

Effects of positive end-expiratory pressure on intraocular pressure and optic nerve sheath diameter in robot-assisted laparoscopic radical prostatectomy

A randomized, clinical trial

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Abstract

Background: There has been no study of the effect of post end-expiratory pressure (PEEP) on intraocular or intracranial pressure during pneumoperitoneum with steep Trendelenburg positioning. We investigated the effects of 5 cmH₂O of PEEP on intraocular pressure and optic nerve sheath diameter as a surrogate for intracranial pressure in robot-assisted laparoscopic radical prostatectomy.

Methods: Fifty patients scheduled for robot-assisted laparoscopic radical prostatectomy were divided into a zero-PEEP (ZEEP) group and a 5 cmH₂O of PEEP (PEEP) group. Intraocular pressure, optic nerve sheath diameter, and respiratory and hemodynamic parameters were measured before induction (T0), 10 minutes after induction of general anesthesia in the supine position before CO₂ insufflation (T1), 5 minutes (T2), and 30 minutes (T3) after steep Trendelenburg positioning with pneumoperitoneum, after desufflation of pneumoperitoneum in the supine position (T4), and after 30 minutes in the recovery room postoperatively (T5).

Results: There was no significant difference in intraocular pressure or optic nerve sheath diameter between the groups during the study. The partial pressure of arterial oxygen and dynamic lung compliance at T1, T2, T3, and T4 were significantly higher in the PEEP than in the ZEEP group. There was no difference in mean arterial pressure or heart rate between groups at any time.

Conclusion: Applying 5 cmH₂O of PEEP did not increase intraocular pressure or optic nerve sheath diameter during pneumoperitoneum with steep Trendelenburg positioning in robot-assisted laparoscopic radical prostatectomy. These results suggest that low PEEP can be safely applied during surgery with pneumoperitoneum and steep Trendelenburg positioning in patients without preexisting eye disease and brain pathology.

Abbreviations: CVP = central venous pressure, HR = heart rate, ICP = intracranial pressure, ION = ischemic optic neuropathy, IOP = intraocular pressure, MAP = mean blood pressure, ONSD = optic nerve sheath diameter, OPP = ocular perfusion pressure, PEEP = post end-expiratory pressure, RALRP = robot-assisted laparoscopic radical prostatectomy, SD = standard deviation, ZEEP = zero positive end-expiratory pressure.

Keywords: intracranial hypertension, intraocular pressure, post end-expiratory pressure, robotic prostatectomy

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1. Introduction

Prostate cancer is one of the most common diagnosed cancer in worldwide men. The robot-assisted laparoscopic radical prostatectomy (RALRP) is the latest and the advanced treatment.^[1] Prostatectomy using Da Vinci robot has many advantages like less bleeding, less postoperative pain, shorter hospital stay, and quick recovery.^[2,3] It also reduces complications including urinary incontinence and impotence.^[4] However, RALRP needs prolonged pneumoperitoneum and steep Trendelenburg position over 30° for surgical exposure. These specific conditions decrease pulmonary functional residual capacity and pulmonary compliance,^[5] which are likely to lead to postoperative respiratory complications. Moreover, the intraocular pressure (IOP) is elevated because the increase in central venous pressure that occurs in the steep Trendelenburg position impairs aqueous outflow into the episcleral venous circulation, which may cause postoperative ophthalmological complications including exacerbate preexisting glaucoma, which may lead to a decrement in postoperative visual acuity and ischemic optic neuropathy.^[6,7]

Also, the intracranial pressure (ICP), which can be commonly evaluated by noninvasive ocular sonography, is increased during pneumoperitoneum with steep Trendelenburg position.^[8–10] Elevated ICP result in delayed emergence from general anesthesia, postoperative delirium, declined cognitive function, and rarely neurologic deficit.^[6,7,11]

