Effect of ulinastatin on the inflammatory response after video-assisted thoracic lobectomy in patients with lung cancer: a randomized controlled study

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Abstract

Background: The first-line treatment for lung cancer is surgical resection, and one-lung ventilation (OLV) is the most basic anesthetic management method in lung surgery. During OLV, inflammatory cytokines are released in response to the lung tissue damage and promote local and contralateral lung damage through the systemic circulation. We designed a randomized, prospective study to evaluate the effect of the urinary trypsin inhibitor (UTI) ulinastatin on the inflammatory response after video-assisted thoracic lobectomy in patients with lung cancer.

Methods: Adult patients aged 19 to 70 years, who were scheduled for video-assisted thoracic lobectomy surgery to treat lung cancer between May 2020 and August 2020, were enrolled in this randomized, prospective study. UTI (300,000 units) mixed with 100 mL of normal saline in the ulinastatin group and 100 mL of normal saline in the control group was administered over 1 h after inducing anesthesia.

Results: The baseline (T0) interferon-γ (IFN-γ)/interleukin-4 (IL-4) ratio was not different between the groups (6941.3 ± 2778.7 *vs.* 6954.3 ± 2752.4 pg/mL, respectively; $P > 0.05$). The IFN-γ/IL-4 ratio was significantly higher in ulinastatin group at 30 min after entering the recovery room than control group (20,148.2 ± 5054.3 *vs.* 6674.0 ± 2963.6, respectively; adjusted $P < 0.017$).

Conclusion: Administering UTI attenuated the anti-inflammatory response, in terms of INF-**γ** expression and the IFN-γ/IL-4 ratio, after video-assisted thoracic surgery in lung cancer patients.

Trial registration: Clinical Research Information Service of Korea National Institute of Health (CRIS), KCT0005533.

Keywords: Ulinastatin; Lung cancer; Video-assisted thoracic surgery; INF-**γ**; IL-4

Introduction

The first-line treatment for lung cancer is surgical resection, and one-lung ventilation (OLV) is the most basic anesthetic management method in lung surgery. However, OLV can have various complications, including post-operative respiratory complications, and increases the mortality rate.[1] About 4% to 15% of patients develop acute lung injury after surgery[2]; this is the leading cause of death after lung surgery and accounts for about 92% of deaths within 1 year.[3-5] The ventilated lung is exposed to high tension secondary to a large non-physiological tidal volume and oxidative stress, as well as capillary shear stress because of hyperperfusion. Surgical manipulation of the non-ventilated lung can lead to lung damage, and reexpansion of collapsed lungs at the end of OLV invariably leads to ischemia-reperfusion injury. Inflammatory cytokines are released in response to lung tissue damage and promote local and contralateral lung damage through the systemic circulation.[6]

The production of certain types of T helper (Th) cells is determined by the differentiation of precursor helper T cells into Th1 or Th2 cells. Th1 cells produce interferon-γ (IFN-γ) and play a role in cell-mediated immune responses. Th2 cells produce interleukin-4 (IL-4) and/or IL-10, and play a role in humoral immunity by controlling the production of antibodies.[7] Surgery suppresses cell mediated immunity by reducing the Th1/Th2 ratio.[8]

Ulinastatin, a urinary trypsin inhibitor (UTI), is a nonspecific protease inhibitor. It is a glycoprotein with a molecular weight of 67 kDa that is extracted from human urine.[9] Ulinastatin has an anti-inflammatory effect.

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Administration of intravenous UTI protects against the development of a systemic inflammatory response and alleviates organ injury secondary to shock and ischemia by inhibiting lysosomal enzymes and the production of free radicals.[10-12] UTI is now commonly used in medical practice to increase microcirculation and improve tissue perfusion in patients with massive blood loss or hemodynamic instability during surgery.[13] However, few studies have reported the effect of UTI after lung lobectomy in patients with lung cancer.[14-16] Thus, we designed this randomized, prospective study to evaluate the effect of UTI on the inflammatory response after video-assisted thoracic lobectomy in patients with lung cancer.

Methods

Ethical approval

The study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital, The Catholic University of Korea (approval No. KC19MESI0364), and was registered with the Clinical Research Information Service of Korea National Institute of Health (identification No. KCT0005533). All patients provided written and verbal informed consent.

