

# Effects of sivelestat on bronchial inflammatory responses after esophagectomy

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**Abstract.** Post-operative pulmonary complications such as systemic inflammatory response syndrome (SIRS), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are strongly associated with morbidity and mortality after esophagectomy. Post-operative administration of sivelestat sodium hydrate (sivelestat), a selective inhibitor of neutrophil elastase (NE), has been shown to improve the post-operative clinical course after esophagectomy. This study aimed to evaluate the effect of prophylactic administration of sivelestat on bronchial inflammatory responses. We randomized 24 patients into two groups. One group received 0.2 mg/kg/h sivelestat from the induction of anesthesia to post-operative day 1 (sivelestat group) and the other group received the same amount of physiological saline (control group). Bronchial alveolar epithelial lining fluid (ELF) samples were obtained from both groups at the induction of anesthesia and at the end of surgery. The serum and ELF levels of interleukin (IL)-6 and IL-8 were measured by enzyme-linked immunosorbent assay, and NE activity was spectrophotometrically determined using the same samples. Although IL-6 levels in the ELF significantly increased at the end of surgery compared with the pre-operative levels in both groups, the IL-8 levels and NE activity did not significantly increase at the end of the surgery compared to the corresponding pre-operative values in the sivelestat group. Moreover, IL-8 levels and NE activity in the ELF were significantly reduced at the end of surgery in the sivelestat group compared with corresponding values in the

control group. The durations of ALI and ARDS were apparently shorter in the sivelestat group and the duration of SIRS was significantly shorter in the sivelestat group compared to the control group. We demonstrated that prophylactic use of sivelestat mitigated bronchial inflammation by suppressing NE activity and IL-8 levels in the ELF and shortened the duration of SIRS after transthoracic esophagectomy.

## Introduction

Esophagectomy is one of the most invasive treatments in gastrointestinal surgery (1). Post-operative pulmonary complications such as pneumonia, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) prolong the duration of mechanical ventilation and have been found to be strongly associated with increased morbidity and mortality after esophagectomy. Surgical procedures for esophageal cancer also induce a systemic inflammatory response syndrome (SIRS), characterized by overproduction of pro-inflammatory cytokines, which elicit excessive stress and may trigger post-operative complications (2).

Neutrophil elastase (NE), which is released from activated neutrophils, is regarded as one of the most important mediators of inflammatory tissue injury (3). It plays a crucial role in modulating the inflammatory response by influencing cytokine production and neutrophil accumulation at the inflammatory sites (4).

Sivelestat sodium hydrate (sivelestat) (Ono Pharmaceutical Co., Osaka, Japan), a specific NE inhibitor, has been developed in Japan (5). Several animal and clinical studies have revealed its ability to restore various types of tissue injuries as well as aspiration pneumonia (6), hepatoenteric ischemia (7), ALI (8) and lung injury associated with SIRS in humans (9). Recently, it has been reported that post-operative sivelestat administration after transthoracic esophagectomy improved the pathophysiological condition of SIRS and the post-operative clinical course even in patients without complications, as well as the deterioration of the PaO<sub>2</sub> (arterial oxygen tension)/FIO<sub>2</sub> (inspired oxygen fractional concentration) ratio in the post-operative

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period following esophagectomy (10,11). However, its prophylactic effect on transthoracic esophagectomy is still unknown.

Ishizuka *et al* have reported that bronchial microsampling (BMS) is a safe and useful technique to monitor pulmonary events, enabling the sequential analyses of biochemical and immunological markers in alveolar epithelial lining fluid (ELF), thereby helping to evaluate their pathophysiological significance at several time points during the progression of ARDS (12). Moreover, an advantage of BMS is its uncomplicated performance, without the use of saline, as opposed to bronchoalveolar lavage (13).