During laparoscopic surgery, applying post end-expiratory pressure (PEEP) increases functional residual capacity and decreases postoperative atelectasis by preventing alveolar collapse.^[12] Also, it helps resolving ventilation-perfusion mismatch which is aggravated during pneumoperitoneum with steep Trendelenburg position. On the contrary, it has been proposed that PEEP can result in increase in IOP and ICP. And its possible mechanism is that PEEP can increase the central venous pressure (CVP), which subsequently may inhibit blood efflux from the intraocular vessels and thereby increase the IOP,^[13] and increase ICP by impeding cerebrospinal flow outflow and cerebral venous drainage.^[14] Therefore, there are some concerns that applying PEEP may be related to further increase of IOP and ICP caused by PEEP during prolonged pneumoperitoneum with steep Trendelenburg position.^[6,7,15,16]

However, there is no study to reveal the effect of PEEP in IOP and ICP during pneumoperitoneum with steep Trendelenburg position. We aimed to investigate the effects of PEEP on IOP and optic nerve sheath diameter (ONSD) as a surrogate for ICP and its effects on hemodynamic and respiratory parameters in RALRP.

2. Methods

This study protocol was approved by the Institutional Review Board of Gangnam Severance Hospital on November 23, 2016 (#3–2016–0263) and the randomized trial was registered at clinicaltrials.gov on January 25, 2017 (NCT03031613), prior to the start of the trial. Also, this manuscript adheres to the applicable CONSORT guidelines.

2.1. Participants

Fifty patients scheduled for RALRP were enrolled in the study after obtaining written informed consents before the day of surgery and divided into 2 groups, zero-PEEP (zero positive end-expiratory pressure) and 5 cmH₂O of PEEP by random using Research Randomizer (<http://www.randomizer.org>). The patient who has medical history on eyes or brain, elevated IOP or ICP, suspected bulla on chest x-ray, and history of pneumothorax was excluded from the study. Patients who had undergone previous ophthalmic surgery or were taking medications for glaucoma, those with current ophthalmic disease (glaucoma, diabetic retinopathy, cataract, and retinal detachment), and those with a baseline IOP of >30 mmHg were excluded.

2.2. Anesthetic protocols

The patient was premedicated by 0.1 mg of glycopyrrolate before entering the operating room. The non-invasive blood pressure, electrocardiogram, oxygen saturation, and bispectral index was monitored. The baseline values of IOP and ONSD were measured and then an arterial catheter was inserted by an anesthesiologist for sampling arterial blood for hemodynamic and respiratory data. Propofol 1.0 to 2.0 mcg kg⁻¹ and 0.6 mg kg⁻¹ of rocuronium

were injected for induction of anesthesia. Sevoflurane 0.8 to 1 MAC with 0.03 to 0.1 μg kg min⁻¹ of remifentanyl were adjusted for maintaining bispectral index to 40 to 60. Also, rocuronium infusion was done for keeping train of four ratio to 1/4 to 2/4. The volume controlled ventilation mode with I:E ratio 1:2, tidal volume to ideal body weight (8 mL kg⁻¹) was set. For maintaining ET CO₂ to 35 to 45 mmHg, respiratory rate was adjusted between 10 and 16 breaths/min. And only PEEP group was applied with 5 cmH₂O of PEEP. Pneumoperitoneum was created by intraperitoneal insufflation with carbon dioxide while the patient was in the supine position. And then patients were placed in the 30° Trendelenburg position. The neck was fixed to straight in the axis of the body and the head was straight not to be rotated. All operations were performed at the same angle on the same table. Throughout the surgery, the intraperitoneal pressure was maintained at 15 mmHg using CO₂ for insufflation. All RALRP procedures were performed by a single experienced surgeon.

2.3. Outcome measurement

The intraocular pressure (IOP) was measured by an anesthesiologist trained in the use of the device and ONSD was measured by another investigator trained in ocular sonography, without any information about the randomization. IOP was measured by Tono-Pen AVIA (Reichert, Buffalo, New York, NY). Sanitized Ocu-flim (Reichert, Buffalo, New York, NY) was covered the tip of Tono-Pen and a drop of 0.5% proparacaine hydrochloride (Alcon, Fort Worth, TX) was instilled in each eye before measuring. The tonometer was calibrated according to the manufacturer's guidelines before each application. The IOP was measured 3 times at each time point, and the mean value was retained for analysis.

