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Effects of Neutrophil Elastase Inhibitor on Progression of Acute Lung Injury Following Esophagectomy

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Abstract The purpose of this study was to evaluate the effect of sivelestat sodium hydrate, a selective inhibitor of neutrophil elastase in the systemic inflammatory response, pulmonary function, and the postoperative clinical course following esophagectomy. Patients with hypoxia associated with surgical stress in the intensive care unit (ICU) immediately after an esophagectomy were eligible for this study. The degree of hypoxia was calculated according to the ratio of arterial oxygen tension (PaO_2) to the fractional concentration of inspired oxygen (FiO_2)—PaO_2/FiO_2. Patients with $PaO_2/FiO_2 < 300$ mmHg were enrolled in this study. Seven patients were treated with sivelestat, and 10 were not so treated. The degree of hypoxia, the criteria for systemic inflammatory response syndrome (SIRS), and the postoperative clinical course were compared between the two groups. The postoperative decreases in the PaO_2/FiO_2 ratio were significantly suppressed in the sivelestat group ($p < 0.05$, by analysis of variance, or ANOVA). Furthermore, 9 of the 10 control group patients developed SIRS on postoperative day 2, whereas only 2 of 7 of the sivelestat group patients developed SIRS ($p < 0.05$). The postoperative increases in the heart rate were significantly suppressed in the sivelestat group ($p < 0.05$, ANOVA). The postoperative decreases in the platelet counts were significantly suppressed in the sivelestat group ($p < 0.05$, ANOVA). The duration of mechanical ventilation and the length of ICU stay for the sivelestat group were shorter than that for the control group. We demonstrated that the postoperative decreases in the PaO_2/FiO_2 ratio following esophagectomy were significantly suppressed in the sivelestat-treated group. This clinical study showed that a neutrophil elastase inhibitor may thus be a potentially useful drug for treating acute lung injury following esophagectomy.

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Surgery for esophageal cancer is one of the most invasive treatments in gastrointestinal surgery [1]. Consequently, in patients who undergo esophagectomy, postoperative complications such as respiratory failure and arrhythmia often occur. To decrease the invasiveness of the surgery even slightly is important for postoperative recovery. We previously reported that a serine protease inhibitor is useful for reducing the surgical stress associated with esophagectomy, although some patients who underwent esophagectomy developed organ dysfunction [2]. Acute lung injury (ALI) is the most common organ dysfunction and sometimes leads to postoperative death in esophageal cancer patients.

Acute lung injury, including acute respiratory distress syndrome (ARDS), is a severe disease with a mortality rate of 30% to 70% [3]. The pathogenesis of ALI includes inflammatory reactions due to neutrophil accumulation in the lungs during the early stage of the disease. Pulmonary vascular hyperpermeability, which is a cause of hypoxemia during the early stage of the disease, could be caused by the neutrophil elastase (NE) released from neutrophils [4]. NE quantitatively represents the major granule component and is well known to be the most potent protease that stimulates airway secretion, accelerates airway inflammation, and damages the airway mucosal tissue.

Sivelestat sodium hydrate (hereafter referred to as sivelestat) is a selective inhibitor of NE [5], which is effective

in endotoxin-induced lung injury models [6]. Based on clinical studies, Tamakuma et al. reported that sivelestat was effective in patients with ALI associated with the systemic inflammatory response syndrome (SIRS), suggesting that the inhibitor may be a potentially useful drug for treating the cause of the disease possibly by directly reducing inflammation in the injured lung [7].

In this study, we evaluated the effect of sivelestat on the systemic inflammatory response, pulmonary function, and postoperative clinical course following esophagectomy.

Patients and Methods

Patients

A total of 63 patients with esophageal carcinoma underwent elective esophagectomy between January 2000 and June 2005 in the Department of Surgery I, National Defense Medical College Hospital. All patients had detailed preoperative risk assessment based on their history, symptoms and signs of chronic lung or heart disease, chest radiography, electrocardiography, and pulmonary function tests. None of the patients had chronic obstructive pulmonary disease (COPD), tachycardia, or arrhythmia. All of the patients underwent esophagectomy and reconstruction with gastric mobilization by right posterolateral thoracotomy and laparotomy.

