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ORIGINAL INVESTIGATION

The effects of positive end-expiratory pressure (PEEP) application on optic nerve sheath diameter in patients undergoing laparoscopic cholecystectomy: a randomized trial

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Abstract
Background: Positive end-expiratory pressure (PEEP) can overcome respiratory changes that occur during pneumoperitoneum application in laparoscopic procedures, but it can also increase intracranial pressure. We investigated PEEP *vs.* no PEEP application on ultrasound measurement of optic nerve sheath diameter (indirect measure of increased intracranial pressure) in laparoscopic cholecystectomy.
Methods: Eighty ASA I—II patients aged between 18 and 60 years scheduled for elective laparoscopic cholecystectomy were included. The study was registered in the Australian New Zealand Clinical Trials (ACTRN12618000771257). Patients were randomly divided into either Group C (control, PEEP not applied), or Group P (PEEP applied at 10 cmH_20). Optic nerve sheath diameter, hemodynamic, and respiratory parameters were recorded at six different time points. Ocular ultrasonography was used to measure optic nerve sheath diameter.
Results: Peak pressure (PPeak) values were significantly higher in Group P after application of PEEP ($p = 0.012$). Mean respiratory rate was higher in Group C at all time points after application of pneumoperitoneum ($p < 0.05$). The mean values of optic nerve sheath diameters measured at all time points were similar between the groups ($p > 0.05$). The pulmonary dynamic compliance value was significantly higher in group P as long as PEEP was applied ($p = 0.001$).
Conclusions: During laparoscopic cholecystectomy, application of 10 cmH_2O PEEP did not induce a significant change in optic nerve sheath diameter (indirect indicator of intracranial pressure) compared to no PEEP application. It would appear that PEEP can be used safely to correct

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respiratory mechanics in cases of laparoscopic cholecystectomy, with no significant effect on optic nerve sheath diameter.

Introduction

Laparoscopic surgical procedures are widely used with laparoscopic cholecystectomy being one of the most frequently applied.

Application of pneumoperitoneum (PP) in laparoscopic surgeries causes changes in respiratory mechanics.[1,2] Due to the creation of pneumoperitoneum, intra-abdominal pressure increases and the expandability of the diaphragm decreases. Pulmonary compliance (PC), functional residual capacity (FRC), and vital capacity (VC) decrease due to the increase in intrathoracic pressure, and as a result an increase in alveolar partial pressure of carbon dioxide ($PaCO_2$), atelectasis, ventilation/perfusion (V/Q) mismatch and hypoxemia may occur.[1,2]

Positive end-expiratory pressure (PEEP) applied at a level of 10 cmH_2O to overcome the changes due to pneumoperitoneum and patient position, have been shown to have positive effects on respiratory compliance and resistance.[3]

The increase in intra-abdominal pressure and application of PEEP also increases intracranial pressure through various physiological mechanisms.[4] Using ultrasound to measure optic nerve sheath diameter is a non-invasive imaging method that provides indirect measurement of an increase in intracranial pressure. There are reports of increased optic nerve sheath diameter in patients with increased intracranial pressure, such as head trauma and cerebrovascular disease,[5,6] but, thus far, there are no studies investigating the effect of pneumoperitoneum and PEEP applications on optic nerve sheath diameter in laparoscopic cholecystectomies.

Our aim was to investigate whether PEEP application at 10 cmH_2O, in patients undergoing laparoscopic cholecystectomy, alters the diameter of the optic nerve sheath compared with conditions where PEEP is not applied.

Methods

A total of 80 ASA (American Society of Anesthesiologists) physical status I—II patients who were scheduled for laparoscopic cholecystectomy between June 2017 and October 2017 were included in the study. Informed consent forms were obtained from all patients, and the study was approved by the local ethics committee (15 May 2017, 38/05). Two patients from both groups were excluded as their surgery was ultimately performed as an open procedure. The study was registered in the Australian New Zealand Clinical Trials (ACTRN12618000771257).