The ONSD is non-invasive and reliable method which correlated well with increased intracranial pressure.^[17,18] They were measured by a linear 13- to 6-MHz transducer (L25x) with a SonoSite M-Turbo Ultrasound Machine (SonoSite Inc, Bothell, WA) in transverse and sagittal planes on both eyes, and the mean values of 4 measurements at each time point were used in the analysis. The probe is located on upper eyelid without exerting too much pressure on the eye. The probe adjusted to show the spot optic nerve entering globe in two-dimensional mode. The measurement was done in 3 mm posterior to globe using electrical caliper. The respiratory data (peak airway pressure, dynamic lung compliance, PaO₂, PaCO₂) and hemodynamic parameters (mean arterial pressure [MAP], heart rate [HR]) were also collected. When the mean blood pressure lowered below 60 mmHg, ephedrine 4 to 8 mg was administered or phenylephrine was continuously infused. Patients received 20 mg of nefopam diluted in 100 mL of normal saline over 10 minutes before 30 minutes of end of operation for control of postoperative pain. At recovery room, if the patient had an NRS pain score of ≥5, then 50 μg of fentanyl was administered.

The measurements of IOP and ONSD were done before induction (T0), at 10 minutes after the induction of general anesthesia with supine position before insufflation of carbon dioxide (T1), at 5 minutes (T2), and 30 minutes (T3) after the patient placed in steep Trendelenburg position with pneumoperitoneum, after desufflation of pneumoperitoneum in the supine position (T4), and at 30 minutes in recovery room after end of surgery (T5).

2.4. Statistical analysis

Sample size was calculated with two-tailed significance level ($\alpha = 0.05$) and 80% power. For verifying the difference of mean IOP, 3.0 mmHg, between the 2 groups with 3.7 mmHg in standard deviation, required sample size was 25 in each group.^[6] Twenty-seven patients in each group were enrolled with consideration of 10% of drop-out rate. Statistical analyses were performed using the Statistical Package for Social Sciences (ver. 20.0 for Windows; SPSS Inc., Chicago, IL) and SAS version 9.3(SAS Institute Inc., Cary, NC). The independent 2 sample *t* test was done for demographic differences between the groups. The linear mixed model and post hoc analysis was used to analyze changes of IOP, ONSD, PaO₂, PaCO₂, peak airway pressure, dynamic lung compliance, MAP, and HR during the study.

3. Results

A total of 54 patients were recruited for the study and 4 patients were excluded. There were no differences between the groups in demographics (Table 1). Mean (SD) baseline value of IOP was 17.4 (1.7) mmHg and 16.6 (2.9) mmHg in ZEEP and PEEP group, respectively, and there was no significant difference between groups. Compared with baseline values of IOP, in ZEEP and PEEP group, IOP reduced to 12.2 (3.5) mmHg versus 11.7 (3.3) mmHg at T1 ($P < .0001$), and increased to 25.1 (5.6) and 30.6 (5.8) mmHg versus 23.7 (6.1) and 28.5 (7.4) mmHg at T2 and T3 ($P < .0001$ and $P < .0001$, respectively). At T4 and T5, the IOP values in ZEEP and PEEP group returned to baseline values, respectively. However, there was no significant difference of IOP values between groups during all study period (Fig. 1(A)). Mean (SD) baseline value of ONSD was 4.6 (0.3) mm and 4.7 (0.3) mm in ZEEP and PEEP group, respectively, and there was no significant difference in groups. The ONSD increased to 4.6 (0.4) and 5.1 (0.3) mm at T2 and T3 in ZEEP group ($P < .01$, respectively) and increased to 0.5 (0.4) mm at T3 in PEEP group ($P < .05$), respectively and returned to baseline values at T4 and T5. However, there was no significant difference of ONSD value between groups during all study period (Fig. 1(B)).