Immediately after surgery each esophagectomy patient was placed on prophylactic mechanical ventilation and admitted to the intensive care unit (ICU). The patients' oxygen saturation was then calculated, and those with hypoxia associated with surgical stress were further evaluated. The degree of hypoxia was calculated according to the ratio of the arterial oxygen tension (PaO_2) to the fractional concentration of inspired oxygen (FiO_2)—PaO_2/FiO_2. If the ratio was <300 mmHg, the patient was enrolled in this study. All patients with esophagectomy stayed in the ICU while on mechanical ventilation.

In total, 17 patients met the criteria, and the subjects were divided into two groups according to the postoperative treatment. One group of 7 patients was administered sivelestat sodium hydrate, a selective inhibitor of neutrophil elastase. The other group of 10 patients was not given sivelestat. The Sivelestat-treated group patients were admitted to our hospital after July 2002, after sivelestat had been approved as a drug by the Ministry of Health and Welfare in Japan.

Sivelestat was started in the ICU immediately after esohagectomy and was administered continuously (0.2 mg/kg/hr) for 5 days. The control group—patients not treated with sivelestat—had been admitted to our hospital between January 2000 and June 2002, when Sivelestat had not yet been approved for use in Japan. Surgical procedures and techniques and the analgesic approach were not changed before and after 2002. Only one patient in each group had undergone irradiation and chemotherapy before surgery. This study was a nonrandomized, nonblinded, cohort analysis of treatment versus control in patients following esophagectomy using sivelestat sodium hydrate. Weaning from mechanical ventilation was conducted in accordance to the criteria defined by the ARDS Network [8] as much as possible.

Postoperative Clinical Course Evaluation

The degree of hypoxia based on the PaO_2/FiO_2 ratio and the criteria for SIRS—such as temperature, heart rate, respiratory rate, and white blood cell count (WBC)—as well as the development of SIRS were monitored immediately after surgery (post) and on postoperative day 1 (POD1), POD2, POD3, and POD5. The criteria for SIRS are the presence of two or more of the following: (1) temperature > 38°C or < 36°C; (2) heart rate > 90 beats per minute; (3) respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg; and (4) WBC > 12,000 cells/mm^3, < 4000 cells/mm^3, or 10% immature forms (bands). These criteria were based on those established during the ACCP/SCCM Consensus Conference [9].

The postoperative clinical course was evaluated by determining the rates of postoperative infectious complications such as pneumonia, wound infection, and intraabdominal abscess.

Statistical Analysis

Numerical values are given as the means ± SD. Statistical analysis was performed using the StatView 4.5 statistical software package (Abacus Concepts, Berkeley, CA, USA). Any differences between the two groups were evaluated by an analysis of variance (ANOVA) for repeated measures. If a significant difference was found by ANOVA, the differences at several time points were checked by Student's *t*-test. The differences in clinical characteristics and postoperative complication rates between the two groups were analyzed by Fisher's exact probability test. Statistical significance was determined at $p < 0.05$.

Results

Patient Background Factors

The background factors for 17 patients with esophageal cancer, including 11 men and 6 women, are listed in Ta-

Table 1 Patients' background factors for the Sivelestat-treated and control groups

Factor	Sivelestat group (n = 7)	Control group (n = 10)	p
Sex			
Male	4	7	NS
Female	3	3	
Age (years)	60.7 ± 11.8	69.5 ± 6.7	NS
pTNM stage			
I	1	2	NS
II	1	3	
III	5	5	
Respiratory function			
VC (%)	103.7 ± 7.7	107.0 ± 21.7	NS
FEV_1 (%)	79.3 ± 7.2	72.7 ± 9.5	NS
Operating time (min)	573.4 ± 72.6	568.7 ± 164.1	NS
Blood loss (ml)	1685.1 ± 1255.3	1032.4 ± 347.7	NS

VC: vital capacity; FEV_1: forced expiratory volume in 1 second

ble 1. The average age of the sivelestat group was 60.7 years, and that of the control group was 69.5 years. There were no statistically significant differences between the two groups in terms of sex, age, location of the esophageal cancer, or preoperative respiratory function. The operative factors for 17 patients are also listed in Table 1. There were no statistically significant differences in the duration of surgery, operative blood loss, or pathologic cancer staging between the two groups.