Patients

Adult patients aged 19 to 70 years, who were scheduled for video-assisted thoracic lobectomy surgery to treat lung cancer between May 2020 and August 2020, were enrolled in this randomized, prospective study. Patients diagnosed with lung cancer stage I from their preoperative computed tomography without medical history other than hypertension and diabetes mellitus were included. Patients with myocardial infarction or coronary artery disease, lung diseases (such as asthma or chronic obstructive pulmonary disease), an elevated aspartate aminotransferase/alanine aminotransferase ratio, or a history of hypersensitivity to inhalation anesthetics or propofol were excluded.

Randomization and masking

Upon arrival to the operating theater, patients were allocated to the UTI (U) or control (C) group using block randomization. An anesthesiologist not involved in the anesthetic management of the patients prepared the study solution and held the randomization codes until the end of the study. Another anesthesiologist who was not involved with perioperative patient evaluation and preparation of study drug conducted the entire course of anesthesia. Both patients and the anesthesiologist in charge were blinded to the group allocation for the study duration.

Intervention

Patients were not permitted to eat or drink for 8 h before the surgery. However, they consumed 200 mL of a carbohydrate drink 2 h before the surgery. Basic monitoring, including electrocardiogram, non-invasive blood pressure, pulse oximetry, and the bispectral index (BIS) was performed. Anesthesia was performed by two anesthesiologists who were specialized in thoracic surgery, and one surgeon performed lobectomies to minimize the variation. Anesthesia procedures were standardized as follows. In both groups, target-controlled infusion of propofol (3–6 μg/mL) and remifentanil (2–6 ng/mL), as well as rocuronium (0.6–1 mg/kg), were administered to induce anesthesia. After tracheal intubation, anesthesia was maintained with propofol (2–4 μg/mL), remifentanil (2–4 ng/mL), and O_2/air (fraction of inspired oxygen [FiO_2] 0.4). The depth of anesthesia in both groups was adjusted to maintain the BIS of 40 to 60. Blood pressure and pulse were maintained at around 20% of the respective baselines. Paravertebral block at the T2 to 3 level with a 22-G Tuohy needle, guided by ultrasound with the patient in the lateral position, was performed. Then, a 5 mg bolus of dexamethasone and 2 g of paracetamol mixed in 100 mL were administered. In addition, 300,000 units of UTI mixed with 100 mL of normal saline in group U, and 100 mL of normal saline in group C, were administered over 1 h during surgery. During OLV, a tidal volume of 4 to 5 mL/kg of predicted body weight, and 5 to 10 cmH_2O of positive end-expiratory pressure (PEEP) with a FiO_2 of 0.4 to 1.0, was maintained according to the anesthesiologist's judgment for oxygen saturation (SpO_2) > 90%. A gentle lung massage was done at the surgeon's request. When the surgery ended, all anesthetics were stopped and 200 mg sugammadex was administered. When spontaneous breathing returned, extubation was performed, and the patient was transferred to the recovery room.

Outcome measures

Blood was collected immediately after inducing anesthesia (T0). The blood samples were also collected 2 h after inducing anesthesia (T1) and 30 min after arrival in the recovery room (T2).

Blood samples were centrifuged at 1500 rpm for 10 min at room temperature. Serum was removed and stored in 200 μL aliquots at −80°C until the assays were performed. Serum was dispensed onto coated enzyme-linked immunosorbent assay (ELISA) plates. The serum levels of cytokines were determined by ELISA using human ELISA kit (Thermo Fisher Scientific, USA), following the manufacturer's instructions. The ELISA plates were analyzed using a microtiter plate reader (BioTek Instruments, Inc., Winooski, VT, USA) at 450 nm after stopping the reaction. IFN-γ concentration was calculated using a 5-parameter standard curve fit and IL-4 concentration was calculated using a 4-parameter standard curve fit.

Statistical analysis

IFN-γ level reported in a previous study was used for the sample size calculation.[17] Based on the reference study, the expected between-group difference in the mean IFN-γ level at T2 was 11 pg/mL, with a standard deviation (SD) of 10 pg/mL. Based on the standard normal probability of 0.85, 14 patients per group were required to achieve a power of 80% ($1-\beta = 0.8$) and a level of significance of 5% (two-sided $a = 0.05$), assuming a 10% drop-out rate.