After post hoc analysis with Bonferonni correction, the values of PaO₂ and dynamic lung compliance at T1, T2, T3, and T4 in PEEP group were significantly higher than those in ZEEP group, respectively. The values of PaCO₂ were comparable between groups except for the slightly lower in PEEP group compared with ZEEP group at T1 while the values of peak airway pressure were comparable between groups except for higher in PEEP group compared with ZEEP group at T1. There was no

significant difference of MAP and HR during all study period between them (Table 2). In either group, respiratory, ocular, and cerebral-related neurologic postoperative complications were not observed.

4. Discussion

A postoperative ischemic optic neuropathy (ION) after RALRP is a catastrophic complication firstly reported by Weber et al^[19] although its complications resulting from steep Trendelenburg position with pneumoperitoneum has not been revealed yet. The steep Trendelenburg position during RARP increases IOP, and an elevated IOP decreases the ocular perfusion pressure (OPP) to the optic nerve, which can lead to increased risks of ION and visual loss. There have been some studies on attenuation of the increase in IOP during surgery in a steep Trendelenburg positioning. Topical application of α -2 agonist, and administration of gabapentin or dexmedetomidine alleviated the increase in IOP^[30-32] and continuous deep neuromuscular block contributed to the attenuation of the IOP increase during pneumoperitoneum in the steep Trendelenburg position.^[33]

In both groups, IOP increased time-dependently during pneumoperitoneum with steep Trendelenburg positioning, which was consistent with previous studies.^[11,20] There have been few literatures regarding the effect of the PEEP on IOP, and moreover the results have been inconsistent. Although it is not clear why previous studies show inconsistent results, the level of the PEEP and the duration of PEEP therapy can be related to IOP. At 5 cmH₂O PEEP in cats, there was no significant change in IOP while the IOP increased significantly at 10 and 15 cmH₂O PEEP.^[21] And length of PEEP therapy was correlated with IOP level and IOP increased in patients with prolonged mechanical ventilation with PEEP.^[13] Those including our result suggest that <10 cm H₂O PEEP in a surgery that takes a few hours should not cause a clinically significant risk for IOP increase. To prevent further increase in IOP, relatively constant ETCO₂ during PEEP is required because increased CO₂ can lead to choroidal vasodilation and consequently increases in IOP.^[11] Mechanical ventilation at high peak airway pressure is also known to cause an increase in IOP by increasing intrapulmonary pressure.^[22] However, peak airway pressure observed in our study were comparable between 2 groups except at immediate after induction, suggesting PEEP-induced lung recruitment achieved during pneumoperitoneum with steep Trendelenburg positioning.

The ONSD using ultrasound is a reliable and useful method to estimate ICP as it is affected by the pressure of cerebrospinal fluid.^[17,18] Steep Trendelenburg position and pneumoperitoneum are risk factors for increased ONSD in patients undergoing robotic surgery. Among the mechanisms which are responsible for increased ONSD during pneumoperitoneum, 2 potential mechanisms can be considered. The first is an immediate mechanical effect mediated by sudden increase in intraabdominal pressure, cranial movement of the diaphragm, elevated intrathoracic pressure, and increased venous pressure that results in decreased venous drainage from the central nervous system. The second is a delayed chemical effect mediated by hypercarbia that results from absorption of CO₂ through the peritoneal membrane and ventilation-perfusion mismatch due to diaphragmatic compression of the lower lobes of the lungs.^[23] In both groups, the mean ONSD significantly increased to 5.0 to 5.1 mm after pneumoperitoneum with steep Trendelenburg, but it did not reach the cut-off value (5.7 to 6.0 mm) of ONSD predicting

Table 1
Baseline characteristics of study population.

	ZEEP (n = 25)	PEEP (n = 25)	P-value
Age, y	65.3 (7.5)	65.7 (7.4)	.850
Height, cm	169.4 (4.6)	168.2 (5.1)	.353
Weight, kg	72.2 (8.6)	70.0 (7.8)	.099
Duration of surgery, min	142.6 (28.5)	143.2 (31.2)	.947
Estimated blood loss, mL	181.2 (194.0)	226.0 (260.2)	.493
Fluid intake, mL	1320.0 (273.9)	1182.0 (359.1)	.133
Comorbidities			
Hypertension	13 (52%)	12 (48%)	
Diabetes mellitus	3 (12%)	4 (16%)	

Values are mean (SD) or number (percentage).
PEEP = positive end-expiratory pressure with 5cmH₂O, SD = standard deviation, ZEEP = zero positive end-expiratory pressure.

