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Title page

Title

Sivelestat (selective neutrophil elastase inhibitor) improves the mortality rate of sepsis associated with both ARDS and DIC patients

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Running head

Sivelestat improves the outcome of severe sepsis

Abstract

Introduction: Neutrophil elastase plays an important role in the development of acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) in sepsis. Sivelestat is a selective neutrophil elastase inhibitor. It is possible that sivelestat improves the outcome of septic patients associated with ARDS and DIC.

Methods: A retrospective data analysis of septic patients associated with ARDS and DIC was conducted to investigate the effects of sivelestat. Observational period was 5days after admission to ICU.

Results: The study included 167 septic patients associated with ARDS and DIC. Control group included 133 patients without sivelestat and sivelestat group included 34 patients started to be administered sivelestat on the admission to ICU. The lung injury scores and Pa_{O_2}/Fi_{O_2} ratio of the sivelestat group were significantly more severe than those of the control group from day 1 to day 4. On day 5, the lung injury score and Pa_{O_2}/Fi_{O_2} ratio of the sivelestat group improved to the same levels of those of the control group. The DIC score of sivelestat group improved on day 3 in comparison to day 1, those of control group remained unchanged until day 4. The length of ICU stay of the sivelestat group was significantly shorter than that of the control group. A stepwise multiple logistic-regression analysis showed the sivelestat administration to be an

independent predictor of survival of the septic patients associated with both ARDS and DIC.

Conclusions: The length of ICU stay of the sivelestat group was significantly shorter than that of the control group. In addition, sivelestat administration was found to be an independent predictor of survival of those patients.

KEY WORDS — Acute lung injury, Critically ill patients, Protease, Leukocyte, Endothelial cell.

INTRODUCTION

Sepsis is an important cause of morbidity and mortality (1). The rate of complications of acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) gradually increases in proportion to the progression of the severity of sepsis (1). Systemic inflammation induces vascular endothelial injury and results in organ dysfunction in severe sepsis (2-4). Leucocytes-endothelial cell interaction resulting from systemic inflammation plays an important role in the pathogenesis of vascular endothelial injury, (2-4). Neutrophil elastase (NE), which is located downstream in the humoral mediator network, is one of the final humoral mediators contributing to development of vascular endothelial injury (2-4). Neutrophil elastase and other mediators synergistically injure vascular endothelial cells, leading to increased permeability, vasodilation, and activation of coagulation cascade (2).

ARDS is defined as a syndrome of inflammation and increased permeability by the American-European Consensus Conference on ARDS (5). Commonly, ARDS is complicated with sepsis, severe sepsis, and septic shock (1). Neutrophils and NE are believed to play an important role in the endothelial injury and increased permeability of the pathogenesis of ARDS (6,7). In addition, neutrophils and NE also play an important role in the pathogenesis of DIC (8). Systemic inflammation, characterized by excessive elevation of proinflammatory

cytokines, activates neutrophils and induces excessive release of NE (2-4). The excessive NE and other proinflammatory mediators synergistically injure the endothelial cells (2-4). Tissue factor is expressed on the injured endothelial cells and activated mononuclear cells (8-11). The expressed tissue factor triggers the procoagulant cascade, induces derangement of coagulation and fibrinolysis, and results in DIC (8-11). We have also demonstrated that NE plays important roles in the pathogenesis of both ARDS and DIC in our previous studies (12-15).

Sivelestat (ONO PHARMACEUTICAL CO., LTD, Osaka, Japan) is a selective neutrophil elastase inhibitor, which has a small molecular weight (434 Da) (16). Two previous large clinical investigations showed discordant effects of sivelestat in patients with acute lung injury (ALI) (17,18). However, both of the two previous studies included heterogeneous groups of the patients with ALI induced by diseases other than sepsis (17,18). The discordant results of the previous studies might be resulted from the difference in the characteristics of patients between the two studies (17-19).

Previous studies suggest that sivelestat will have a beneficial effect on septic patients with both ARDS and DIC, associated with endothelial injury induced by excessive NE. The present study evaluated the effects of sivelestat on organ functions as well as mortality in patients with both ARDS and DIC associated with severe sepsis.