This study aimed to evaluate the effect of prophylactic administration of sivelestat on bronchial inflammatory responses in patients undergoing transthoracic esophagectomy by using the BMS method, which enables the recovery of ELF from the airway to quantify the levels of inflammatory cytokines and the NE produced or released in the local milieu. Furthermore, we investigated the effect of sivelestat on the post-operative respiratory functions and clinical courses. For these purposes, we enrolled patients undergoing right-sided transthoracic esophagectomy with cervical esophagogastrostomy and two- or three-field lymph node dissection, which is the most invasive surgery for the treatment of esophageal cancer.

## Materials and methods

We studied 24 patients who had undergone esophagectomy for esophageal cancer between 2006 and 2007 at Juntendo University Hospital. This study was approved by our institutional ethics committee, and written informed consents was obtained from all patients. Twenty-two patients underwent cervico-thoraco-abdominal three-field lymph node dissection through a right thoracotomy (3F) and 2 underwent thoraco-abdominal two-field lymph node dissection (2F).

The exclusion criteria were as follows: i) pre-operative chemotherapy, radiation therapy or immunotherapy, ii) older than 76 years, iii) pre-operative complications such as liver cirrhosis or diabetes mellitus, with <60 ml/min creatinine clearance, <80% vital capacity or <70% forced expiratory volume/second, iv) multiple cancers and v) old tuberculous lesions.

All operations were performed by an experienced surgical team. The patients were pre-operatively randomized into 2 groups. The sivelestat group received 0.2 mg/kg/h sivelestat intravenously from anesthesia induction to post-operative day (POD) 1, and the control group received the same amount of physiological saline. Anesthesia was induced with 2-2.5 mg/kg propofol, and a single spiral tube was placed after intravenous vecuronium administration (0.1 mg/kg). The initial ventilation settings were tidal volume, 8-10 ml/kg based on ideal body weight; respiratory rate, 10/min; inspiratory/expiratory ratio, 1:2; and FIO<sub>2</sub>, 0.6. General anesthesia was maintained using sevoflurane with epidural anesthesia using ropivacaine and 3 mg morphine hydrate. During esophagectomy, one-lung ventilation (OLV) was performed using an endobronchial blocker tube (Coodeck, Osaka, Japan), and the FIO<sub>2</sub> of gas supplied to the dependent lung was controlled to maintain SaO<sub>2</sub> >90%. If the peak inspiratory pressure exceeded 30 cm H<sub>2</sub>O, the blockage position was confirmed using a fiber-optic bronchoscope, and bronchial suction was performed. The

Table I. Patient characteristics.

Features	Control (n=12)	Sivelestat (n=12)
Operation (2F/3F)	1/11	1/11
Gender (male/female)	9/3	9/3
Age (years)	60±8	59±5
Height (cm)	163±8	164±9
Weight (kg)	56±12	63±14
VC (%)	103±12	96±11
FEV1.0% (%)	88±5	80±4
PaO <sub>2</sub> (mmHg)	95±17	88±9
Anesthesia (min)	457±92	470±49
Operation (min)	363±85	387±57
Thoracotomy (min)	173±56	172±34
Blood loss (ml)	376±166	488±229
Fluid administration (ml)	4295±1608	4798±1105

Statistical analysis did not identify significant differences between the two groups; 2F, two-field lymph node dissection; 3F, three-field lymph node dissection; VC, vital capacity; FEV, forced expiratory volume; PaO<sub>2</sub>, arterial oxygen tension.

tidal volume was reduced to 5-7 ml/kg, if necessary. After the thoracic esophagus was removed and the posterior mediastinal lymph nodes dissected, the right lung was manually inflated until visible atelectasis disappeared, and two-lung ventilation was resumed. Thereafter, the patients were placed in the supine position. Post-operative analgesia was provided with continuous epidural infusion of 0.2% ropivacaine plus 5 mg morphine/day. A gastric or colonic tube was constructed, and cervical esophagogastrostomy was performed at laparotomy. The patients were transferred to the intensive care unit (ICU) prior to extubation, if the PaO<sub>2</sub>/FIO<sub>2</sub> ratio was >300 mmHg, the forced vital capacity was >15 ml/kg and the circulation was stable.

