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Original Article

Effects of Thoracic Epidural Anesthesia on Systemic and Local Inflammatory Responses in Patients Undergoing Lung Cancer Surgery: A Randomized Controlled Trial

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Objective: Inflammatory responses play major roles in the development of acute lung injury following lung cancer surgery. The authors tested the hypothesis that thoracic epidural anesthesia (TEA) during surgery could attenuate both systemic and local inflammatory cytokine productions in patients undergoing lung cancer surgery.
Design: A prospective randomized controlled trial.
Setting: At Keio University Hospital, Tokyo, Japan.
Participants: Patients scheduled for lung cancer surgery.
Interventions: Sixty patients were randomly allocated into two groups (n = 30 each group): the epidural group (group E), in which anesthesia was maintained with propofol, fentanyl, rocuronium, and epidural anesthesia with 0.25% levobupivacaine; or the remifentanil group (group R), in which a remifentanil infusion was used as a potent analgesia instead of epidural anesthesia.
Measurements and Main Results: The lung epithelial lining fluid (ELF) and blood sampling were collected prior to one-lung ventilation (OLV) initiation (T1) and at 30 minutes after the end of OLV (T2). The concentrations of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10 in the ELF at T2 were increased significantly compared with those at T1 in both groups. The ELF concentration of IL-6 in group E was significantly lower than that in group R at T2 (median [interquartile range]: 39.7 [13.8-80.2] *versus* 76.1 [44.9-138.2], p = 0.008). Plasma IL-6 concentrations at T2, which increased in comparison to that at T1, were not significantly different between the two groups. The plasma concentrations of TNF-α did not change in both groups.
Conclusions: This randomized clinical trial suggested that TEA could attenuate local inflammatory responses in the lungs during lung cancer surgery.

Key Words: lung cancer surgery; epidural anesthesia; remifentanil analgesia; one-lung ventilation; acute lung injury; inflammatory response

A NUMBER of factors, such as shear stress to alveoli exacerbated by mechanical ventilation, ischemic-reperfusion injury elicited by hypoxic pulmonary vasoconstriction (HPV) during one-lung ventilation (OLV), and direct surgical manipulation, are associated with the development of acute lung injury (ALI) after thoracic surgery, including lung cancer surgery.[1] As a consequence of these factors, local and systemic inflammatory responses, characterized by increased production of inflammatory cytokines, play major roles in the development of postoperative ALI.[2]

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Thoracic epidural anesthesia (TEA), one of the potent measures to attenuate surgical stress and postoperative pain, has been shown to reduce systemic inflammatory responses during major surgery, such as esophagectomy or colectomy.[3,4] Meanwhile, remifentanil, a narcotic analgesic to potentially attenuate surgical stress, also may have the ability to reduce the systemic inflammatory response in patients undergoing major surgeries.[5] Considering that TEA has the ability to suppress sympathetic nervous system (SNS) activity associated with the modulation of immune function, possibly through the direct action of local aesthetics,[6,7] and to induce pulmonary artery vasodilation resulting in the attenuation of HPV,[8] it is plausible to hypothesize that TEA is superior to remifentanil infusion in attenuating both systemic and local lung inflammation during lung cancer surgery requiring OLV.

In this prospective randomized trial, the study authors investigated whether the application of TEA could attenuate systemic inflammatory response and local inflammation in the lungs in patients undergoing lung cancer surgery, compared with remifentanil analgesia during general anesthesia.

Methods

Ethics

This study was approved by the local Ethics Committee of the Keio University School of Medicine (Approval No. 20160075) and registered prior to patients enrollment at the University Hospital Medical Information Network (UMIN) Center (UMIN000023139, Principal investigator: Takeshi Suzuki, Date of registration: July 21, 2016). This trial conformed to the Consolidated Standards of Reporting Trials (CONSORT) guideline. Written informed consent was obtained from all patients before enrollment in the study.