MATERIALS AND METHODS

Patient Selection and Data Collection

From January 2000 to December 2007, all patients with sepsis who were admitted to the intensive care unit (ICU) and were also complicated with both ARDS and DIC were selected as participants for this study. Patients with severe liver cirrhosis, previous liver transplantation, and chronic obstructive pulmonary disease were excluded. Patients with known clotting disorders or who were receiving anticoagulant therapy were also excluded. Patients with and without sivelestat administration were defined as the sivelestat group and the control group, respectively. The observational period was 5 days after admission to the ICU. The clinical backgrounds of the patients and the measured variables were retrospectively collected from computer-based patient records. The usual laboratory data and some variables were prospectively clinically measured based on the daily routine ICU protocols.

Definitions

Sepsis (included severe sepsis and septic shock in the present study) and systemic inflammatory response syndrome (SIRS) were defined according to the definition of the American College of Chest Physicians/Society of Critical

Care Medicine consensus conference (20). ARDS was defined based on the American-European Consensus Conference on ARDS (5). The scoring system for Japanese Association for Acute Medicine DIC was used for diagnosis of DIC. The DIC diagnostic algorithm for scoring DIC includes following variables; platelet counts, prothrombin time, fibrin/fibrinogen degradation products level, and SIRS criteria. The details of the algorithm have previously been presented elsewhere (21). The severity of illness of the patients was evaluated according the Acute Physiology and Chronic Health Evaluation (APACHE) II score (22). Organ failure was assessed by the Sequential Organ Failure Assessment (SOFA) score (23). Lung injury was assessed by the scoring system proposed by Murray *et al.* (24).

Intervention and Treatment

All patients received mechanical ventilation in pressure-controlled and pressure-support ventilation mode with a positive end-expiratory pressure. Ventilator management was performed based on a lung protective strategy as designed by the ARDS network (25). Antibiotics were selected by each ICU physician and thus were appropriately administered. Parental nutritional support was started immediately after admission to the ICU, and thereafter it was gradually converted to enteral nutrition within the first several days. No patient

received any Immune-enhancing nutrition. A high and low dose of steroid was not administered for ARDS. However, a low dose of steroids was administered for the treatment of septic shock. Sivelestat was intravenously administered to patients at a rate of 0.2 mg/kg/hr on the day of the admission to ICU. The sivelestat administration was continued until discharge from the ICU or for 14 days.

DIC treatment required anticoagulant therapy with intravenous infusion of gabexate mesilate (ONO PHARMACEUTICAL CO., LTD, Osaka, Japan) at a rate of 39mg/kg/day to all patients from the two groups. All patients were automatically administered ~700-2,000 IU heparin/day for anticoagulation of the arterial, central venous, or pulmonary arterial catheters. For the prevention of deep venous thrombosis, an intermittent pneumatic compression was used and no patients received prophylactic heparin administration. Heparin was not administered for the treatment of DIC. A red blood cell concentrate, fresh frozen plasma, and a platelet concentrate were all administered, respectively, when the hemoglobin level was < 70 g/L, the prothrombin time was >20 sec, and the platelet counts were < $30 \times 10^9/L$.

Statistical Analysis

Unless otherwise indicated, all measurements are expressed as the

mean \pm SD. The SPSS 15.0J statistical software package (SPSS Inc., Chicago, Illinois) was used for all statistical calculation analysis. Comparisons between the groups were made using Student's *t*-test, the Mann-Whitney U test, and the chi square test. Bonferoni correction was used if needed. A stepwise multiple logistic-regression analysis was used to assess the relationship between the survival exit rate from ICU and variables as follows; age, gender, lung injury score, DIC score, SIRS score, SOFA score, and sivelestat administration. A value of $P < 0.05$ was considered to be statistically significant.

RESULTS

The present study included 167 septic patients complicated with both ARDS and DIC. All patients met the SIRS criteria (SIRS score ≥ 2). The control group included 133 patients without sivelestat administration and the Sivelestat group included 34 patients with sivelestat administration. The characteristics of the patients on day 1 are presented in Table 1. The APACHE II, SIRS, DIC, SOFA scores, and the infection sites were also comparable between the two groups on day 1. However, the lung injury score and Pa_{O_2}/Fi_{O_2} (P/F) ratio of the sivelestat group were worse than those of the control group.