Blood and ELF were obtained from the artery and the left segmental bronchus at anesthesia induction and after the surgery. Cytokine levels were quantified by a sandwich enzyme-linked immunosorbent assay (ELISA) with Ready-Set-Go (eBioscience, San Diego, CA) and DuoSet ELISA Development kits (R&D Systems, Minneapolis, MN) for interleukin (IL)-6 and IL-8, respectively. Serum and ELF NE activities were evaluated using Meo-Suc-Ala-Pro-Val-pNA as the substrate. A mixture containing 0.1 M Tris-HCl buffer (pH 8.0), 0.5 M NaCl pentose nucleic acid, and the substrate (final concentration: 1 mM) was incubated with the sera or ELF at 37°C for 24 h, and the liberated pNA was spectrophotometrically assayed at 405 nm (5,14).

The PaO<sub>2</sub>/FIO<sub>2</sub> ratio, respiratory index (A-aDO<sub>2</sub>/PaO<sub>2</sub>), and ALI and ARDS were evaluated throughout the post-surgical period. ALI and ARDS were defined according to the American European consensus conference on ARDS criteria (15). Additional criteria included bilateral infiltrations on plain chest radiographs and no clinical evidence of left arterial hypertension. The duration of SIRS after surgery was evaluated according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine. SIRS is charac-

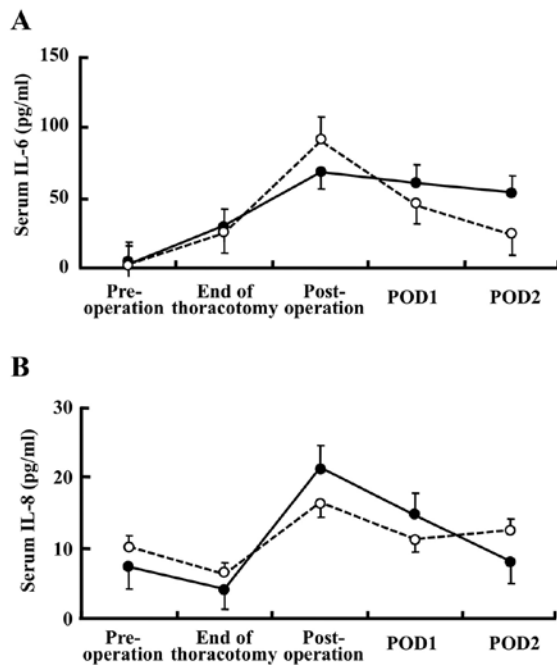


Figure 1. Changes in the serum levels of IL-6 and IL-8 before and after esophagectomy. The serum levels of (A) IL-6 and (B) IL-8 were measured before (pre-operation) and after the surgery (end of thoracotomy, post-operation, POD1 and POD2) in the control group (closed circles) and the sivelestat group (open circles). POD1, post-operative day 1; POD2, post-operative day 2. Data are presented as mean  $\pm$  SD.

terized by 2 or more of the following conditions: i) temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ , ii) heart rate  $>90$  beats/min, iii) respiratory rate  $>20$  beats/min or  $\text{PaCO}_2 <32$  mmHg and iv) white blood cell (WBC) count  $>12,000$  cells/ $\text{mm}^3$ ,  $<4,000$  cells/ $\text{mm}^3$  or 10% immature (band) forms (16).

Data are presented as the means  $\pm$  SD. Statistical significance was determined by analysis of variance. Comparisons were carried out by the Fisher's exact test. GraphPad Prism 5 was used for the analysis. A P-value  $<0.05$  indicates statistical significance.

## Results

**Patient characteristics.** Patient characteristics are presented in Table I. The duration of the operation, anesthesia, and thoracotomy; the volume of intra-operative fluid administered, and the estimated blood loss did not significantly differ between the groups. Except for one patient in each group, all the patients were successfully able to be extubated at the end of surgery.