Patient Selection

Adult patients with the American Society of Anesthesiologists (ASA) physical status (PS) Ⅰ or Ⅱ, scheduled to undergo surgical pulmonary resection for lung cancer or suspected lung cancer at Keio University Hospital, were enrolled in this randomized control study. Patients were excluded if they were younger than 18 years, or had a New York Heart Association functional classification II-to-IV cardiac disease, or had PaO_2 (arterial oxygen tension) less than 60 mmHg under room air, or had chronic obstructive pulmonary disease with percent predicted forced expiratory volume in one second ($\%FEV_1$) less than 50%, or had thrombocytopenia with platelet count less than $1 \times 10^5/\mu L$, or had coagulopathy (prothrombin time-international normalized ratio more than 1.5). Besides, patients undergoing right upper lobe resection also were excluded since a blocker catheter could interfere with the surgical procedure, and simultaneous deflation of the right upper lobe during OLV might not be sufficient due to its possible dislocation caused by surgical manipulation.

Study Protocol

The patients were randomly allocated into two groups at a 1:1 ratio: the epidural (group E) or remifentanil group (group R). Randomization was performed with a computer-generated assignment sequence with a 2 x 2 block size by an anesthesiologist who did not participate in this study. The assignment was blinded to participants and assessors of outcomes. All patients in both study groups received an epidural catheter insertion between levels Th5 and Th8 before the induction of general anesthesia. To obviate the misplacement of the epidural catheter, a 2-mL test dose of 1% lidocaine was administered routinely in both groups. In group E, after the placement of an epidural catheter, general anesthesia was induced and maintained with propofol, with a target-controlled infusion at the concentration of 2-to-5 μg/mL, fentanyl (induction dose 2 μg/kg) and rocuronium (induction dose of 0.6 mg/kg, maintenance dose 5-7 μg/kg/min) without remifentanil throughout the surgery. Before skin incision, 5-to-15 mL of 0.25% levobupivacaine were injected and infused continuously at the rate of 3-to-10 mL/h through an epidural catheter during the surgical procedure. In group R, after the epidural catheter insertion, the induction and maintenance of general anesthesia were performed with the same dose of propofol, fentanyl, and rocuronium as group E, and remifentanil at the rate of 0.5-to- 0.8 μg/kg/min without epidural anesthesia during the surgical procedure. In both groups, the infusion dose of drugs was adjusted at the discretion of the attending anesthesiologist, but an additional fentanyl dose was allowed to be used only during the placement of an epidural catheter and a blocker catheter to obviate additional stress. The depth of anesthesia was controlled to keep the bispectral index value between 40 and 60. The OLV was performed during surgery using a blocker catheter (Coopdech endobronchial blocker tube, BBT-B3060, Daiken Medical Co., Japan) inserted into the nondependent lung, guided by bronchoscope after intubation. After confirming the adequate position of the blocker catheter, OLV was initiated at 100% oxygen before a skin incision in both study groups. Mechanical ventilation of the dependent lung during OLV was managed in the volume-control mode, with 6 mL/kg (ideal body weight) of tidal volume and 5 cmH_2O positive end-expiratory pressure at 1:2 of inspiration/expiration ratio. Peak airway pressure was kept at less than 30 cmH_2O, and the tidal volume was reduced to 4 mL/kg if the peak airway pressure exceeded 30 cmH_2O. Continuous positive airway pressure (CPAP) was not applied to the nondependent lung during OLV. End-tidal carbon dioxide was maintained between 35-to-45 mmHg by adjusting the respiratory rate. If oxygen saturation (SpO_2) could not be kept equal to or above 90% during OLV, one of the following three measures was applied to the nondependent lung, and these patients were excluded from the study: application of CPAP, administration of oxygen, or manual two-lung ventilation during the temporary interruption of the surgery. For intraoperative hypotension, intermittent or continuous phenylephrine administration was used to maintain a mean arterial pressure equal to or greater than 60 mmHg. When the heart rate was less than 50 beats/min, 4-to-8 mg of

ephedrine or 0.25 to 0.5 mg of atropine were administered. A recruitment maneuver was performed at the end of OLV with 20 cmH_2O plateau pressure for 30 seconds to reopen the collapsed nondependent lung. In group R, 5-to-10 mL of 0.25% levobupivacaine werw administered through an epidural catheter to relieve postoperative pain 30 minutes after the termination of OLV. Postoperative pain was controlled with patient-controlled epidural analgesia in both groups. All patients were extubated after confirmation of postoperative chest x-ray and complete emergence from general anesthesia.