All data were analyzed using SPSS software (ver. 18.0; SPSS Inc., Chicago, IL, USA). The student t test, chi-square

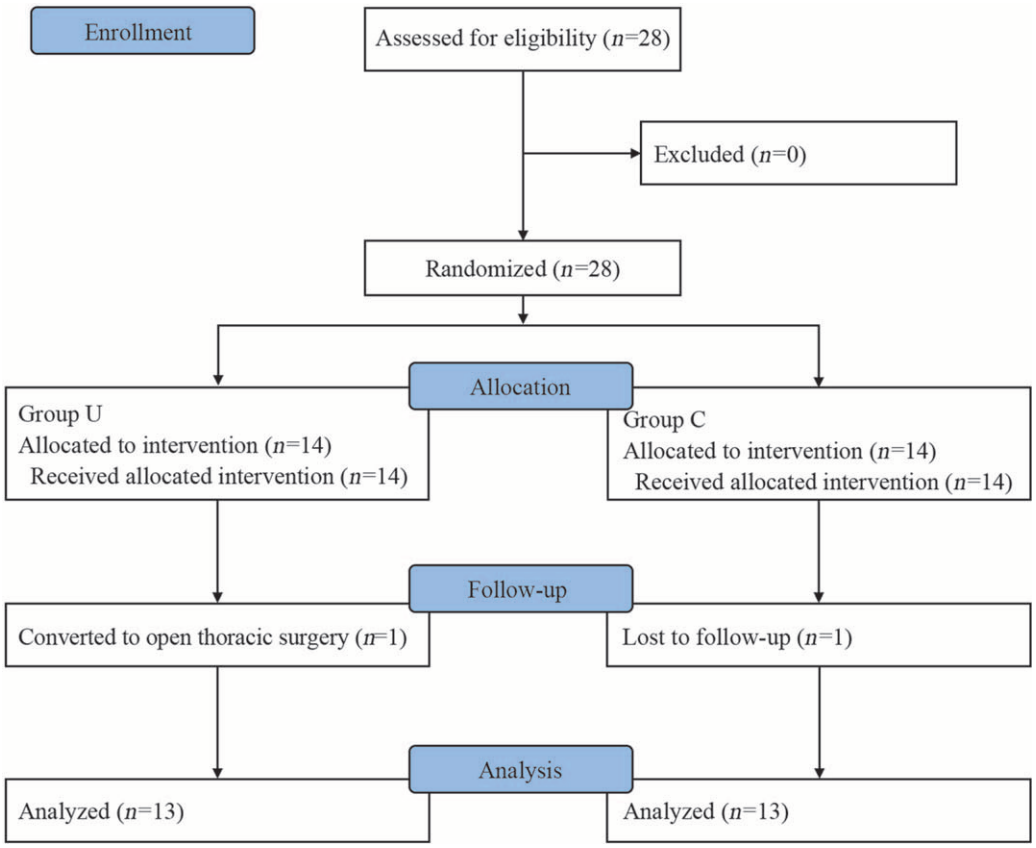

Figure 1: CONSORT flow diagram.

test or Fisher test was used to compare demographic and perioperative data such as surgery and anesthesia time, blood loss, and length of hospital stay. Repeated-measures one way analysis of variance was performed to compare cytokine levels between the groups, with group and time point as independent variables, after confirming the normality of the distribution with the Shapiro–Wilk test ($P > 0.05$). Bonferroni's correction was applied for multiple testing. Categorical variables are shown as numbers and other variables of demographic and perioperative data are shown as mean ± standard deviation (SD). Inflammatory outcomes are shown as mean ± standard error of the mean (SEM). A P value < 0.05 was considered significant. For Bonferroni correction, the adjusted P value < 0.017 was considered significant.

Results

Twenty-eight patients were recruited to the study and 14 patients were randomized to each group. Two patients were excluded from the data analyses (one in each group) because of conversion to open thoracotomy and loss to follow-up [Figure 1] between May 2020 and August 2020.

General and clinical characteristics

Seven cases of left upper lobectomy, three cases of left lower lobectomy, six cases of right upper lobectomy, six cases of right middle lobectomy, and four cases of right lower lobectomy were done. Seven patients (three from group U and four from group C) showed pleural effusion in post-operative chest X-rays without clinical symptoms, and no patients complained of post-operative pulmonary complications such as pneumonia during the hospital stay. The demographic and perioperative data are shown in Table 1.