**Serum IL-6 and IL-8 levels.** The serum cytokine levels at different time points are shown in Fig. 1. The IL-6 and IL-8 levels peaked at the end of the surgery and decreased thereafter in both groups. There was no significant difference between the groups.

**ELF IL-6 and IL-8 levels.** The IL-6 and IL-8 levels in the ELF are depicted in Fig. 2. The post-operative IL-6 level was significantly higher than the pre-operative levels in both the groups ( $P<0.05$ ), but the difference was not significant between the 2 groups. In the control group, the post-operative IL-8 level was higher than the pre-operative level ( $P<0.05$ );

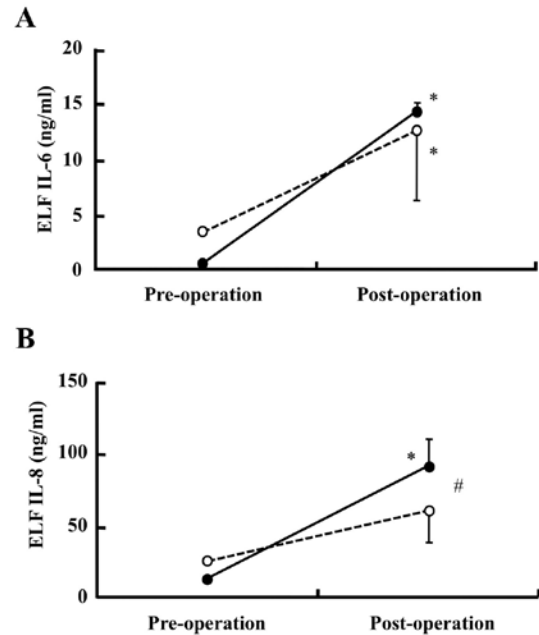


Figure 2. Changes in the IL-6 and IL-8 levels in the epithelial lining fluid (ELF) before and after esophagectomy. (A) IL-6 and (B) IL-8 levels in the ELF were measured before (pre-operation) and after the surgery (post-operation) in the control group (closed circles) and the sivelestat group (open circles). Data are presented as mean  $\pm$  SD. \* $P<0.05$  compared with pre-operation; # $P<0.05$  compared with control group.

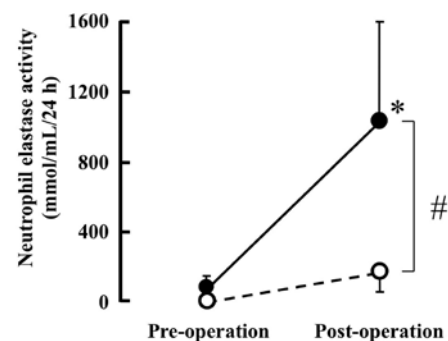


Figure 3. Changes in the epithelial lining fluid (ELF) levels of neutrophil elastase activity before and after esophagectomy. Neutrophil elastase activity in the ELF was measured before (pre-operation) and after the surgery (post-operation) in the control group (closed circles) and sivelestat group (open circles). Data are presented as mean  $\pm$  SD. Values are compared between the control and sivelestat groups. \* $P<0.05$  compared with pre-operation; # $P<0.05$  compared with the control group.

however, the pre- and post-operative IL-8 levels in the sivelestat group did not significantly differ. Importantly, the post-operative IL-8 level was significantly lower in the sivelestat group than in the control group ( $P<0.05$ ).

**Serum and ELF NE activity.** Serum NE activity was undetectable (data not shown); however, ELF NE activity was detected in both the groups. The post-operative NE activity was significantly higher than the pre-operative value in the control group, whereas this difference was not significant in the sivelestat group (Fig. 3). The post-operative NE activity was significantly suppressed in the sivelestat group ( $P<0.05$ ).