Patients with acute or chronic eye disease, uncontrolled hypertension, asthma and known lung disease, any neurological disease, body mass indices (BMI) above 35 $kg.(m^2)^{-1}$, patients using drugs known to affect intracranial pressure, and those patients who refused to participate in the study after giving their informed consent were excluded from the study.

This study was a non-blind, randomized, placebo-controlled trial. Patients included in the study were divided into two groups using the random numbers method. In the control group (Group C) PEEP was not applied during the procedure, while in the PEEP group (Group P), PEEP was applied at a level of 10 cmH_2O, 10 minutes after creation of pneumoperitoneum. Standard monitorization procedures; electrocardiography (ECG), measurements of peripheral oxygen saturation (SpO_2), noninvasive arterial blood pressure, and end-expiratory CO_2 ($EtCO_2$), were performed during the procedure. In addition, patients' depth of anesthesia was monitored using the bispectral index (BIS). Propofol (2—3 $mg.kg^{-1}$), fentanyl (1 $mcg.kg^{-1}$), rocuronium (0.6 $mg.kg^{-1}$), and lidocaine (1 $mg.kg^{-1}$) were used intravenously (IV) for the induction of anesthesia. Endotracheal intubation was performed with a cuffed endotracheal tube with an internal diameter of 7.0—8.5 mm, under the guidance of direct laryngoscopy after adequate muscle relaxation was achieved. For the maintenance of anesthesia, inhalation of a mixture 40% O_2, 60% N_2O, and 2% sevoflurane was used. All patients underwent volume-controlled mechanical ventilation at a respiratory rate of 12/minute, with a tidal volume of 8 $mL.kg^{-1}$, and an inspiration/expiration ratio of 1:2. During surgery, the frequency was adjusted to be within the range of 35—40 mmHg $EtCO_2$. PEEP was applied at a level of 10 cmH_2O to the patients in Group P, 10 minutes after creation of pneumoperitoneum and elevation of the patient's head.

Heart rate, mean arterial blood pressure, SpO_2, airway peak pressure (Ppeak), dynamic lung compliance values, tidal volume (TV), respiratory rate (RR), minute volume (MV), $EtCO_2$, and optic nerve sheath diameters (ONSD) were measured and recorded at six different time points, i.e., at baseline (after the patient was brought into the operation room and monitored, but before induction of anesthesia) (t1), after intubation and initiation of mechanical ventilation (t2), 10 minutes after creation of pneumoperitoneum (t3), 10 minutes after application of PEEP (t4), 5 minutes after desufflation (t5), and five minutes after extubation (t6) (Table 1).

Table 1 Diagram of timeline for data measurement.

t1	Baseline (after the patient was brought into the operation room and monitored, but before induction of anesthesia)
t2	After intubation and initiation of mechanical ventilation
t3	10 minutes after creation of pneumoperitoneum
t4	10 minutes after application of PEEP
t5	5 minutes after desufflation
t6	5 minutes after extubation

Table 2 Distribution of general characteristics of all patients (n = 76) (mean ± SD and percentage).

	Group C (n = 38)	Group P (n = 38)	*p*
Age (year)	49±11	44±11	0.082
Gender (F/M)	67/33	65/35	0.813
ASA (I/II)	78/22	85/15	0.39
BMI ($kg.m^{-2}$)	25.53±2.82	25.58±2.24	0.93

F, female; M, male; ASA, American Society of Anesthesiologists physical status; BMI, body mass index.

Once the surgery was complete, tramadol (1 $mg.kg^{-1}$, IV) was administered for postoperative analgesia. Dexketoprofen trometamol (50 mg, IV) was administered to those patients needing additional analgesia. For the prophylaxis of postoperative nausea and vomiting, ondansetron (4 mg, IV) was also administered post-surgery. On completion of the procedure, sevoflurane and N_2O inhalation were discontinued, the neuromuscular block was relieved with neostigmine (0.04 $mg.kg^{-1}$, IV) and atropine (0.01 $mg.kg^{-1}$, IV), and the patient was extubated when his/her spontaneous breathing was at a sufficient level. Any drugs used during surgery were recorded. Patients were taken out of the operating room and sent to the ward when their Aldrete scores reached 9−10 points in the recovery unit.

