cohen's "d" effect size ($d = 0.5$) were considered. This test yielded a sample size of 34 individuals for detecting the specified effect. In order to comply with this inference, data from 40 individuals were used in this work.

The level of significance was set at 0.05. Statistical analyses were performed using R Studio software (R version 3.1.2). All ROC curve analyses was performed using pROC package¹⁶ for R software.

RESULTS

A total of 40 ASA 1-2 patients (26 women [65%] and 14 men [35%]), scheduled for laparoscopic procedures (15 hemicolectomies [37.5%], 14 ovariosalpingectomies [35%], 11 gastric bypasses [27.5%]) were recruited. In our institution, all these procedures require, at least for a certain time, the same degree and timing of Trendelenburg and pressure of the PP.

The mean age of the study participants was 52.8 ± 18.7 (range 34-79). The mean height was 169.2 ± 9.9 cm and the mean weight was 70.9 ± 17.9 kg. Eight patients had a diagnosis of hypertension (20%), three suffered from Chronic Obstructive Pulmonary Diseases (COPDs) (7.5%), two from diabetes (5%), 11 were affected with obesity (27.5%) and 8 were smokers (20%).

The mean duration of surgery was 110.1 ± 47.7 min; the mean duration of PP was 81 ± 36.6 min and the mean fluid administration was 1652 ± 590.5 mL. None of the patients received any vasoactive drugs during the study period.

In table 1, we present the median (interquartile range [IQR]) values of ONSD, ICP_{FVd} , ICP_{PI} , ICP_{ONSD} , CPP_{FVd} , CPP_{PI} , CPP_{ONSD} , FVs, FVd, FVm, $ETCO_2$ and ABPm at each time point.

Within the variables evaluated, ONSD, FVs, FVd, FVm, CPP_{FVd} and CPP_{PI} presented normal distributions at all time points.

Figure 2 shows the distribution for ONSD, ICP_{FVd} , and ICP_{PI} . ONSD (as well as ICP_{ONSD}) was not significantly increased from baseline after pneumoperitoneum, but it increased significantly after Trendelenburg position (B versus TP+PP, PP versus TP+PP), compared to baseline and to the application of only pneumoperitoneum. At the end of the procedure, in supine position and after pneumoperitoneum disinflation, ONSD was

significantly reduced compared to TP+PP (TT+PP versus A).

ICP_{PI} increased significantly between baseline and combined PP and Trendelenburg position application (B versus TP+PP) and between PP and combined PP and TP (PP versus TP+PP). ICP_{FVd} increased significantly between baseline and PP (B versus PP), after Trendelenburg position application (B versus TP+PP and PP versus TP+PP), decreasing significantly at the end of the procedure (TP+PP versus A).

Figure 3 summarises the analysis of variance for ONSD, ICP_{FVd}, and ICP_{PI}, showing parallel coordinates plots with post-hoc p-values for the differences between time points. In these plots, each line represents a different individual.

Non-invasive CPPs at the end of the procedure were significantly lower compared to all the other time points. Compared to baseline, they did not change significantly during PP or Trendelenburg position (B versus PP; B versus TP+PP; $p>0.05$). The application of Trendelenburg position itself did not significantly increase non-invasive CPPs (PP versus TP+PP; $p>0.05$).

ABPm at the end of the procedure was significantly lower compared to all the other time points; but compared to baseline, it did not change significantly during PP or Trendelenburg position (B versus PP; B versus TP+PP; $p>0.05$). The application of Trendelenburg position itself did not significantly increase ABPm (PP versus TP+PP; $p=0.91$).

ETCO₂ was significantly increased after PP and after PP in Trendelenburg position compared to baseline (B versus PP; B versus TP+PP), but the application of Trendelenburg position itself did not significantly increase ETCO₂ (PP versus TP+PP; $p=0.51$). After PP deflation and in supine position, ETCO₂ had similar values compared to baseline (B versus A; $p=0.98$), and it was significantly decreased compared to values found after PP or PP in Trendelenburg position (A versus PP; A versus TP+PP, $p<0.05$).