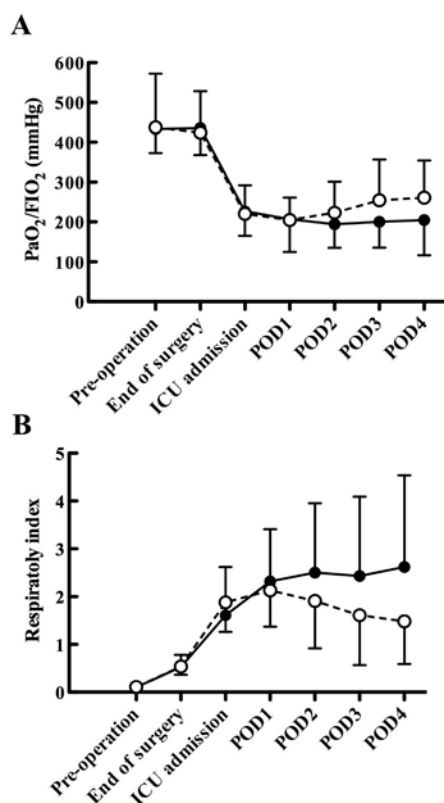


Figure 4. Changes in the levels of the  $\text{PaO}_2/\text{FIO}_2$  ratio and respiratory index before and after esophagectomy. The  $\text{PaO}_2/\text{FIO}_2$  ratio (A) and respiratory index (B) were measured before (pre-operation) and after the surgery (end of surgery, ICU admission, POD1, POD2, POD3 and POD4) in the control group (closed circles) and the sivelestat group (open circles). POD1, post-operative day 1; POD2, post-operative day 2; POD3, post-operative day 3; POD4, post-operative day 4. Data are presented as mean  $\pm$  SD.

**$\text{PaO}_2/\text{FIO}_2$  and respiratory index during the post-operative course.** The post-operative  $\text{PaO}_2/\text{FIO}_2$  ratio decreased (Fig. 4A) and the respiratory index increased (Fig. 4B) compared to the pre-operative values in both groups. These changes were apparently suppressed by sivelestat administration, although the difference was not statistically significant the control group.

**SIRS development.** There were no significant differences in the post-surgical respiratory rate, temperature, heart rate, or WBC count between the groups (data not shown). There were fewer incidences of SIRS (Table II) in the sivelestat group

Table II. Development of SIRS during the post-operative course in the sivelestat and control groups.

Group	POD1	POD2	POD3	POD4
Control	9	9	7	5
Sivelestat	3	5	2 <sup>a</sup>	1

POD1, post-operative day 1; POD2, post-operative day 2; POD3, post-operative day 3; POD4, post-operative day 4. Values are compared between the control and sivelestat groups. <sup>a</sup> $P < 0.05$ .

than in the control group; this difference was statistically significant on POD3.

**Durations of SIRS, ALI and ARDS.** The duration of SIRS was significantly shorter in the sivelestat group than in the control group ( $P < 0.05$ ). The durations of ALI and ARDS were shorter in the sivelestat group than in the control group, but the difference was not statistically significant (Fig. 5).

## Discussion

In the present study we have demonstrated that i) prophylactic sivelestat treatment during transthoracic esophagectomy decreased the post-surgical NE activity and IL-8 levels in the ELF and ii) sivelestat shortened the duration of SIRS following transthoracic esophagectomy.

Hypercytokinemia elicits excessive stress that may trigger post-operative pulmonary complications (17). Transthoracic esophagectomy induced considerably higher post-operative serum IL-6 levels than distal gastrectomy for gastric cancer (18), and could induce an excessive inflammatory response leading to SIRS and pulmonary complications (19).

Activated neutrophils can cause tissue injury by releasing proteases and oxygen radicals (20).  $\text{PaO}_2/\text{FIO}_2$  and IL-8 in bronchoalveolar lavage fluid (BALF) have been reported to be significantly correlated in patients with acute ARDS (21). Furthermore, Tsukada *et al* have indicated that BALF IL-8 rather than serum IL-8 could predict post-operative pulmonary complications after esophagectomy (22). In our study, sivelestat significantly suppressed IL-8 but not IL-6, and may have improved the clinical course after transthoracic esophagectomy.