Inflammatory outcomes

No significant differences in preoperative baseline (T0) cytokine levels were observed between the groups (mean ± SEM). The IFN-γ level at T1 in groups U and C was 4.4 ± 1.7 pg/mL and 4.3 ± 1.3 pg/mL, respectively (mean difference, 0.5 pg/mL; 95% confidence interval (CI), −4.4 to 4.5 pg/mL; $P > 0.05$). IFN-γ did not increase at T1 (4.3 ± 1.7 pg/mL *vs.* 4.7 ± 2.1pg/mL, respectively; mean difference, −0.4 pg/mL; 95% CI, −6.0 to 5.3 pg/mL; $P > 0.05$) in either group. However, it was significantly higher at T2 in group U than group C (5.5 ± 2.0 pg/mL *vs.* 2.4 ± 0.5 pg/mL, respectively; mean difference, 3.1 pg/mL; 95% CI, −1.1 to 7.3 pg/mL; adjusted P value < 0.017). In group C, it showed the tendency of decrease in T2 compared with T0 without statistical significance [Figure 2]. The IL-4 level at T0 in groups U and C was 0.7 ± 0.3 pg/mL and 0.6 ± 0.3 pg/mL, respectively (mean difference, 0.1 pg/mL; 95% CI, −0.7 to 0.9 pg/mL; $P > 0.05$). IL-4 tended to be lower in group U compared with group C (0.6 ± 0.2 pg/mL *vs.* 0.6 ± 0.2 pg/mL [mean difference, −0.1 pg/mL; 95% CI, −0.7 to 0.6 pg/mL] in T1, and 0.2 ± 0.1 pg/mL *vs.*

Table 1: Patient demographic and perioperative data.

Parameters	Ulinastatin group ($n = 13$)	Control group ($n = 13$)	*Statistics*	*P* value
Age (years)	60.6 ± 9.3	61.5 ± 8.3	−0.263*	0.794
Gender (male/female)	8/5	6/7	0.619†	0.695
Height (cm)	160.6 ± 9.6	162.4 ± 9.8	−0.501*	0.621
Weight (kg)	61.9 ± 7.4	64.2 ± 8.1	−0.616*	0.544
History of DM	3	3	0†	1.000
History of hypertension	7	5	0.619†	0.695
Surgery time (min)	196.2 ± 41.5	206.8 ± 40.5	0.724†	0.431
Anesthesia time (min)	259.2 ± 40.9	262.1 ± 40.2	−0.689*	0.497
Blood loss (mL)	106.9 ± 11.1	121.4 ± 17.1	−0.522*	0.658
Crystalloid infused (mL)	917.7 ± 350.9	932.1 ± 369.4	0*	0.488
Colloid infused (mL)	200.0 ± 50.0	200 ± 34.6	−0.681*	0.998
Urine output (mL)	286.2 ± 79.6	319.3 ± 39.6	−0.328*	0.745
Length of hospital stay (days)	7.4 ± 1.4	8.0 ± 1.4	−1.042*	0.245

Categorical variables are shown as numbers and other variables are shown as mean ± SD. * Student t test. † Chi-square test. DM: Diabetes mellitus; SD: Standard deviation.

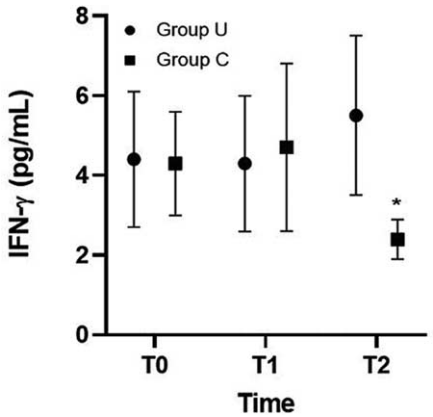

Figure 2: Changes in the IFN-γ level over time. T0, preoperative baseline; T1, 2 h after Inducing anesthesia; T2, 30 min after entering the recovery room, Bonferroni correction for multiple comparisons (adjusted *P* value for significance < 0.017). The top and bottom whisker marks represent standard deviation. IFN-γ: Interferon-γ.

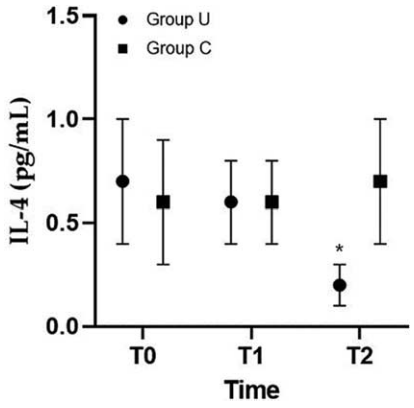

Figure 3: Changes in IL-4 level over time. T0, preoperative baseline; T1, 2 h after inducing anesthesia; T2, 30 min after entering the recovery room, Bonferroni correction for multiple comparisons (adjusted *P* value for significance < 0.017). The top and bottom whisker marks represent standard deviation. IL-4: Interleukin-4.