Four patients presented values of ONSD above 5.8 mm (i.e., the cut-off value for prediction of ICP above 20 mmHg in previous studies¹⁷) at time point TP+PP (in

particular, two patients had an ONSD of 6.0 mm and two of 7.0 mm; 16 and 20 mmHg according to our formula, respectively). All these four patients presented a concomitant increase of nICP measured with TCD derived formulae ($ICP_{PI} = 20-25$ mmHg and $ICP_{FVd} = 21-24$ mmHg). In all the remaining cases, TCD-derived methods did not detect ICP values above 20 mmHg. Neurological complications, assessed through neurological examination at the end of the procedure, were not observed in any of the enrolled patients during the intraoperative or postoperative periods.

Results from the ROC analysis are shown in table 2 and figure 4. Among the three methods, ICP_{FVd} showed the highest AUC after PP and at TP+PP time point compared to baseline. Considering B versus PP, the difference between the AUCs values obtained was significant for ONSD vs ICP_{FVd} ($p=0.003$) and ICP_{FVd} vs ICP_{PI} ($p=0.01$), but not for ONSD vs ICP_{PI} ($p=0.08$). Considering the effects of application of Trendelenburg position and PP from baseline (B versus TP+PP), a significant difference between AUCs was found just between ICP_{FVd} and $nICP_{PI}$ ($p=0.02$).

DISCUSSION

The primary objective of this work was to use non-invasive ICP assessment procedures to discover potential changes of ICP during laparoscopy. Nevertheless, in order to provide the reader a quantitative assessment of the application of these non-invasive ICP methods in clinical practice, we also discuss and compare the use of each method as a secondary objective of this work.

Our results demonstrate that laparoscopic surgery in the Trendelenburg position increases estimated ICP based on ONSD and TCD techniques. Such an increase was rarely above 20 mmHg, demonstrating that in patients with no neurological diseases, it is unlikely that the estimated increase in ICP has clinical significance.

It is well known that intra-abdominal CO_2 insufflation is associated with an increase of ICP^{9,18}. However, there is little information about the effects of combination of PP and Trendelenburg position on ICP invasively measured. A study conducted in neurosurgical

patients under general anaesthesia and direct measurement of ICP demonstrated that Trendelenburg position and head rotation and/or flexion could significantly increase ICP¹⁹. Kamine et al., in a small number of patients (N=9) subjected to laparoscopy, who needed a ventriculoperitoneal shunt placement because of neurological causes, demonstrated that during laparoscopy ICP increased linearly with intra-abdominal pressure up to 25 mmHg. However, no neurological complications were found²⁰.

Some authors have documented rare severe neurological complications during laparoscopy related to cerebral ischemia and cerebral oedema²¹. Generally, neurological complications are rare^{22,23}; more frequently, minor clinical symptoms such as nausea, and headache that could be associated with increased ICP have been reported after laparoscopy²⁴. The general low incidence of neurological complications following laparoscopy makes it difficult to recommend more extensive screening procedures for intracranial hypertension. Therefore, in the past years, many authors have studied the effect of pneumoperitoneum and Trendelenburg position on ICP using non-invasive methods (reviewed by Robba et al.¹⁰).

Non-invasive estimation of ICP is a developing field, and several attempts have been made to find a method that can be safely used in the operating room and in intensive care¹². Nevertheless, at present, none of these methods seem to be reliable and accurate enough to substitute the invasive ICP measurement. The ideal non-invasive ICP monitoring method should be safe, low cost, easily available, suitable for emergency settings and accurate.

ONSD ultrasonography is a simple bedside tool, widely used and seems to have high reproducibility²⁵. Several authors found good correlation coefficients with invasive ICP and good specificity and sensitivity, demonstrating high accuracy for this method^{26,27}. In general, the cut-off value for predicting elevated ICP (>20 mmHg) assessed with ONSD ranges from 5.7 to 5.8 mm^{17,28,29}.