Outcomes

The primary outcome was the change of interleukin (IL)-6, one of the proinflammatory cytokines, in the epithelial lining fluid (ELF) collected from the main bronchus mucosa in the nondependent lung. The study authors selected IL-6 levels in the ELF as the primary outcome since previous studies demonstrated that changes in plasma IL-6 levels were associated with postoperative morbidity in patients undergoing esophagectomy in whom OLV was required during surgery.[9,10] The sampling of the ELF was performed twice using a bronchoscopic microsampling method, as previously described,[11] before the initiation of OLV just after intubation (T1) and 30 minutes after the termination of OLV (T2). The advantage of this method is the ability to collect ELF directly without dilution compared with bronchoalveolar lavage fluid (BALF).[11] The ELF sample was stored in the −80℃ freezer until the cytokine measurements were performed.

The secondary outcomes were the changes of other cytokines, including tumor necrosis factor (TNF)-α, as another proinflammatory mediator characterized by more rapid discharge, and IL-10 as an anti-inflammatory mediator in the ELF, and plasma concentrations of these cytokines and malondialdehyde (MDA), the last of which is a representative marker of oxidative stress. Blood samples were obtained at the same time as the ELF. The plasma was stored in a freezer at −80℃ until the assays were conducted after centrifugal separation (2,000 g at 4℃ for 20 minutes). Blood gas analyses also were performed at T1, T2, and an additional blood gas analysis was taken 30 minutes after the initiation of OLV (T-OLV). The change of PaO_2/F_IO_2 (fraction of inspiratory oxygen) (P/F) ratio during the surgical procedure was evaluated. Postoperative pulmonary (ALI, pneumonia, pulmonary fistula, pneumothorax, and chylothorax) and other organ complications, the incidence of redo surgery, postoperative pain evaluated by the numerical rating scale at the day of surgery and postoperative day one, and the length of hospital stay also were recorded and compared between both groups. In this study, ALI was defined as persistent postoperative hypoxia requiring supplemental oxygen for more than 72 hours after surgery, without apparent causes.

Sample Size

Before the study was commenced by the study authors, a sample size calculation was performed based on a previous study that compared the concentration of cytokines in the ELF between sevoflurane and propofol anesthesia in patients undergoing esophagectomy.[12] Although surgical stress to evoke inflammatory cytokines apparently is greater in esophagectomy than those in lung surgery, the authors here were unable to find comparative data. In that study, propofol anesthesia reduced the IL-6 level of ELF by 40% compared with sevoflurane anesthesia. The authors, therefore, chose a 40% reduction of cytokine discharge to find a significant difference in the ELF. Considering that the IL-6 concentration in the ELF in group R was 20 ng/mL and the TEA reduced this value by 40% with a standard deviation of 10 ng/mL, a calculation with a power of 80% and an alpha error of 0.05 revealed that 30 patients each group were required.

Statistical Analysis

Continuous data were analyzed with a Student *t*-test for normally distributed values and a Mann-Whitney *U* test for non-normally distributed values and presented as mean ± standard deviation or median (interquartile range) where appropriate. A two-way repeated-measured ANOVA followed by the Bonferroni test repeatedly were used for data measured. A comparison was made with a chi-square test or Fisher exact test for proportional data. A multiple linear regression analysis was performed to detect independent factors that affected the primary outcome, IL-6 concentration in the ELF. A p value of < 0.05 was considered statistically significant. Statistical analyses were performed using Sigma Plot 14.5 (Systat Software Inc., San Jose, CA).

Results

Of the 113 patients assessed for eligibility, 37 patients did not meet the inclusion criteria, and 15 patients declined to participate in the study. One patient was excluded from the study after informed consent was obtained since the use of a double-lumen tube was requested by the surgeons. Finally, 60 patients were enrolled and randomized into group E or group R, comprising 30 patients in each group (Fig 1). All operative procedures were performed by video-assisted thoracic surgery. No study protocol violations or adverse events were reported during the study period, allowing all 60 patients to be included in the final analyses. During OLV, no patients had episodes of hypoxemia and a high peak pressure of more than 30 cmH_2O. The baseline characteristics are summarized in Table 1. Apart from urine volume during the surgery, gender ratio, and forced vital capacity (FVC), there were no significant differences between the two groups. The difference in FVC could be accounted for by their gender ratio. The duration of OLV was similar in both study groups.