Comparison of the SIRS Criteria Between the Two Groups During the Postoperative Course

The postoperative increases in the heart rate were significantly suppressed in the sivelestat group ($p < 0.05$, ANOVA) (Fig. 1).fig1 Furthermore, the heart rates in the sivelestat group on POD1 were significantly lower than that in the control group. There were no significant differences in the respiratory rate, temperature, or WBC between the two groups.

Comparison of the Degree of Hypoxia with PaO_2/FiO_2 Between the Two Groups During the Postoperative Course

The postoperative decreases in the PaO_2/FiO_2 ratio were significantly suppressed in the sivelestat group ($p < 0.05$, ANOVA) (Fig. 2).fig2 Furthermore, the PaO_2/FiO_2 ratio in the Sivelestat group on POD3 was significantly higher than that in the control group.

Comparison of the Development of SIRS and Platelet Counts Between the Two Groups During the Postoperative Course

The postoperative development of SIRS was compared between the two groups (Table 2). Nine of the ten control group patients developed SIRS on POD2, whereas only 2 of the 7 sivelestat group patients developed SIRS ($p < 0.05$).

The postoperative decreases in the platelet counts were significantly suppressed in the sivelestat group ($p < 0.05$, ANOVA), and the platelet counts in the Sivelestat group on POD5 were significantly higher than those in the control group (Table 3).

Comparison of Clinical Data and Postoperative Infectious Complications

The postoperative clinical course of each patient was carefully monitored on a daily basis to screen for postoperative complications. The duration of mechanical ventilation and the length of ICU stay were also compared between the two groups (Table 4). The duration of mechanical ventilation and the length of the ICU stay for the sivelestat group were shorter than for the control group. However, there were no significant differences between the two groups regarding the rate of postoperative infectious complications (Table 4).

Discussion

In the present study, we demonstrated that the postoperative decreases in the PaO_2/FiO_2 ratio following esophagectomy were significantly suppressed in the sivelestat-treated group. Furthermore, the development of SIRS, the duration of the ventilation time, and the stay in the ICU showed a decreasing tendency in the sivelestat-treated group.

Transthoracotic esophagectomy is considered one of the most invasive surgical procedures in gastrointestinal surgery. We have previously reported that transthoracic esophagectomy induced much higher postoperative serum interleukin-6 levels than distal gastrectomy for gastric cancer, and that esophagectomy led to extensive activation of granulocytes as determined by their CD11b/CD18 expression [10]. Esophagectomy may thus produce an excessive inflammatory response, which may subsequently lead to the development of SIRS and postoperative pulmonary complications.

In this study, about 30% of all patients following esophagectomy met the ALI criteria ($PaO_2/FiO_2 < 300$). The current treatment for ALI is the respiratory manage-