ONSD ultrasonography during PP and Trendelenburg position has been studied in adult and paediatric population³⁰⁻³⁴. Many authors^{33,34,36} demonstrated a significant increase

of ONSD during PP and TP. According to Kim et al.³⁴, in 15% of the patients, ONSD increased by values equivalent to an ICP above 20 mmHg. However, Verdonck et al.³¹ did not find any changes in ONSD during head-down position, suggesting that increases in ICP were likely to be small.

TCD could be a safe and accurate non-invasive method for ICP assessment, and it is commonly used in standard care of neurocritical care patients³⁵⁻⁴⁰. Many TCD-derived estimation formulas have been studied on humans³⁶⁻⁴⁰ and animals⁴¹ to non-invasively predict ICP, including PI, ICP_{PI} and ICP_{FVd} ^{13,15}. Nevertheless, it is still unclear which one works best for a given clinical scenario⁴².

Effects of PP and Trendelenburg position on PI-derived methods have been studied in adults and children with discordant results¹⁰: most authors found an increase of CO_2 after PP, but not all authors observed a concomitant increase of FV. In particular, PI seems not to be significantly influenced by PP and head down position in most of the studies¹⁰. A recent case report of a patient with an intracranial tumour undergoing laparoscopic procedure and monitored with non-invasive methods¹⁰ indicated that ONSD and ICP_{FVd} methods may be able to detect changes in estimated ICP modulated by intra-abdominal pressure variations, whereas TCD-derived PI may not.

At our knowledge, this is the first clinical study combining these three non-invasive methods during PP and Trendelenburg position. According to our results, all the nICP methods seem to have a good concordance in the detection of ICP changes during laparoscopic procedures. All of them showed a significant increase of estimated ICP after the concomitance of PP and Trendelenburg position. Only ICP_{FVd} increased significantly after PP alone, likely consequent to the concomitant increase of $ETCO_2$ ($p < 0.05$), promoting passive vasodilation and consequent increase of cerebral blood volume. $ETCO_2$ was significantly increased not only after PP, but also after PP in TP compared to baseline. This suggests that the CO_2 -induced vasodilatation could be responsible for the increase of ICP detected by all the methods after PP and Trendelenburg position, and in particular by ICP_{FVd} after PP, as previously described¹⁰. However, in these procedures just a moderate Trendelenburg was assessed.

Results from the ROC curve analysis showed that ICP_{FVd} performs best to differentiate between time points, compared to ICP_{PI} and ONSD. No statistically significant differences between methods were found regarding the application of Trendelenburg position after PP. ICP_{FVd} performed better to distinguish the application of PP (B vs PP).

Taken together, these data indicate that the concomitance of PP and Trendelenburg position causes an increase of ICP that can be detected with non-invasive methods; the effects of PP alone seem to be less strong, even if an increase of ICP can be detected with ICP_{FVd} method. CO₂ increases due to PP and the consequent cerebral vasodilatation may act as the main mechanism involved in the observed ICP increase. However, in our study, ETCO₂ never increased above 6 kPa, which is considered the threshold for risk of deranged cerebrovascular reactivity in patients during sevoflurane anaesthesia⁴³. Finally, in our study, PP and Trendelenburg position did not significantly alter ABPm or estimated CPP. Thus, the increase in ICP_{FVd} in our cohort, mathematically estimated via changes in ABPm and diastolic cerebral blood flow velocity, is unlikely to be explained by haemodynamic changes, or reduction of CPP.

Our results suggest that in patients at risk of developing intracranial hypertension (such as cerebral tumours, or any previous neurological diseases) undergoing laparoscopic procedures, a non-invasive assessment of ICP would be useful to assess and eventually treat pathological increases of ICP (with the use of osmotic agents, hyperventilation, converting to an open procedure or even abandoning the procedure).