Patients whose intraoperative heart rates were raised more than 20% from their preoperative values received fentanyl (1 $mcg.kg^{-1}$, IV bolus doses), as the depth of anesthesia was inadequate. Hypotension was considered if mean arterial pressure was below 60 mmHg, and when BIS values were between 40−60, ephedrine (5 mg, IV) was administered. In addition, if BIS values were between 40 and 60, and the heart rate was 20% below baseline values, then atropine (0,5 mg, IV) was administered.

Measurement of the optic nerve sheath diameter was performed by the anesthesiologist following application of ultrasound gel to the upper eyelid of the left eye while the patient was in the supine position. The linear ultrasound probe (Sonosite M-Turbo, Bothell, USA) operating at 7.5 MHz was placed on the gel in a transverse plane to capture the most appropriate image between the retrobulbar echogenic fat tissue and the vertical hypoechoic band. The optic nerve sheath diameter was measured 4.5 mm behind the optic disc. Single measurements were performed at six time points and data were recorded.

Dynamic lung compliance was calculated using the following formula: Dynamic Lung Compliance = Tidal volume (VT)/peak airway pressure (Ppeak-PEEP).

Statistical analysis

In a study by Dip F et al.,[7] the optic nerve sheath diameters during laparoscopic procedures were found to be 4.8 ± 1.0 mm at baseline, 5.5 ± 1.1 at 15 minutes, and 5.9 ± 1.0 at 30 minutes. A power analysis was performed using this information, and the alpha error was calculated to be 0.05, the effect size to be 0.70, and the minimum number of patients required to achieve a statistical power of 80% was calculated to be 34 patients per group and 68 patients in total. A total of 80 patients per group were included in our study, taking into account possible losses during the study period.

Statistical analysis of the data was performed using the SPSS for Windows 11.5. package program. For intergroup comparisons of qualitative and quantitative variables the *chi*-square and Student's *t*-test were used, respectively. For the comparison of time-dependent changes in quantitative variables in groups, the paired sample *t*-test was used. On repetitive samples, the two-way ANOVA test was employed to determine the effects of both groups and time on the variables.

The statistical significance was accepted as $p = 0.05$.

Results

Two patients from each study group were excluded, resulting in a total of 76 patients included in the study.

No statistically significant differences were found between the two groups in terms of demographic data ($p > 0.05$) (Table 2).

No statistically significant differences were detected between the groups in terms of mean arterial pressure and heart rate values ($p > 0.05$).

Peak airway pressure values were significantly higher in Group Pat time point t4 ($p = 0.012$).

Mean $EtCO_2$ values did not differ statistically significantly between the groups ($p > 0.05$).

Minute respiratory volume (MV) values were significantly higher in Group C compared to Group P at time points t3 and t4 ($p = 0.05$ and $p = 0.023$, respectively). The mean respiratory rates (RR) measured at t3, t4, and t5 were found to be significantly higher in Group C compared to Group P ($p = 0.007$, $p = 0.007$, and $p = 0.007$, respectively) (Table 3).

Although there was a statistically significant difference in intragroup referring to the baseline values (t1) (Fig. 1), no

Table 3 Minute respiratory volume (MV) ($L.min^{-1}$), and respiratory rate (RR) (breaths/min) values for both groups (mean ± SD).

MV RR	Group C (n = 38)	Group P (n = 38)	*p*
MV (t3)	6.97 ± 0.73	6.56 ± 1.06	0.05[a]
MV (t4)	7.03 ± 0.74	6.55 ± 1.09	0.023[a]
MV (t5)	7.08 ± 0.85	6.7 ± 1.16	0.091
RR (t3)	12.13 ± 0.46	11.85 ± 0.43	0.007[a]
RR (t4)	12.13 ± 0.46	11.83 ± 0.5	0.007[a]
RR (t5)	12.13 ± 0.46	11.83 ± 0.5	0.007[a]

MV, minute respiratory volume; RR, minute respiratory rate.