The concentrations of cytokines in the ELF and plasma are shown in Figures 2 and 3. In the ELF, all cytokine concentrations (TNF-α, IL-6, and IL-10) in both groups increased significantly at T2, compared with those at T1 (Fig 2). The primary outcome, the concentration of IL-6 in the ELF at T2, was significantly lower in group E than group R (39.7 [13.8-

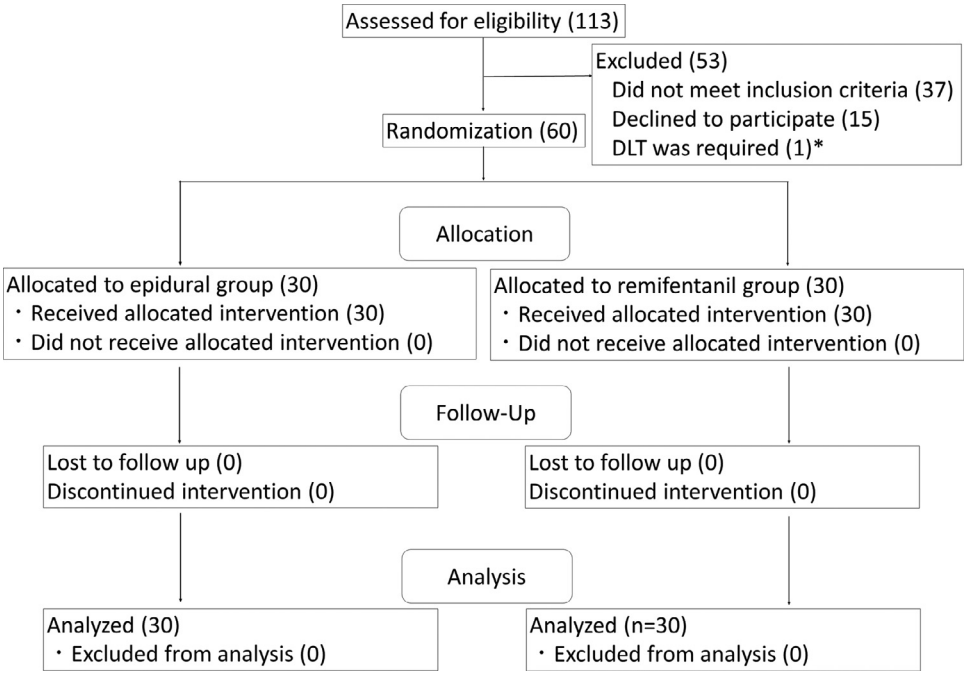

Fig. 1. The flow diagram of participants in this randomized trial. All randomized patients are included in the final analysis. DLT, double lumen tube. *This patient was excluded from the study after informed consent was obtained, since the use of DLT was requested by the surgeons.

80.2] *v* 76.1 [44.9-138.2] pg/mL; p = 0.008) (Fig 2). A multiple linear regression analysis, including allocated group (group E or R), measurement time (T1 or T2), gender ratio, age, body mass index, comorbidities, $\%FEV_1$, FVC, past history of smoking, the side of surgery, duration of OLV, surgery time, anesthesia time, and ASA PS, revealed that only the allocated group and measurement time affected the IL-6 concentration in the ELF. Although the plasma IL-6 concentration at T2 was higher than that at T1 in each group, there was no significant difference between group E and R (30 [15.3-47.2] *v* 42.8 [17.2-68.3] pg/mL; p = 0.29) (Fig 3). The plasma concentrations of TNF-α did not change at T2 compared with T1 in either group (Fig 3). The concentrations of plasma IL-10 were under the measurement limit in many patients (data not shown). The plasma concentration of MDA did not increase at T2 compared with T1 in either group and did not differ between both groups (Table 2). The other secondary outcomes, P/F ratio during the study procedure, respiratory and other organ complications, the incidence of redo surgery, postoperative pain evaluated by the numerical rating scale, and the length of hospital stay, were similar between the two groups (Table 2). Two patients in group R presented a postoperative ALI.

Discussion

In this randomized clinical trial, the application of TEA during lung cancer surgery attenuated the local inflammatory response, as reflected in a significant reduction of IL-6 in the ELF from the non-dependent lung, without affecting systemic inflammatory response compared with remifentanil infusion during general anesthesia. Considering that local inflammatory responses contribute to the development of ALI,[2,13] and the upregulation of inflammatory cytokines was likely to evoke postoperative pulmonary complications and delay postoperative recovery after major surgery,[10,14] such beneficial effects of TEA potentially may reduce the development of ALI after thoracic surgery.