Limitations

In this study, there are several limitations to be mentioned. Primarily, this study did not compare non-invasive with invasive methods and therefore the absolute accuracy of these nICP methods cannot be assessed. As previously demonstrated^{41, 42}, non-invasive methods to assess ICP, in particular TCD-derived methods, are very helpful to detect relative changes of ICP but they are less accurate in the absolute measurement of ICP. As a result, they are more useful to distinguish the changes of nICP values for the

individual patients between the different time points, rather than to assess ICP “as a number”.

Moreover, a more accurate estimation of the effects of PP and Trendelenburg position on cardiac and cerebral haemodynamics would require more aggressive monitoring, including the measurement of invasive ABPm with arterial blood gases measurement of partial pressure of carbon dioxide (PCO₂), cardiac output, and central venous pressure (CVP) to determine the degree of venous drainage impairment. However, due to the lack of evidence supporting the use of invasive hemodynamic monitoring in patients undergoing elective laparoscopic procedures, these techniques were not performed.

The complicated relationship between CVP increase and CPP decrease during Trendelenburg position has been previously studied⁴⁴. In particular, changes in CPP observed in Trendelenburg position can be in this setting related to changes in CVP. Indeed, as CPP is estimated as the difference between MAP and the greater of ICP and CVP, if CVP increases, CPP can deviate from theoretical values. However, changes in CVP are included in conceptual changes of CPP (expressed as MAP-ICP) as any changes in CVP affects ICP.

Finally, the current cohort included patients undergoing different procedures, potentially introducing heterogeneity to our results. However, every effort was made to minimise unnecessary heterogeneity; all patients were ASA grade 1 or 2, all patients were submitted to the same degree of Pneumoperitoneum and Trendelenburg position, and all measurements were made at the same time-points; therefore, we believe that this is a relatively homogenous group of patients with respect to cerebral haemodynamics.

CONCLUSION

All non-invasive methods assessed in this study demonstrated increased nICP after the combination of PP and Trendelenburg position, suggesting that a potential increase of ICP occurs during these procedures.

Patients undergoing laparoscopic procedures should be counselled about the risks of intracranial hypertension which may occur during PP and even more during Trendelenburg position.

Further observational/contingency based trials and controlled studies aimed at comparing these methods with the invasive gold standard are necessary to validate these findings.

Authorship

CR: study design patient recruitment and writing up the final draft of the paper, answer to reviewers.

MC, ML: study design.

BM: study design, manuscript review, answer to reviewers

DC, JD, NB, SB, BC, XL: data analysis, manuscript review.

AB: data collection and writing up of the first draft of the paper.

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Tables:

Table 1. Median values (IQR) of the studied parameters at different time points.

Abbreviations: cerebral perfusion pressure (mmHg) measured through Flow Velocity Diastolic (CPP_{FVd}), Pulsatility Index (CPP_{PI}) and optic nerve sheet diameter method (CPP_{ONSD}) method; End-Tidal CO₂ (kPa) (ETCO₂); intracranial pressure (mmHg) measured using Pulsatility Index (PI) (ICP_{PI}), optic nerve sheet diameter (ONSD) and Flow Velocity Diastolic methods (ICP_{FVd}); mean arterial blood pressure (mmHg) (ABPm); middle cerebral artery flow velocities (cm/s) systolic (FVs), diastolic (FVd) and mean (FVm); ONSD (mm) (optic nerve sheet diameter); pneumoperitoneum (PP); pneumoperitoneum and Trendelenburg position (PP+TP).