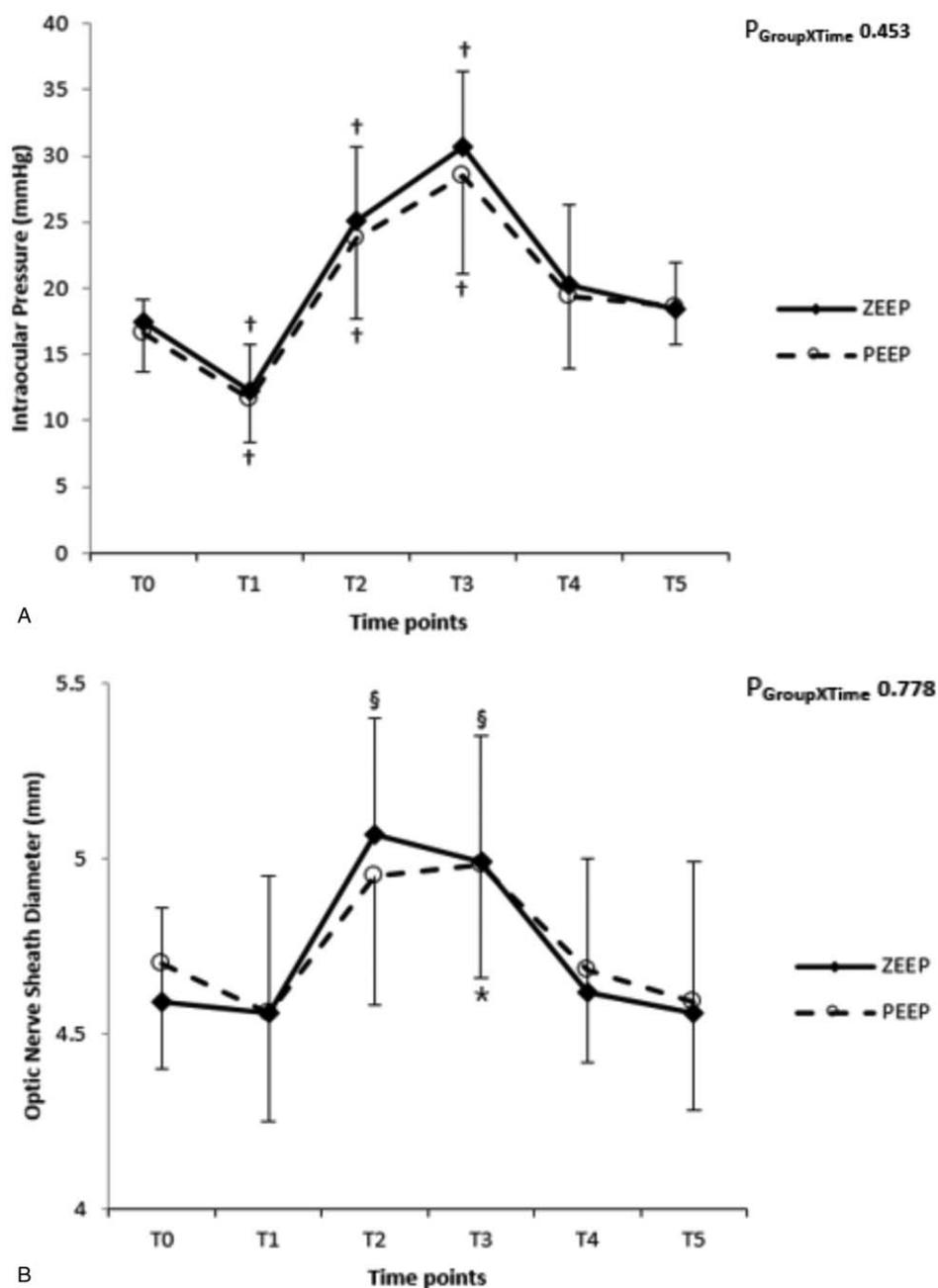


Figure 1. Changes in intraocular pressure (A) and optic nerve sheath diameter (B). Values are shown as the mean (standard deviation). T0, before induction of general anesthesia; T1, after induction in the supine position, T2, after 5 minutes in the steep Trendelenburg position with pneumoperitoneum; T3, after 30 minutes in the steep Trendelenburg position with pneumoperitoneum; T4, desufflation in the supine position; T5, at 30 minutes after end of surgery in recovery room. *Significantly different when compared with baseline value ($P < .05$); †Significantly different when compared with baseline value ($P < .01$); ‡Significantly different when compared with baseline value ($P < .001$). $P_{\text{Group} \times \text{Time}}$ = P -value of group-time interaction in linear mixed model. PEEP = positive end-expiratory pressure with 5 cmH₂O; ZEEP = zero positive end-expiratory pressure.

intracranial hypertension (ICP >20 mmHg).^[10] And unlike time-dependent increase in IOP, ONSD remained constant without further increase during pneumoperitoneum with steep Trendelenburg, which was similar to other results.^[9,24] This observation might be attributed to adjusted cerebral blood flow over time during surgery and partial compensation induced by cerebrospinal fluid translocation. In addition, maintaining relatively constant end-tidal CO₂ via adjustment of ventilator parameters might minimize the effect of hypercapnia as a mechanism of ICP elevation during pneumoperitoneum.