0.7 ± 0.3 pg/mL [mean difference, −0.5 pg/mL; 95% CI, −1.5 to 0 pg/mL] in T2, respectively; $P > 0.05$), but the difference was not significant [Figure 3].

The baseline (T0) IFN-γ/IL-4 ratio was not different between the groups (6941.3 ± 2778.7 *vs.* 6954.3 ± 2752.4, respectively; mean difference, −13.0; 95% CI, -8085.2 to 8059.2; $P > 0.05$). The IFN-γ/IL-4 ratio in group U tended to be higher compared with that in group C at T1 (10,433.5 ± 3140.8 pg/mL *vs.* 6298.2 ± 1752.4 pg/mL, respectively; mean difference, 4235.3; 95% CI, −6780.0 to 14070.9; $P > 0.05$). The IFN-γ/IL-4 ratio was significantly higher in group U at T2 than group C (20,148.2 ± 5054.3 *vs.* 6674.0 ± 2963.6, respectively; mean difference, 13,474.6; 95% CI, 1382.0 to 25,567.2; adjusted *P* value for significance < 0.017) [Figure 4].

Discussion

Administration of UTI during surgery increased the level of IFN-γ, the signature cytokine of Th1 cells, and the IFN-γ/IL-4 ratio after video-assisted thoracic lobectomy surgery under general anesthesia with OLV, suggesting that UTI plays an immunoregulatory role during lung cancer surgery and general anesthesia.

Surgery suppresses the immune system by activating the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, releasing stress hormones such as cortisol, norepinephrine, and epinephrine. In addition to the surgical stress response, general anesthesia suppresses the immune response directly by inhibiting the function of immune cells, and indirectly by modulating the stress response.[18] The immune response is known to decline beginning 2 h after anesthesia is induced.[19] The most important defense mechanism in the immune response is the oxidative sterilization induced by neutrophils.[20] Neutrophils affect the function of dendritic cells, that is, they can regulate T-cell function and the T-cell immune response.[21] Th cells are classified according to the cytokines that they produce.[22] Th1 cells secrete IFN-γ, which consequently activates cytotoxic T cells and

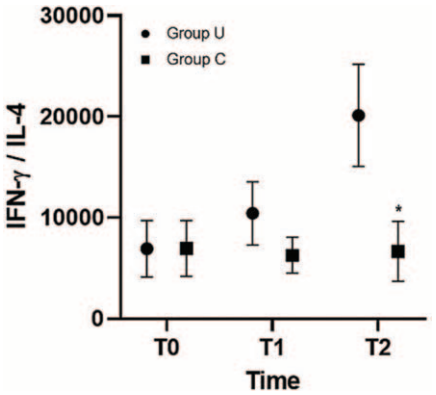

Figure 4: Changes in the IFN-γ/IL-4 ratio over time. T0, preoperative baseline; T1, 2 h after inducing anesthesia; T2, 30 min after entering the recovery room, *Bonferroni correction for multiple comparisons (adjusted *P* value for significance < 0.017). The top and bottom whisker marks represent standard deviation. IFN-γ: Interferon-γ; IL-4: Interleukin-4.

macrophages. Th1 cells promote the cell-mediated immune response, which confers a protective effect. In contrast, Th2 cells secrete cytokines, such as IL-4 and IL-10, which promote antibody production. Th2 cells are associated with humoral immunity, which suppresses cell-mediated immune responses.[7] Together with Th1 cells, natural killer (NK) cells, which have an anti-tumor effect, destroy cancer cells via IFN-γ release, while Th2 cells depress NK cell activity.[19,23-25]

In addition to surgical and anesthetic stress, patients undergoing lung cancer surgery experience OLV. Because of hyperperfusion, ventilated lungs are exposed to high gas tension, oxidative stress, and capillary shear stress.[26-30] The surgical manipulation itself can lead to lung damage, and re-expansion of collapsed lungs at the end of OLV may result in ischemia-reperfusion injury.[30] Inflammatory cytokines are released in response to local damage and promote local and contralateral lung damage.[6] Neutrophils also play a crucial role in acute lung injury.[31] Therefore, we designed this study to investigate the effect of UTI on reducing the inflammatory response in patients undergoing lung cancer surgery.