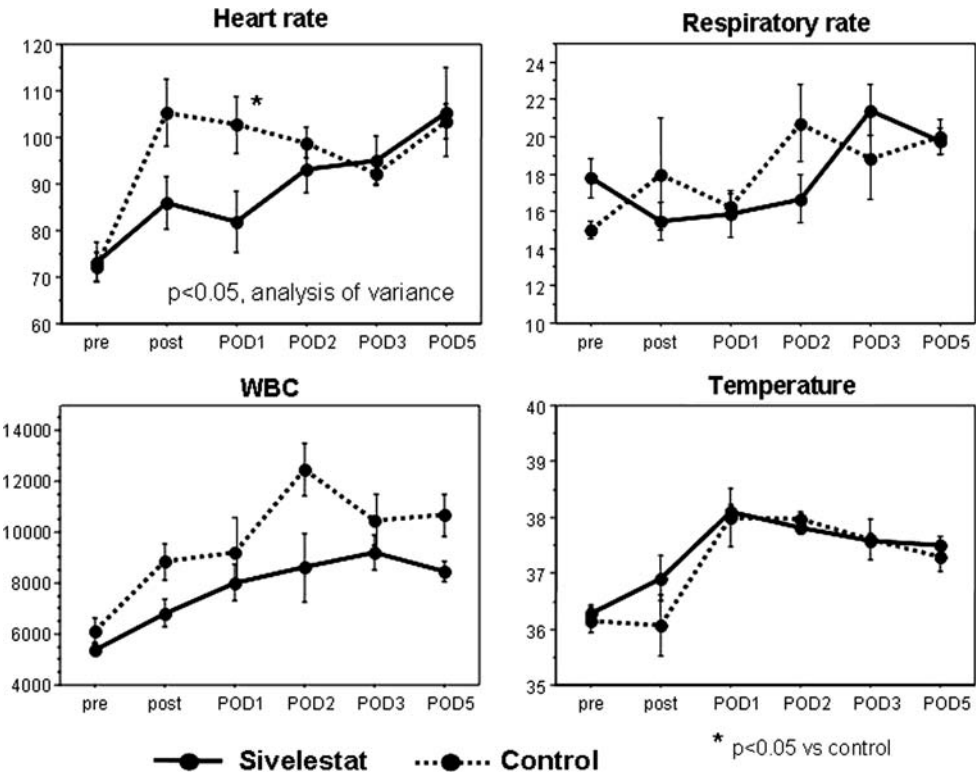

Fig. 1 Comparison of the systemic inflammatory response syndrome (SIRS) criteria for the two groups during the postoperative course. The postoperative increases in the heart rate were significantly suppressed in the Sivelestat-treated group ($p < 0.05$, analysis of variance)

ment for hypoxemia using mechanical ventilation. However, mechanical ventilation cannot alleviate the pathogenesis of ALI. Ventilator management and nutritional support were not changed before and after 2002 during this period. A ventilator management scheme with low tidal volume was introduced after this study in our institution. We demonstrated that the postoperative hypooxygenation significantly improved in the sivelestat-treated group in this study. Our findings suggest that the selective neutrophil elastase inhibitor may therefore be a potentially useful drug for treating the cause of the ALI. In other words, the neutrophil elastase inhibitor reduced pulmonary inflammation and improved pulmonary function. In turn, the improved pulmonary function can make possible early weaning from mechanical ventilation and early discharge from the ICU. In fact, this study demonstrated that the duration of the ventilation time and the stay in the ICU tended to decrease in the sivelestat-treated group in comparison to the control group.

Although our study was limited because of the small number of patients evaluated, we did not observe any difference in postoperative complications between the two groups in this study. However, our data revealed that 9 of 10 control group patients developed SIRS on POD2, whereas only 2 of the 7 Sivelestat group patients developed

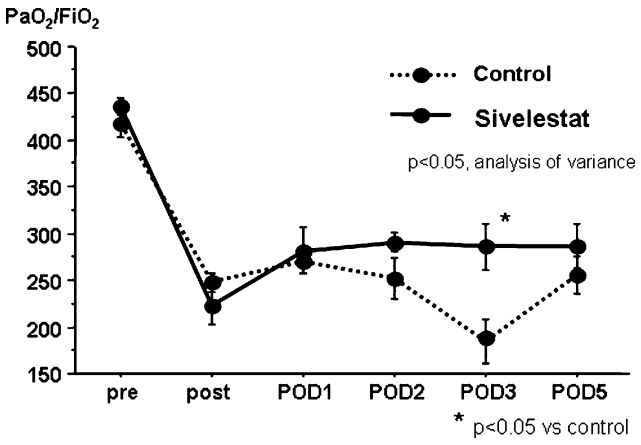

Fig. 2 Comparison of the degree of hypoxia with PaO_2/FiO_2 between the two groups during the postoperative course. The postoperative decreases in the PaO_2/FiO_2 were significantly suppressed in the Sivelestat-treated group ($p < 0.05$, analysis of variance)