Parameter	Baseline (B)	PP	TP+PP	End of procedure (A)
ONSD	4.3 (3.7-4.7)	4.3 (3.9-4.8)	4.8 (4.5-5.5)	4.5 (4.0-4.9)
ICP_{FVd}	3 (0.75-6)	8.5 (2.75-14.25)	12 (5.5-20)	5 (1.0-9.25)
ICP_{PI}	12.91 (12.15-13.67)	13.67 (12.15-14.43)	13.67 (12.91-15.19)	12.91 (12.72-14.62)
ICP_{ONSD}	8.27 (9.85-5.35)	8.05 (10.52-6.14)	10.3 (13.45-8.84)	8.95 (10.75-6.70)
CPP_{FVd}	80.50 (88.50-75.50)	82 (90.25-74.50)	82 (91.25-75.75)	70 (80-64)
CPP_{PI}	69.97 (80.36-65.60)	81.69 (87.52-67.60)	75.33 (86.45-67.95)	62.09 (72.86-54.03)
CPP_{ONSD}	77.28 (85.11-70.71)	86.40 (95.01-71.03)	79.42 (91.55-69.45)	68.59 (78.33-58.66)
FVs	89 (79.75-96.50)	85.5 (77-95)	85 (75.75-95.50)	87.5 (79-98)
FVd	50.5 (42-56)	48 (38-50)	44.5 (35-53)	45 (39.50-50)
FVm	64.5 (55.25-69.25)	60 (52.5-67)	55 (44-64)	61.5 (55.75-66)
ETCO₂	3.99 (3.99-4.26)	4.53 (4.36-4.66)	4.59 (4.39-4.66)	4.13 (3.99-4.26)
ABPm	82.5 (78.75-94.25)	96 (79.75-101)	89 (82-100)	75 (67-85.75)

Table 2. Receiver Operator Characteristic (ROC) analysis.

Area under the curve (AUC) values with 95% Confidence Interval showing the performance to distinguish between different time points for each non-invasive ICP method assessed.

Abbreviations: Baseline (B); intracranial pressure measured using PI (ICP_{PI}) e FVd methods (ICP_{FVd}); optic nerve sheet diameter (ONSD); pneumoperitoneum (PP); pneumoperitoneum and Trendelenburg position (PP+TP).

Time points	ONSD	ICP_{FVd}	ICP_{PI}
B vs PP	0.45 (95% CI 0.32-0.57)	0.71 (95% CI 0.59- 0.82)	0.6 (95% CI 0.47-0.72)
B vs TP+PP	0.75 (95% CI 0.65-0.86)	0.8 (95% CI 0.7-0.9)	0.7 (95% CI 0.58-0.81)
PP vs TP+PP	0.72 (95% CI 0.60-0.83)	0.61 (95% CI 0.48-0.73)	0.6 (95% CI 0.47 -0.7)

Figures

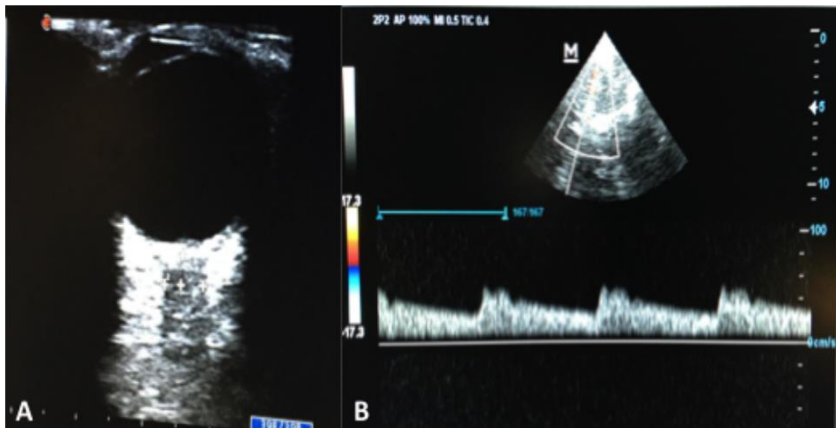


Figure 1.

A. Ultrasonographic picture of the optic nerve. The ONS is visualized in the sagittal plane and appears as a sharply defined hypoechoic band. The ONSD is measured using electronic calipers and 3 mm behind and in a perpendicular vector with reference to the orbit. B. Transcranial colour Doppler: Spectral waveform with peak systolic velocity and end diastolic velocity on the MCA.