The lung injury scores and P/F ratio of the sivelestat group were

significantly more severe than those of the control group from day 1 to day 4 (Figures 1 and 2). On day 5, the lung injury score and P/F ratio of the sivelestat group improved to the same levels of those of the control group (Figures 1 and 2). Over 5 days, the DIC scores were not different between the two groups (Fig. 3). While the DIC score of sivelestat group improved on day 3 in comparison to day 1, those of control group remained unchanged until day 4 (Fig. 3). The mortality rates in the ICU were not different between the two groups, however, the length of ICU stay of the sivelestat group was significantly shorter than that of the control group (Table 2). A stepwise multiple logistic-regression analysis showed the sivelestat administration to be an independent predictor of survival of the septic patients associated with both ARDS and DIC (Fig. 4).

DISCUSSION

The present study retrospectively demonstrated that sivelestat administration improved the prognosis of patients with both ARDS and DIC associated with severe sepsis. Although the P/F ratio and the lung injury score of the sivelestat group were more severe than those of the control group on day 1, sivelestat improved the lung injury score and P/F ratio to the level of the control group by day 5. Furthermore, the DIC score of the sivelestat group was improved more promptly than that of the control group. In the sivelestat group,

the length of the ICU stay was significantly shorter than that of the control group. No difference in the survival rate was observed between the groups, however, a multiple logistic-regression analysis showed the possibility that the administration of sivelestat may be an independent predictor of the survival in these patients.

ARDS is a syndrome of inflammation and increased permeability of the lung and is commonly associated with severe sepsis (1,5). Neutrophil and NE play an important role in the endothelial injury and increased permeability of the pathogenesis of ARDS (6,7). In addition to inflammation, several studies have proposed that coagulation abnormalities are involved in the pathogenesis of ARDS (7,26,27). Thrombin-induced intravascular coagulation enhances inflammatory responses by increasing vascular permeability, activating endothelial cells to produce proinflammatory cytokines and other mediators, inducing the accumulation of neutrophils (26,27). Intravascular and intraalveolar fibrin deposition is frequently observed in ARDS (26,27). These findings suggest a critical link between coagulation and inflammation in ARDS (26,27).

DIC is characterized by the widespread activated coagulation and suppression of fibrinolysis, thus resulting in intravascular fibrin formation and thrombotic occlusion of microvessels (8-11). The thrombotic occlusion of microvessels compromises the blood supply to various organs and contributes

to multiple organ dysfunction, including ARDS (8-11). Although DIC is induced by various clinical insults, sepsis is the most important clinical condition that leads to DIC (1,8-11). Systemic inflammation, which is characterized by an excessive elevation of proinflammatory cytokines in severe sepsis, induces vascular endothelial injury (2-4). The expression of tissue factor on the injured endothelial cells induces the activation of coagulation and impairment of fibrinolysis, resulting in DIC (8-11). Leucocytes-endothelial cell interactions play an important role in the pathogenesis of the vascular endothelial injury (2-4,8). NE is one of the final humoral mediators contributing to development of vascular endothelial injury in the leukocyte-endothelial cell interactions (2-4). There is a close relationship between the excessive elevation of NE and the pathogenesis of ARDS and DIC (8,12-14). NE plays an important role in sepsis, especially severe sepsis complicated with ARDS and DIC. Consequently, in the present study, a selective neutrophil elastase inhibitor (sivelestat) improved the pulmonary function and coagulation derangement, and then reduced the mortality rate of the septic patients complicated with ARDS and DIC.