UTI is secreted when inter-α-trypsin inhibitors are broken down by neutrophil elastase. UTI attenuates the elevation of pro-inflammatory cytokine levels to prevent organ damage by directly inhibiting their secretion. In addition, UTI exerts an anti-metastatic effect by inhibiting the expression of urokinase-type plasminogen activator and inhibiting the cell-binding plasmin and cathepsin B activities involved in tumor cell proliferation and progression.[9-12] Various studies have demonstrated a protective effect of UTI in the immune response and cancer metastasis.[32-36] They reported that UTI reduced cancer metastasis by inhibiting cancer adhesive molecules, inhibiting expression of phospho-extracellular signal-regulated kinase gene, or its anti-plasmin activity.

However, this is the first study to evaluate the effect of UTI on immune response after video-assisted thoracic surgery in terms of the IFN-γ/IL-4 ratio (Th1/Th2 ratio). Thoracic surgery may disrupt this ratio more than other surgeries because patients must undergo OLV, which has a negative effect on the inflammatory response. The results of this study showed that IFN-γ expression and the IFN-γ/IL-4 ratio increased after administration of the UTI during lung cancer surgery. Several studies have reported the clinical implication of an imbalance in the IFN-γ/IL-4 ratio. Decker *et al*[8] reported that the surgical stress induces a shift in the Th1/Th2 balance toward Th2, suggesting that the decreased Th1/Th2 ratio resulted in suppressed cell-mediated immunity after surgery. Tan *et al*[37] reported that shift the Th1/Th2 (IFN-γ/IL-4) ratio toward Th1 could result in decreased nosocomial infection rate. Therefore, based on the result of this study, we assume a beneficial effect of UTI with respect to preventing cancer metastasis and recurrence, as well as preserving the postoperative immune balance (IFN-γ/IL-4 ratio).

The changes in the IFN-γ level at T2 in this study were relatively smaller compared with the previous study.[17] We attribute this difference to the anesthetic method used. To promote faster recovery, we instructed patients to consume a carbohydrate drink 2 h before surgery, to attenuate the stress response to surgery and thus promote early recovery.[38] Moreover, we applied a paravertebral block to control post-operative pain, which is known to lower the level of inflammation.[39] We also used protective ventilation during surgery by applying a tidal volume of 4 to 5 mL/kg of predicted body weight and 5 to 10 cmH_2O PEEP. Zhou *et al*[15] reported that administration of highdose UTI during lung cancer surgery did not reduce the post-operative neutrophil count. Unlike this study, they applied the conventional anesthetic method without lung-protective ventilation. We assumed that these anesthetic methods to enhance early recovery might promote the perioperative cell-mediated immune response. However, the statistical difference between groups was made by decreased IFN-γ level in group C rather than by increased IFN-γ level in group U in this study. This suggests that the anesthetic method used to promote early recovery did not show immune protective effect enough to overcome reactions caused by the surgical and anesthetic stress in the acute post-operative period. We speculate that UTI administration maintained the immune balance, attenuating the immune-suppressive reaction caused by the surgical and anesthetic stress.

There were some limitations to this study. First, we only evaluated the immune response in a short-term period of follow-up without clinical correlation. Second, we included a relatively small number of patients in a short period of study. A decline of immunity because of surgery and anesthesia is known to occur roughly from 2 h after induction of anesthesia, and the peak of immunosuppression occurs 3 days after surgery.[19] Therefore, we may have presented better results if we analyzed both the inflammatory reaction 3 days after surgery and clinical outcomes such as acute/chronic respiratory complications and cancer metastasis/recurrence. However, we originally planned this study as a preliminary study to investigate the relationship between UTI and NK cell activity and their effect on cancer metastasis/recurrence. As shown in the

results of this study, the immune balance related to NK cell activity is maintained simply by additional administration of UTI, which suggests that long-term laboratory and clinical follow-up may show the effect of UTI on preventing metastasis/recurrence in lung cancer patients. As UTI has anti-inflammatory and anti-metastatic actions, based on our data, we are planning a future study evaluating the effect of intraoperative administration of UTI on NK cell activity and post-operative clinical outcomes in a large study population with long-term follow-up.

In conclusion, UTI attenuated the anti-inflammatory response, in terms of INF-γ expression and the IFN-γ/IL-4 ratio, after video-assisted thoracic surgery in lung cancer patients, suggesting that it may prevent postoperative metastasis or recurrence. This suggests that the administration of UTI might influence the daily clinical practice in patients receiving lung cancer surgery in terms of preventing post-operative metastasis or recurrence. However, this study only shows laboratory results over a short-term period without clinical correlation. Thus, a long-term follow-up study evaluating inflammatory cytokines in relation to clinical outcomes such as cancer metastasis/recurrence is required.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

None.

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