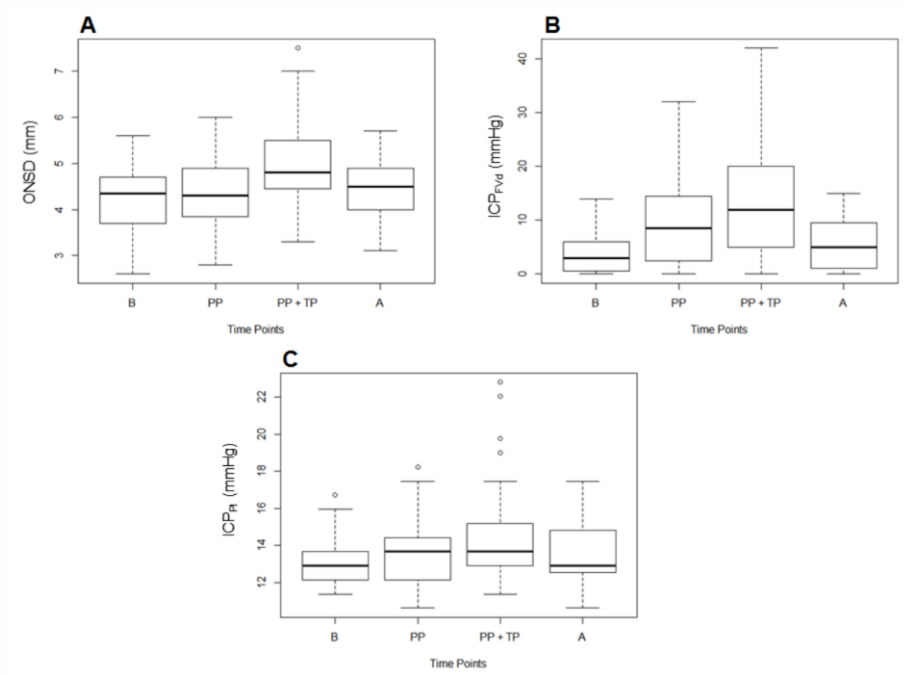


Figure 2.

Distribution of optic nerve sheath diameter (ONSD) (A), ICP measured with ICP_{Fvd} formula (B) and with ICP_{PI} (C) values measured at each time point.