Two large clinical investigations previously demonstrated discordant effects of sivelestat in patients with ALI (17,18). The Japanese clinical study by Tamakuma *et al.* (18) included 230 ALI/ARDS patients associated with SIRS and sivelestat was continuously administered up to 14 days. The study demonstrated

that sivelestat administration shortened length of ICU stay of the patients (18). However, the overall mortality was not improved by the sivelestat administration (18). These results indicated that sivelestat might have beneficial effect on the pulmonary function of the ALI/ARDS patients associated with SIRS (18). In the Sivelestat Trial in ALI Patients requiring Mechanical Ventilation (STRIVE) (17), 492 patients with ALI/ARDS were included. In the STRIVE study, intravenous sivelestat had no effect on 28-day all cause mortality or ventilator-free days in the patients with ALI/ARDS (17). The STRIVE study indicated that sivelestat might have no beneficial effects on the pulmonary function of the patients with ALI/ARDS (17). In addition, sivelestat might aggravate the outcome of the patients with ALI/ARDS (17). The results of the two clinical studies were completely different. In the Japanese clinical study, 69% of the patients has sepsis as did 40% of the patients in the STRIVE study (17,18). The rates of the patients with sepsis between in the two studies were significantly different ($P = 0.009$). All of patients in the present study and the Japanese clinical study met the SIRS criteria (18). On the other hand, in the STRIVE study, 89% of the ALI/ARDS patients had SIRS (17). In other words, the STRIVE study included 21% ALI/ARDS patients without SIRS. Systemic inflammation may have already passed in these patients without SIRS. It is therefore important to emphasize that sivelestat should be administered to the ALI/ARDS patients with systemic

inflammation associated with severe sepsis. In fact, several studies have previously demonstrated the administration of sivelestat to have a beneficial effect on ALI/ARDS patients in the early stage of severe sepsis (19,28,29). To clarify the effects of sivelestat, a large prospective clinical trial which focuses on septic patients with ARDS may therefore be needed in the future.

Limitations; because the present study was a retrospective study that covered the period of the previous 7 years, the overall treatment for sepsis has gradually improved during this 7-year period. Furthermore, the opportunity to administer sivelestat has also gradually increased during this period because sivelestat is a drug that has only recently been approved in Japan. Therefore, the sivelestat group included more recent cases than the control group. The improvement of the outcome in the sivelestat group may therefore be related to the improvement in the overall treatment for sepsis.

In conclusion, the present study demonstrated that the sivelestat administration shortened the length of ICU stay of septic patients with both ARDS and DIC. In addition, the sivelestat administration was found to be an independent predictor of survival of those patients.

REFERENCES

1. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP:
The natural history of the systemic inflammatory response syndrome (SIRS).
A prospective study. *JAMA* 273: 117-123, 1995.
2. Russell JA: Management of sepsis. *N Engl J Med* 355: 1699-1713, 2006.
3. Ueno H, Hirasawa H, Oda S, Shiga H, Nakanishi K, Matsuda K:
Coagulation/fibrinolysis abnormality and vascular endothelial damage in the
pathogenesis of thrombocytopenic multiple organ failure. *Crit Care Med* 30:
2242-2248, 2002.
4. McGill SN, Ahmed NA, Christou NV: Endothelial cells: role in infection and
inflammation. *World J Surg* 22: 171-178, 1998.
5. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M,
Legall JR, Morris A, Spragg R: The American-European Consensus
Conference on ARDS. Definitions, mechanisms, relevant outcomes, and
clinical trial coordination. *Am J Respir Crit Care Med* 149: 818-824, 1994.
6. Abraham E: Neutrophils and acute lung injury. *Crit Care Med* 31:
S195-S199, 2003.
7. Moraes TJ, Chow CW, Downey GP: Proteases and lung injury. *Crit Care
Med* 31: S189-S194, 2003.