Among several factors, OLV, an imperative anesthetic technique during thoracic surgery, has been recognized to prominently contribute to the development of ALI, the leading cause of postoperative mortality.[2,15] In the collapsed nondependent lung, oxidative stress and the local inflammatory response induced by ischemic-reperfusion injury associated with HPV during OLV contributed to the lung injury.[16-18] In patients undergoing esophagectomy, CPAP to the nondependent lung reduced the inflammatory cytokines collected from the BALF in the nondependent lung.[19] Another clinical study showed that volatile anesthetics, compared with propofol anesthesia, attenuated the local inflammatory response in the lung during thoracic surgery[20-22] through the decrease of proinflammatory cytokines in the BALF collected from both lungs. One possible mechanism by which either CPAP or volatile anesthetics attenuated the local inflammatory response might be the suppression of HPV, which can cause ischemic-reperfusion injury.[13,23] Given no differences of P/F ratio during OLV and MDA levels between the groups in this study, decreased IL-6 level of ELF was unlikely to be associated directly with attenuation of HPV.

Modulation of immune function brought about by the application of TEA could be the possible mechanism for the reduction of IL-6 in the lung ELF. Since the activity of SNS influences the immune function,[24] the neuroendocrine response blunted by TEA could modulate a surgically-induced

Table 1
Patient Characteristics

	Group E (n = 30)	Group R (n = 30)	p Value
Sex, male:female, n	21:9	13:17	0.04
Age, y	64 ± 13	66 ± 11	0.38
Body mass index	22 ± 3	21 ± 3	0.46
ASA PS, 1:2, n	11:19	9:21	0.58
%FEV_1 (%)	74.1 ± 8.9	74.0 ± 7.4	0.97
FVC, % (IQR)	3.6 (3.2-4.1)	3.0 (2.6-3.7)	0.03
Comorbidities, n	10	15	0.19
Hypertension	7	9	0.56
Diabetes mellitus	1	4	0.35
COPD	1	2	1.0
CKD	1	0	1.0
Past history of smoking, n	21	17	0.28
Malignant: Benign, n	29: 1	25: 5	0.09
Lobectomy: Partial resection, n	20: 10	19: 11	0.79
Right side: Left side	10: 20	4: 26	0.07
Operation time, min	121 ± 40	121 ± 38	0.98
Anesthesia time, min	200 ± 51	206 ± 40	0.62
OLV time, min	116 ± 37	113 ± 37	0.78
Fluid, mL	969 ± 205	1016 ± 200	0.36
Urine, mL	107 ± 72	223 ± 190	0.003
Blood loss, mL (IQR)	0 (0-0)	0 (0-27)	0.26
Hypoxemia episode during OLV, n	0	0	1.0
Fentanyl, μg/kg	3.5 ± 1.4	3.3 ± 1.2	0.61
Ephedrine, n	26	29	0.35
Phenylephrine, n	17	15	0.61
Atropine, n	0	0	1.0
0.25% Levobupivacaine, mL (IQR)	26 (19.6-28)	–	–
Remifentanil, mg	–	5 ± 2	–

Abbreviations: %FEV_1, percent predicted forced expiratory volume in one second; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; FVC, forced vital capacity; IQR, interquartile range; OLV, one-lung ventilation.

immunologic reaction. Besides, the application of TEA could modulate systemic and local inflammatory responses through the suppression of SNS due to, in part, a direct action of local anesthetics.[25] Pi et al revealed that, compared to no application of epidural anesthesia during intraoperative and postoperative periods, epidural anesthesia during perioperative periods reduced the incidence of short-term adverse events through the attenuation of systemic inflammatory cytokines in lung surgery.[26] However, they did not evaluate the effect of epidural anesthesia on lung inflammation. In the present study, TEA reduced IL-6 concentration in the ELF from the nondependent lung compared with remifentanil infusion. No study, to date, has evaluated the effect of TEA application on lung inflammation using ELF collected by bronchoscopic microsampling, which allows clinicians to more easily, noninvasively, and accurately collect ELF.[11] Postoperative epidural analgesia was applied in the same manner in both groups in this study, whereas the effects of intraoperative epidural anesthesia might have existed even in the postoperative periods.