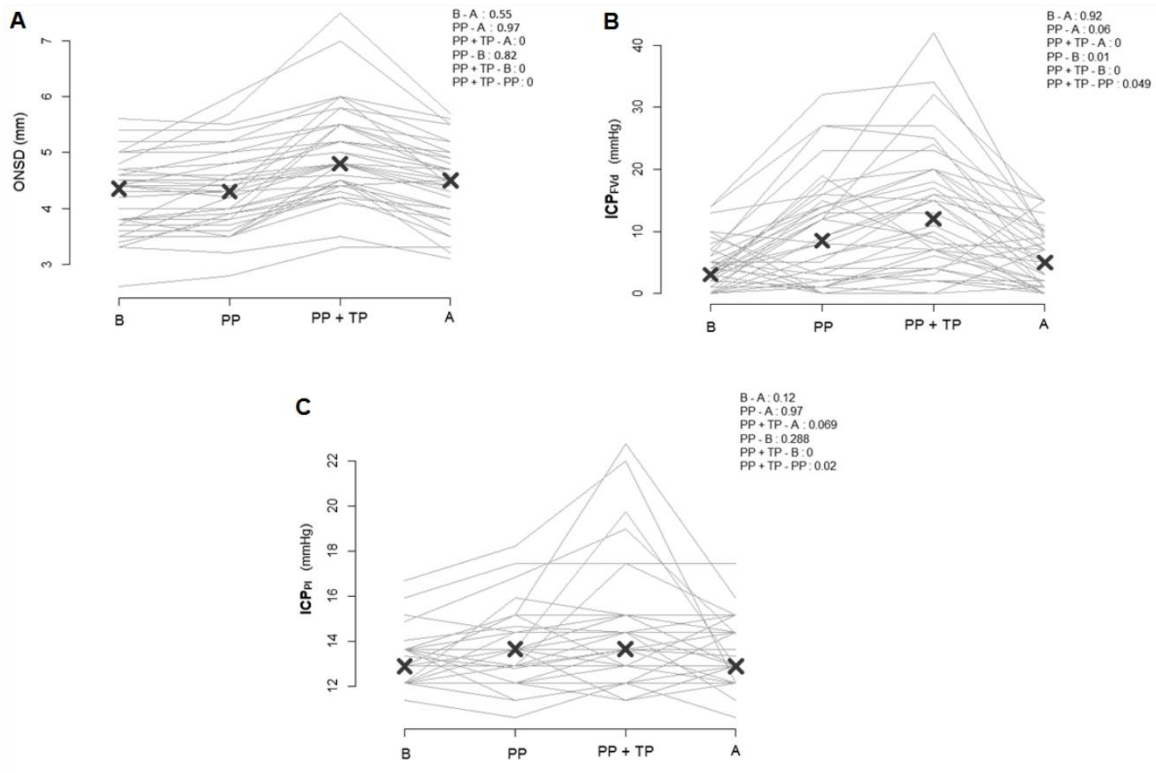


Figure 3.

Parallel coordinates plot showing the progression of ONSD (A), ICP_{Fvd} (B), and ICP_{Pi} (C) for each individual (parallel lines) across all stages of the procedure. “X” points at each stage is representative of the median values. Post-hoc p-values of the differences between time points are provided.

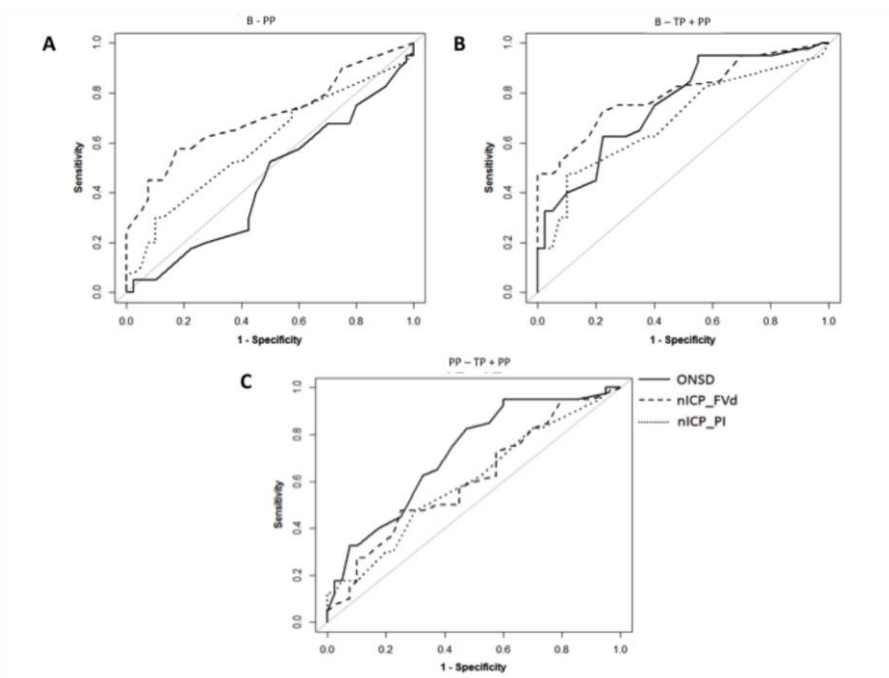


Figure 4.

Univariate Receiving Operator Curve (ROC) analysis of the different non-invasive parameters. On the upper left panel (A), univariate ROC analysis taking in account the use PP (B versus PP); in the upper right panel (B), it takes in account the concomitant application of PP and Trendelenburg position (B versus TP+PP). In the lower panel (C), it takes in account the changes in ICP occurring between PP and the application of Trendelenburg position (PP versus TP+PP). Considering time points B versus PP and B versus TP+PP, ICP_{FVd} presented the highest AUC value. Assessing the effects of application of Trendelenburg position after PP (PP versus TP+PP), ONSD showed to have the highest AUC compared to ICP_{FVd} and ICP_{PI} (see table 2).