8. Slofstra SH, Spek CA, Ten Cate H: Disseminated intravascular coagulation. *Hematol J* 4: 295-302, 2003.
9. Levi M, Ten Cate H: Disseminated intravascular coagulation. *N Engl J Med* 341: 586-592, 1999.
10. Ten Cate H: Pathophysiology of disseminated intravascular coagulation in sepsis. *Crit Care Med* 28: S9-S11, 2000.
11. Levi M: Disseminated intravascular coagulation. *Crit Care Med* 35: 2191-2195, 2007.
12. Gando S, Kameue T, Matsuda N, Sawamura A, Hayakawa M, Kato H: Systemic inflammation and disseminated intravascular coagulation in early stage of ALI and ARDS: role of neutrophil and endothelial activation. *Inflammation* 28: 237-244, 2004.
13. Gando S, Kameue T, Morimoto Y, Matsuda N, Hayakawa M, Kemmotsu O: Tissue factor production not balanced by tissue factor pathway inhibitor in sepsis promotes poor prognosis. *Crit Care Med* 30: 1729-1734, 2002.
14. Gando S, Kameue T, Matsuda N, Hayakawa M, Hoshino H, Kato H: Serial changes in neutrophil-endothelial activation markers during the course of sepsis associated with disseminated intravascular coagulation. *Thromb Res* 116: 91-100, 2005.
15. Gando S, Hayakawa M, Sawamura A, Hoshino H, Oshiro A, Kubota N,

- Jesmin S: The activation of neutrophil elastase-mediated fibrinolysis is not sufficient to overcome the fibrinolytic shutdown of disseminated intravascular coagulation associated with systemic inflammation. *Thromb Res* 121: 67-73, 2007.
16. Kawabata K, Suzuki M, Sugitani M, Imaki K, Toda M, Miyamoto T: ONO-5046, a novel inhibitor of human neutrophil elastase. *Biochem Biophys Res Commun* 177: 814-820, 1991.
17. Zeiher BG, Artigas A, Vincent JL, Dmitrienko A, Jackson K, Thompson BT, Bernard G: Neutrophil elastase inhibition in acute lung injury: results of the STRIVE study. *Crit Care Med* 32: 1695-1702, 2004.
18. Tamakuma S, Ogawa M, Aikawa N, Kubota T, Hirasawa H, Ishizaka A, Taenaka N, Hamada C, Matsuoka S, Abiru T: Relationship between neutrophil elastase and acute lung injury in humans. *Pulm Pharmacol Ther* 17: 271-279, 2004.
19. Okayama N, Kakihana Y, Setoguchi D, Imabayashi T, Omae T, Matsunaga A, Kanmura Y: Clinical effects of a neutrophil elastase inhibitor, sivelestat, in patients with acute respiratory distress syndrome. *J Anesth* 20: 6-10, 2006.
20. The ACCP/SCCM Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of

- innovative therapies in sepsis. *Crit Care Med* 20: 864-874, 1992.
21. Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K, Koseki K, Mayumi T, Murata A, Ikeda T, Ishikura H, Ueyama M, Ogura H, Kushimoto S, Saitoh D, Endo S, Shimazaki S: A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med* 34: 625-631, 2006.
22. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. *Crit Care Med* 13: 818-829, 1985.
23. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S: Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 26: 1793-800, 1998.
24. Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 138: 720-723, 1988.
25. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342: 1301-1308, 2000.

26. Idell S: Coagulation, fibrinolysis, and fibrin deposition in acute lung injury.
Crit Care Med 31: S213-S220, 2003.
27. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS: Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia - a review. *Crit Care Med* 34: 871-877, 2006.
28. Kadoi Y, Hinohara H, Kunimoto F, Saito S, Goto F, Kosaka T, Ieta K: Pilot study of the effects of ONO-5046 in patients with acute respiratory distress syndrome. *Anesth Analg* 99: 872-877, 2004.
29. Endo S, Sato N, Yaegashi Y, Suzuki Y, Kojika M, Yamada Y, Yoshida Y, Nakadate T, Aoki H, Inoue Y: Sivelestat sodium hydrate improves septic acute lung injury by reducing alveolar dysfunction. *Res Commun Mol Pathol Pharmacol* 119: 53-65, 2006.

FIGURE LEGENDS

FIG. 1. **Lung injury scores for the first 5 days after admission to the**

ICU.

Closed circles, sivelestat group; open circles, control group;

⁺*P*<0.05 vs. Day 1 in each group; **P*<0.05 between the two groups.

FIG. 2. **Pa₀₂/Fi₀₂ ratio for the first 5 days after admission to the ICU.**

Closed circles, sivelestat group; open circles, control group;

⁺*P*<0.05 vs. Day 1 in each group; **P*<0.05 between the two groups.

FIG. 3. **Disseminated intravascular coagulation scores for the first**

5 days after admission to the ICU.