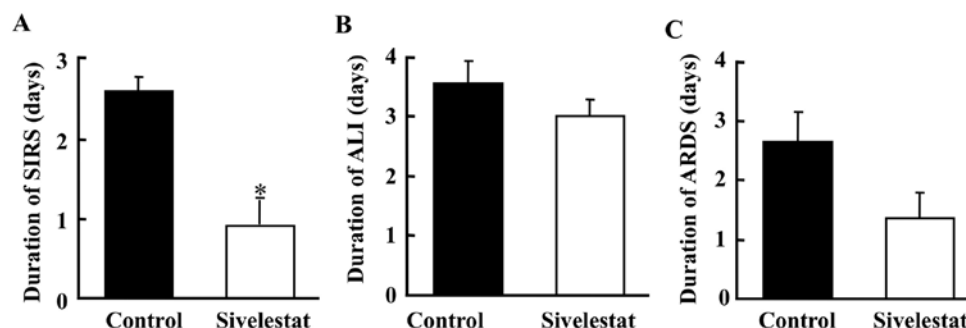


Figure 5. Evaluation of the durations of SIRS, ALI and ARDS. Durations of SIRS (A), ALI (B) and ARDS (C) were compared between the control group (black bars) and sivelestat group (white bars). Data are presented as mean  $\pm$  SD. \* $P < 0.05$  compared to the control group.

Collapse and re-expansion of the non-dependent lung during thoracotomy induces injury by an ischemic/reperfusion mechanism, and re-ventilation of the dependent lung could produce injury by micro-barotrauma (23). Kooguchi *et al* have reported high IL-6 and IL-8 levels in alveolar macrophages after esophagectomy, supporting the notion that cytokines are mainly produced and secreted in the operative field (24). Nakamura *et al* have also reported increased IL-8 concentration after lung collapse and re-expansion (25). SIRS occurs after esophagectomy via stimulation of the primed lung by chemical mediators and cytokines (26). Consistent with these observations, we observed higher IL-6 and IL-8 levels in the ELF than in the blood following esophagectomy.

NE is released from neutrophils under surgical stress (27), and induces IL-8 production (28). Sivelestat has been approved for use to treat ALI in humans in Japan (29), although there is no consensus regarding its benefits (30). Tamakuma *et al* have suggested that sivelestat may function by reducing inflammatory reactions in the injured lung (29). Several studies have reported the relationships between the severity of sepsis, trauma, and burns with SIRS (31). SIRS is considered to be induced by hypercytokinemia, and the longer its duration, the likelier it is to progress to multiple organ dysfunction (1,32). Our study is the first to demonstrate that NE activity is locally increased in the ELF after esophagectomy and that this increase can be suppressed by prophylactic sivelestat administration.

A recent study demonstrated that sivelestat administration resulted in a higher PaO<sub>2</sub>/FIO<sub>2</sub> ratio and reduced respiratory index during the post-operative course in pediatric patients who underwent cardiovascular surgery with cardiopulmonary bypass (33). Our study revealed that these changes were suppressed in the sivelestat group during the post-operative course, although the suppression was not statistically significant.

The NE inhibitor, sivelestat, is a downstream modulator of the inflammatory cascade, while corticosteroids are upstream modulators (34). Thus, cytokine modulators that regulate pathways downstream of the cascade may be clinically useful for the prophylaxis and treatment of surgical stress-induced complications. Therefore, we hypothesized that sivelestat could be effective when administered during surgery-induced trauma.

The sample size of our study was small. Therefore, a large-scale prospective randomized control study is required to confirm our findings. In conclusion, we have demonstrated that prophylactic sivelestat administration reduced the NE activity and suppressed IL-8 levels in the ELF, thereby shortening the duration of SIRS after transthoracic esophagectomy.

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