[a] Difference between Groups C and P, $p \leq 0.05$

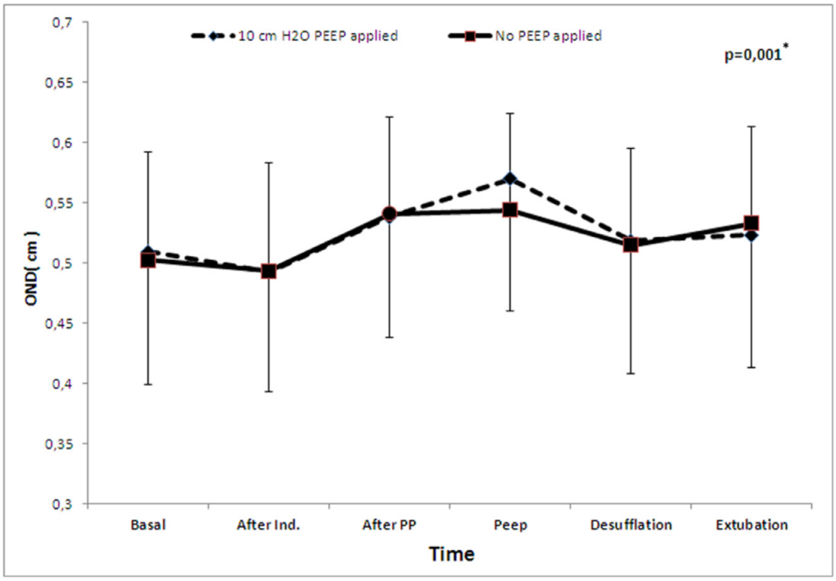

Figure 1 Average optic nerve sheath diameter (OND, cm) values for the two patient groups (PEEP applied and no PEEP applied). *Intragroup difference according to baseline values.

clinically significant difference in intergroup was detected in mean optic nerve sheath diameters among all measurements (Table 4).

Mean dynamic lung compliance values were significantly higher in Group P at time point t4 ($p = 0.001$) (Table 5).

Discussion

In this study we observed that application of PEEP in hemodynamically stable patients who underwent laparoscopic cholecystectomy did not cause a significant increase in the optic nerve sheath diameter, and thus in intracranial pressure.

The creation of pneumoperitoneum in laparoscopic cholecystectomies and other laparoscopic surgeries is known to increase intracranial pressure.[8,9] Increases in intra-abdominal and intrathoracic pressures due to pneumoperitoneum prevent systemic venous return and cerebral venous blood flow, which lead to an increase in intracranial pressure.[8] In addition, diffusion of CO_2 gas from the peritoneum into the vascular system during pneumoperitoneum causes reflex arterial vasodilation in the central nervous system, further increasing intracranial pressure.[10,11] Although invasive methods are used in the measurement of intracranial pressure, noninvasive methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), are also frequently used. However, a real-time intracranial pressure measurement cannot be accurately performed using these imaging modalities. These methods also take a considerable amount of time and it is not possible to repeat these imaging methods within a short period of time.[12,13] Thanks to the use of noninvasive ocular ultrasonography, which measures the optic nerve sheath diameter, intracranial pressures can be more frequently evaluated and the results have been shown to have a high degree of consistency and accuracy when compared to intracranial pressure measurements using intraventricular or intraparenchymal devices.[14,15]

A pressure change in the subarachnoid space is reflected in the diameter of the optic nerve sheath surrounded by dura mater and cerebrospinal fluid (CSF), and changes in intracranial pressure can be monitored by measuring the diameter of the optic nerve sheath.[16] In previous studies where gold standard measurement methods of optic nerve sheath diameter and intracranial pressure were compared, optic nerve sheath diameter values over 5.8 mm were shown to be associated with a 96% increase in intracranial pressure of 20 mmHg.[17] These data were obtained from centers where laparoscopic surgery, with the aid of carbon dioxide

Table 4 Mean optic nerve sheath diameter (ONSD) values for both patient groups (mean ± SD) at various time points.