Table 2 Development of SIRS during the postoperative course in the Sivelestat-treated and control groups

Group	Post	POD1	POD2	POD3	POD5
Sivelestat (%)	28.5	14.3	28.5*	28.5	28.5
Control (%)	40.0	50.0	90.0	70.0	60.0

Post, immediately after operation; POD1, postoperative day 1; POD2, postoperative day 2; POD3, postoperative day 3; POD5, postoperative day 5

*$p < 0.05$ vs. control. Fisher's exact probability tests were used to compare between-group differences

Table 3 Platelet counts during the postperative course for the Sivelestat-treated and control groups

Group	Pre	Post	POD1	POD2	POD3	POD5
Sivelestat (/mm^3)	24.7 ± 3.2	17.1 ± 2.9	18.7 ± 2.7	17.0 ± 2.2	19.1 ± 2.6	28.4 ± 4.5*
Control	21.0 ± 2.7	16.7 ± 1.9	16.4 ± 1.9	13.2 ± 1.7	12.8 ± 1.9	18.2 ± 1.8

Pre, preoperation

*$p < 0.05$ vs. control. Student's *t*-tests were used to compare between-group differences

Table 4 Clinical data and complications during the postoperative course for the Sivelestat-treated and control groups

Parameter	Sivelestat ($n = 7$)	Control ($n = 10$)	*p*
Duration of mechanical ventilation (hours)	17.4 ± 8.7	58.0 ± 17.0	0.07
Length of ICU stay (hours)	50.0 ± 17.0	75.3 ± 46.2	0.09
Postoperative complications			
Pneumonia	0/7	4/10	NS
Anastomotic leakage	3/7	2/10	NS

ICU: intensive care unit

SIRS. Neutrophil elastase may thus contribute to both the postoperative development of SIRS and to an increased susceptibility to postoperative organ dysfunction. SIRS is thought to be induced by proinflammatory mediators; and the longer the duration of SIRS, the more likely it is that it will progress to multiple organ dysfunction syndrome (MODS) [11, 12]. This difference in the development of SIRS according to sivelestat treatment after surgery might therefore contribute to differences in the cytokine production from peripheral blood mononuclear cells. We recently reported that sivelestat pretreatment significantly decreased lipopolysaccharide (LPS)-induced macrophage inflammatory protein-2 production in macrophage cell lines [13]. These findings suggest that inhibition of neutrophil elastase may thus make it possible to prevent organ injury not only by directly inhibiting the activity but also by suppressing further induction of chemokines induced by LPS.

Our data also revealed that the decrease in the platelet counts in the sivelestat group was suppressed significantly more than that in the control group. The decrease in platelet counts after surgical stress may contribute to the activation of neutrophils and endothelial cells (ECs). An EC injury model by activated neutrophils has been demonstared in SIRS, ARDS, and MODS. Kotake et al. reported that sivelestat is able to suppress neutrophil priming induced in an ischemia-reperfusion injury model [14]. Nakatani et al. reported that sivelestat inhibited neutrophil-mediated EC injury in vitro by suppressing the activation of either the extracellular elastase secreted by the neutrophils or the intracellular elastase in them [15].

Conclusions

The clinical study results showed that a selective neutrophil elastase inhibitor, sivelestat, was effective in the treatment of patients with hypoxia following esophagectomy, suggesting that this inhibitor may be a potentially useful drug for the treatment of ALI. However, a prospective, randomized, controlled trial is necessary to truly answer the question as to whether this drug can be of benefit to patients with ALI following esophagectomy.

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