Some may argue that the duration of the study appeared not to be long enough to detect the responses of proinflammatory and antiinflammatory cytokines. In the present study of lung surgery, however, the study authors showed the significant elevation and, in turn, the attenuation of cytokine discharges in the lungs within relatively short study periods. If lung resection surgery lasted longer in their institution, the ranges of cytokine alteration might be augmented. On the other hand, the absence of the reduction of systemic inflammatory cytokines might be attributable to the less-invasive surgical procedure, relatively short surgery time, and/or recruitment of relatively healthy patients (ASA PS Ⅰ-Ⅱ).

There are several limitations to interpret the data herein. First, despite the attenuation of the local inflammatory response, the application of TEA during surgery did not affect

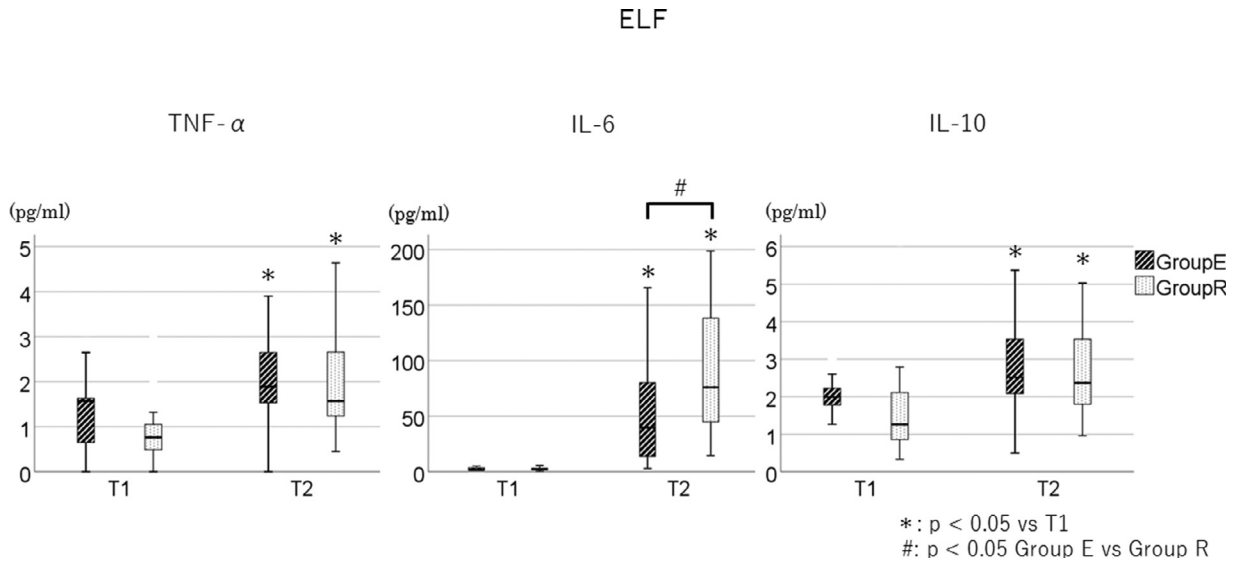

Fig. 2. The change of inflammatory cytokines in the epithelial lining fluid (ELF) collected from the nondependent lung. All inflammatory cytokines (TNF-α, IL-6, and IL-10) were increased significantly at T2 compared with those at T1. IL-6 in group E was significantly less than that in group R at T2. Two-way repeated-measured ANOVA, followed by Bonferroni test, were used to compare intra- and intergroup differences. T1: before the initiation of OLV just after intubation. T2: 30 minutes after the termination of OLV. Group E: epidural anesthesia group. Group R: remifentanil anesthesia group.