Although there have been few reports about the effect of PEEP on ONSD in patients during pneumoperitoneum with steep Trendelenburg position, applying PEEP is a still concern because it may aggravate ONSD increase. However, our result showed that 5 cmH₂O PEEP did not increase ONSD further during pneumoperitoneum with steep Trendelenburg which was consistent with the findings of Chin et al,^[25] who underwent 8 cmH₂O PEEP in RALRP surgery. It might be explained that a transmission of PEEP to the intracranial component was attenuated in patients with decreased lung compliance induced

Table 2
Variables in the ZEEP and PEEP groups at each time point.

	ZEEP (n=25)	PEEP (n=25)	P-value
PaO ₂ , mmHg			
T0	90.5 (15.5)	92.3 (9.8)	.676
T1	195.3 (50.3)	228.8 (51.6)	.024
T2	158.5 (41.6)	192.7 (38.9)	.005
T3	159.1 (39.4)	189.0 (45.5)	.018
T4	171.9 (36.9)	203.0 (41.4)	.009
T5	85.9 (15.7)	93.1 (12.9)	.224
PaCO ₂ , mmHg			
T0	34.7 (3.0)	35.7 (3.2)	.318
T1	36.0 (3.2)	34.0 (2.7)	.016
T2	41.4 (4.7)	42.3 (12.6)	.755
T3	46.2 (7.7)	43.5 (6.8)	.198
T4	46.1 (7.7)	45.9 (8.4)	.953
T5	39.4 (4.6)	37.3 (5.3)	.263
Peak airway pressure, cmH ₂ O			
T1	14.5 (1.7)	15.8 (1.7)	.009
T2	34.7 (4.6)	35.7 (4.2)	.446
T3	35.3 (4.8)	35.1 (4.2)	.875
T4	18.8 (4.2)	18.7 (1.9)	.888
Cdyn, mLcmH ₂ O ⁻¹			
T1	34.9 (4.5)	46.6 (8.6)	<.001
T2	14.6 (2.4)	16.5 (3.4)	.027
T3	14.7 (1.9)	17.2 (3.5)	.003
T4	27.5 (4.4)	35.8 (9.5)	<.001
Mean arterial pressure, mmHg			
T0	100.0 (12.9)	104.2 (11.3)	.265
T1	76.0 (8.4)	79.7 (9.0)	.134
T2	106.2 (14.3)	99.4 (23.2)	.225
T3	94.6 (12.8)	90.8 (8.5)	.219
T4	80.2 (16.9)	79.9 (12.5)	.940
T5	94.9 (28.1)	98.3 (12.7)	.665
Heart rate, min ⁻¹			
T0	70.9 (13.2)	76.3 (16.9)	.223
T1	64.6 (11.9)	66.3 (13.8)	.647
T2	62.2 (9.2)	62.3 (12.6)	.990
T3	62.4 (9.4)	64.5 (13.3)	.534
T4	65.5 (9.8)	66.8 (13.2)	.699
T5	78.0 (11.8)	76.9 (9.6)	.773

Values are mean (SD).