ONSD	Group C (n = 38) (cm)	Group P (n = 38) (cm)	*p*
ONSD (t1)	0.5 ± 0.09	0.5 ± 0.11	0.755
ONSD (t2)	0.49 ± 0.09	0.49 ± 0.1	0.982
ONSD (t3)	0.54 ± 0.08	0.53 ± 0.1	0.906
ONSD (t4)	0.54 ± 0.08	0.57 ± 0.1	0.212
ONSD (t5)	0.51 ± 0.08	0.52 ± 0.1	0.882
ONSD (t6)	0.53 ± 0.08	0.52 ± 0.1	0.672

ONSD, optic nerve sheath diameter.

Table 5 Mean dynamic lung compliance values (Cdyn) of both patient groups ($mL.cm^{-1} H_2O$) (mean ± SD).

Cdyn	Group C (n = 38)	Group P (n = 38)	*p*
Cdyn (t2)	38.98 ± 9.4	37.83 ± 9.4	0.587
Cdyn (t3)	24.88 ± 4.63	26.43 ± 5.77	0.19
Cdyn (t4)	25.35 ± 5.8	36.50 ± 9.84	0.001[a]
Cdyn (t5)	37.95 ± 9.25	37.45 ± 9.86	0.816

Cdyn, Dynamic lung compliance.
[a] Difference between Groups C and P, $p \leq 0.05$.

pneumoperitoneum, was performed on 86% of their patients on an outpatient basis. In our study, the difference between optic nerve sheath diameters measured at baseline and after application of pneumoperitoneum was not statistically significant. This may be because a laparoscopic cholecystectomy is performed within a short time, and, as such, the duration of pneumoperitoneum in our study did not exceed 20 minutes. The difference may be observed more clearly in longer surgical procedures. However, Dip et al.[7] showed significant increases in optic nerve sheath diameter, and therefore intracranial pressures, at 15 and 30 minutes after creation of pneumoperitoneum.

Respiratory mechanics dependent on pneumoperitoneum are also negatively affected, as mentioned above. These negative effects of pneumoperitoneum can be increased with the effect of general anesthesia. The use of PEEP, which is one of the recruitment maneuvers, is widely used to overcome the worsening pulmonary functions observed during this surgery. However, there are reports that intracranial pressure may increase due to the use of PEEP.[11] While PEEP application increases intrathoracic pressure, it partially blocks venous return from the sagittal sinus. We observed that application of 10 cmH_2O PEEP in hemodynamically stable patients, aided the maintenance of lung function within normal range, and did not cause a significant increase in the optic nerve sheath diameter.

In a recent study performed by Bedirli et al.[18] on pigs, the authors reported that PEEP pressure at 10 cmH_2O maintained the intracranial pressure and brain perfusion pressure in laparoscopic surgery performed with the aid of pneumoperitoneum. In their study, PEEP pressures of 15 cmH_2O and 20 cmH_2O were shown to increase intracranial pressure and significantly decrease brain perfusion pressure. We used 10 cmH_2O PEEP and are thus unable to comment on the applications of PEEP at the higher values of 15 and 20 cmH_20.

Verdonck et al.[19] demonstrated that pneumoperitoneum and Trendelenburg position did not change the diameter of the optic nerve sheath in laparoscopic prostatectomy patients, in stark contrast with other studies showing that pneumoperitoneum and Trendelenburg position in laparoscopic surgeries significantly increased the diameter of the optic nerve sheath.[20,21] The increase in intracranial pressure due to the Trendelenburg position and pneumoperitoneum is thought to be due to the increase in intrathoracic and cerebral venous pressures.[22,23] In contrast to laparoscopic prostatectomy, in laparoscopic cholecystectomy, as in our study, the reverse Trendelenburg position is preferred. While the cardiopulmonary effects of this position are generally well tolerated, their effects on optic nerve sheath diameter and intracerebral physiology are not clearly demonstrated.[24,25]

Chin et al[5] compared optic nerve sheath diameters in patients who had and had not undergone PEEP applications at 8 cmH_2O during laparoscopic prostatectomies. They determined that optic nerve sheath diameter increased significantly when PEEP was applied before creation of pneumoperitoneum.