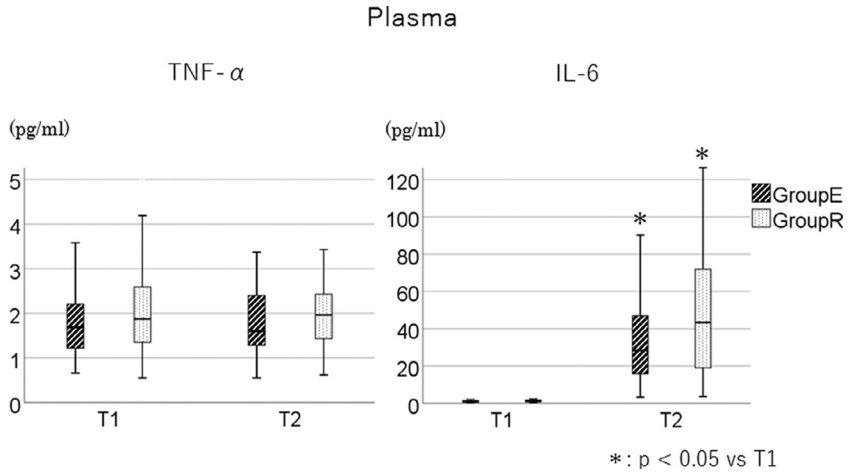

Fig. 3. The change of plasma inflammatory cytokines. The plasma concentration of IL-6 at T2 was significantly higher than that at T1, while TNF-α did not change significantly in both groups. The concentration of IL-10 was under the detectable limit in both groups. Two-way repeated measured ANOVA, followed by Bonferroni test, were used to compare intra- and intergroup differences. T1: before the initiation of OLV just after intubation. T2: 30 minutes after the termination of OLV. Group E: epidural anesthesia group. Group R: remifentanil anesthesia group

the incidence of postoperative pulmonary complications. A larger sample size may be required to detect such clinical endpoints. Second, gender differences between the groups might have affected the concentration of IL-6 in the ELF. However, a multiple linear regression analysis revealed that gender was not an independent factor. Third, due to its clinical advantage, the authors here used a similar dose of fentanyl to minimize the stress of the insertion of the epidural catheter, endotracheal intubation, and blocker catheter placement in both study groups. Despite a small dose of fentanyl (median dose of 200 μg) injected during the induction of anesthesia, it could be another confounding factor to interpret the present data. In addition, the study authors applied a relatively high dose of remifentanil in Group R, in which the average dose of remifentanil was 0.44 μg/kg/min. Fourth, due to several factors described in Figure 1, it took two and a half years to complete this clinical study. However, considering that both surgical and anesthetic procedures did not change during the study period, the duration of the study had little effect on the results. Finally, it should be noted that remifentanil-based analgesia during cardiac surgery attenuated the cell-mediated immune response, as well as cytokine signaling at the systemic level, resulting in a shorter stay in the intensive care unit.[27] Although the authors here do not have another approach clinically available as the control group, such characteristic aspects of remifentanil might be latent.

Table 2
Other Secondary Outcomes

	Group E (n = 30)	Group R (n = 30)	p Value
Plasma MDA at T1, U/L	87 ± 26	84 ± 21	0.53
Plasma MDA at T2, U/L	83 ± 31	76 ± 19	0.29
P/F ratio at T1	497 ± 62	489 ± 78	0.67
P/F ratio at T-OLV	295 ± 150	272 ± 111	0.52
P/F ratio at T2	481 ± 91	505 ± 57	0.21
Respiratory complication, n	3*	5†	0.48
Other complication, n	0	2‡	0.49
Re-operation, n	2§	0	0.15
NRS at the day of surgery (IQR)	2 (0-5)	2 (0-5)	0.72
NRS at postoperative day 1 (IQR)	0 (0-2)	0 (0-1)	0.78
Length of hospital stay, d (IQR)	6 (5-7)	6 (5-7)	0.77

Abbreviations: MDA, malondialdehyde; NRS, numerical rating scale; OLV, one-lung ventilation; P/F ratio, PaO_2 (arterial oxygen tension)/F_IO_2 (fraction of inspiratory oxygen) ratio; T1, before the initiation of OLV just after intubation; T2, 30 minutes after the termination of OLV; T-OLV, 30 minutes after the initiation of OLV.

* Pulmonary fistula and 2 chylothorax.

† Two acute lung injury, pleural effusion, pulmonary fistula, and chylothorax.

‡ Arrhythmia and neuralgia.

§ Due to chylothorax in both patients.

In conclusion, the application of TEA during general anesthesia for lung resection surgery could attenuate local inflammatory response in the lungs. Further studies are warranted to examine if TEA during thoracic surgery in which OLV is required minimizes the risk of pulmonary morbidity like ALI.

Conflict of Interest

No conflicts of interest to be declared.

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