PEEP=positive end-expiratory pressure with 5cmH₂O, SD=standard deviation, T0=before induction, T1=after the induction of general anesthesia in the supine position, T2=5 minutes after the patient was in Trendelenburg position with pneumoperitoneum, T3=after 30 minutes in Trendelenburg position with pneumoperitoneum, T4=desufflation with supine position, T5=full recovery from general anesthesia; ZEEP=zero positive end-expiratory pressure.

by pneumoperitoneum and steep Trendelenburg position.^[26] In another way, Mascia et al^[27] explicated that effects of PEEP on cerebral hemodynamics depend on recruitment or hyperinflation of alveolar units. The ONSD would increase significantly in patients where PEEP induces alveolar hyperinflation with a consequent increase in PaCO₂ whereas the ONSD could remain constant in patients where PEEP causes alveolar recruitment with unchanged PaCO₂, which is similar to our result.

Various perioperative factors that influence IOP and ONSD in the steep Trendelenburg position should be considered. Patients' medical history (including increased intracranial pressure, increased intraocular pressure), BMI, degree of head-down tilting, intraabdominal pressure, the neck and head position, and duration of surgery can be confounding factors affecting the level of IOP and ONSD.^[11,16,20] Some manageable factors including hemodynamic, respiratory parameters, and fluid management should be appropriately maintained to minimize changes in IOP

and ICP.^[7] The MAP maintained constantly near physiological normal range despite a little fluctuation during pneumoperitoneum with steep Trendelenburg in both groups, and the MAP in PEEP group were comparable to that in ZEEP group during study period. For safe IOP and ONSD maintenance, it will be important to keep the MAP constant during pneumoperitoneum with steep Trendelenburg position. Increase of MAP can lead to increase in aqueous humor ultrafiltration by means of increased ciliary artery pressure, and thus an increase in IOP,^[28] while decreasing MAP lowers ocular perfusion pressure and cerebral perfusion pressure. Our results suggest that applying 5cmH₂O PEEP has minimal or no effect on OPP and CPP as well as IOP and ONSD.^[29]

Our study has some limitations. First, we could not check the long-term effect of PEEP on IOP and ONSD because RALRP usually lasted around 2 to 3 hours. It is possible that longer duration of PEEP may be related to increase in IOP. Thus, the clinical effect of long-term PEEP on IOP should be explored. Second, IOP or ONSD was measured in normal patients without preexisting eye disease or elevated ICP. Patients with ocular hypertension or intracranial hypertension with pneumoperitoneum and steep Trendelenburg can be at risk for ocular or cerebral complications. Whether PEEP will increase IOP or ONSD further in those patients will need further evaluation. Lastly, we did not investigate the effect of >5cmH₂O PEEP on IOP and ONSD during pneumoperitoneum with steep Trendelenburg position. However, from a clinical point of view, pneumoperitoneum and steep Trendelenburg position already increase peak airway pressure so applying higher PEEP does not seem to be desirable because it may lead to lung barotrauma.

5. Conclusions

During pneumoperitoneum with steep Trendelenburg position in RALRP surgery, decreased lung compliance can interrupt patient's oxygenation resulting in increased risk of postoperative respiratory complications and applying PEEP is considered to be beneficial. However, many anesthesiologists are concerned about the PEEP may aggravate further increase of ICP and IOP. However, according to our results, applying 5cmH₂O of PEEP did not increase IOP and ONSD further while it improved oxygenation without causing hemodynamic instability, suggesting that low PEEP can safely applied during surgery with pneumoperitoneum and steep Trendelenburg position in patients without pre-existing eye disease and brain pathology.

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