When pneumoperitoneum was applied, it was reported that the diameter of the optic nerve sheath increased in both groups compared to the baseline and time points of PEEP applications, but it did not cause a significant increase in the optic nerve sheath diameter in the group of 8 cmH_2O of PEEP compared to the group without PEEP. Kwak et al.[26] reported that PEEP application did not cause an increase in intracranial pressure and suggested that the lack of any increase in intracranial pressure following PEEP application was due to a decrease in dynamic lung compliance related to creation of pneumoperitoneum (which limits the intracranial effects of PEEP). Similarly, Caricato et al[27] also demonstrated that application of PEEP in patients with decreased lung compliance exerted minimal effects on intracranial pressure.

In our study, since we applied PEEP following creation of pneumoperitoneum, we could not examine the effect of PEEP application on the optic nerve sheath diameter before creation of pneumoperitoneum. We showed that dynamic lung compliance values decreased in both groups due to pneumoperitoneum, relative to baseline values. The decrease in lung compliance due to creation of pneumoperitoneum that we observed may mask the potential adverse effects of PEEP on intracranial pressure, therefore optic nerve sheath diameter may not be affected. This seems to be consistent with the theory proposed by Caracito et al.[27]

Since there is no consensus regarding the normal and upper limit of normal values of the optic nerve sheath diameter, a comparison of the baseline values of all patients as well as intergroup comparisons were made, and the impact of pneumoperitoneum, position of the patient, and PEEP on the optic nerve diameter were examined. In our study, the diameter of the optic nerve sheath increased with applications of pneumoperitoneum and PEEP, but this increase was not statistically and clinically significant. Maude et al.[28] identified the mean baseline optic nerve sheath diameter to be 4.41 mm (4.25–4.7) in 136 normal individuals, while Dip et al.[17] determined it to be 4.81 mm. In our study, the mean baseline optic nerve sheath diameter in both groups was 5.0 mm. It can be argued that this difference between studies makes it difficult to achieve standardization of values.

We also measured and recorded heart rate, mean arterial blood pressure, SpO_2, airway peak pressure (Ppeak), dynamic lung compliance values, tidal volume (TV), respiratory rate (RR), minute volume (MV), and $EtCO_2$ at six different time points, and we were thus able to follow the hemodynamic and respiratory parameters of the patients during this period. There was no observed hemodynamic instability or respiratory distress that would have affected the optic nerve sheath diameter.

In our study, $ETCO_2$ levels were continuously monitored and maintained within a constant interval by adjusting respiratory frequency during the operation, thus preventing an increase in $ETCO_2$, which might otherwise have led to an increase in intracranial pressure. None of the patients had signs and symptoms related to increased intracranial pressure before and after surgery.

The use of ocular ultrasonography is an important method in this study because it is a practical, fast, real-time, and noninvasive means to measure intracranial pressure. It shows the change in the diameter of the optic nerve sheath and guides us in estimating the intracranial pressure.

The limitation of this investigation was that a blind study design could not be achieved since application of PEEP could not be concealed from the researcher measuring the diameters of the optic nerve sheaths.

Future studies are needed to determine the effect of higher PEEP values on optic nerve sheath diameter, particularly for those patient groups where PEEP values higher than 10 cmH_2O may be required to control respiratory mechanics, such as obese patients.

In conclusion, the data we obtained suggest that PEEP application used to assist in the maintenance of normal lung function in hemodynamically stable patients, does not cause a significant increase in the optic nerve sheath diameter, and therefore in intracranial pressure, and that PEEP application can be used safely in laparoscopic cholecystectomy operations.

Conflicts of interest

The authors declare no conflicts of interest.

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