Closed circles, sivelestat group; open circles, control group;

⁺*P*<0.05 vs. Day 1 in each group.

FIG. 4. **The odds ratios and 95% confidence intervals (CI) for**

**survival in the ICU based on a stepwise multiple
logistic-regression analysis.**

TABLE 1. **Characteristics of the patients on day 1**

	Control group (n=133)	Sivelestat group (n=34)	<i>P</i> value
Age (year)	54.1 ± 21.2	59.4 ± 20.3	NS
Sex (male / female)	75 / 58	24 / 10	NS
APACHE II score	20.5 ± 12.4	23.2 ± 13.4	NS
SIRS score	3.2 ± 0.7	3.4 ± 0.7	NS
Lung injury score	2.0 ± 0.6	2.9 ± 0.7	< 0.001
P/F ratio	128.9 ± 42.7	89.8 ± 44.1	< 0.001
DIC score	5.5 ± 1.3	5.9 ± 1.4	NS
SOFA score	13 ± 3	14 ± 3	NS
Infection site (%)			
chest	41	56	
abdomen	46	42	NS
blood stream	14	18	

APACHE, Acute Physiology and Chronic Health Evaluation; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; P/F ratio, Pa_{O2}/Fi_{O2} ratio; SOFA, sequential organ failure assessment.

TABLE 2. Outcomes of the patients

	Control group	Sivelestat group	<i>P</i> value
Length of ICU stay (day)	15.0 ± 16.4	5.0 ± 3.6	0.001
Length of ICU stay of the survivors (day)	15.2 ± 17.4	5.2 ± 3.8	0.004
Mortality rate in ICU (%)	23.3	20.6	NS

ICU, intensive care unit.

FIG. 1

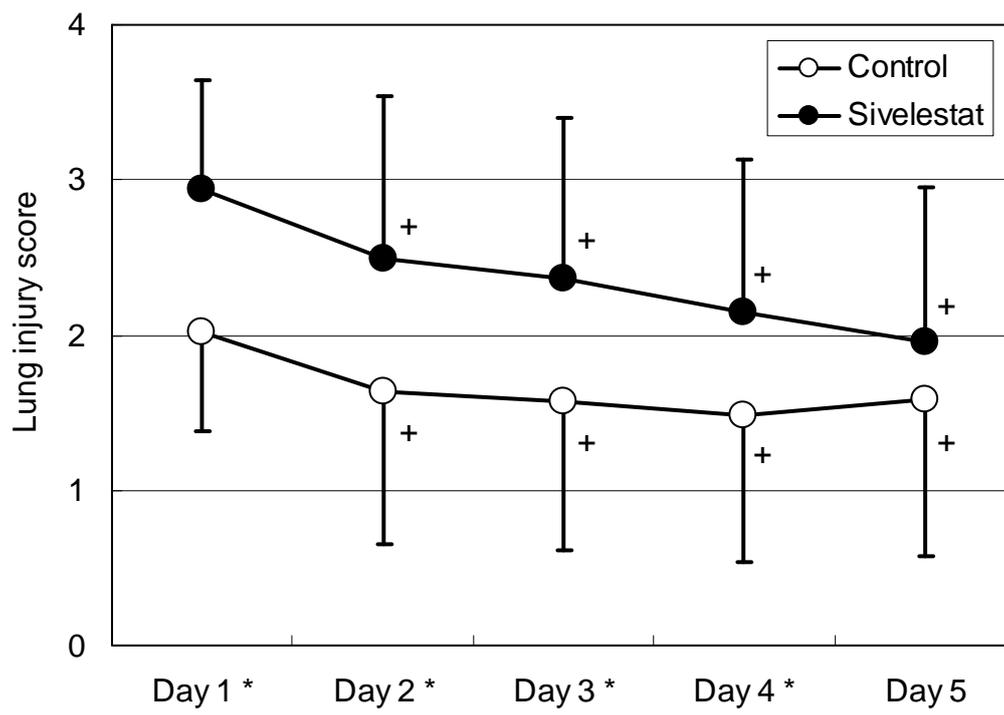


FIG. 2

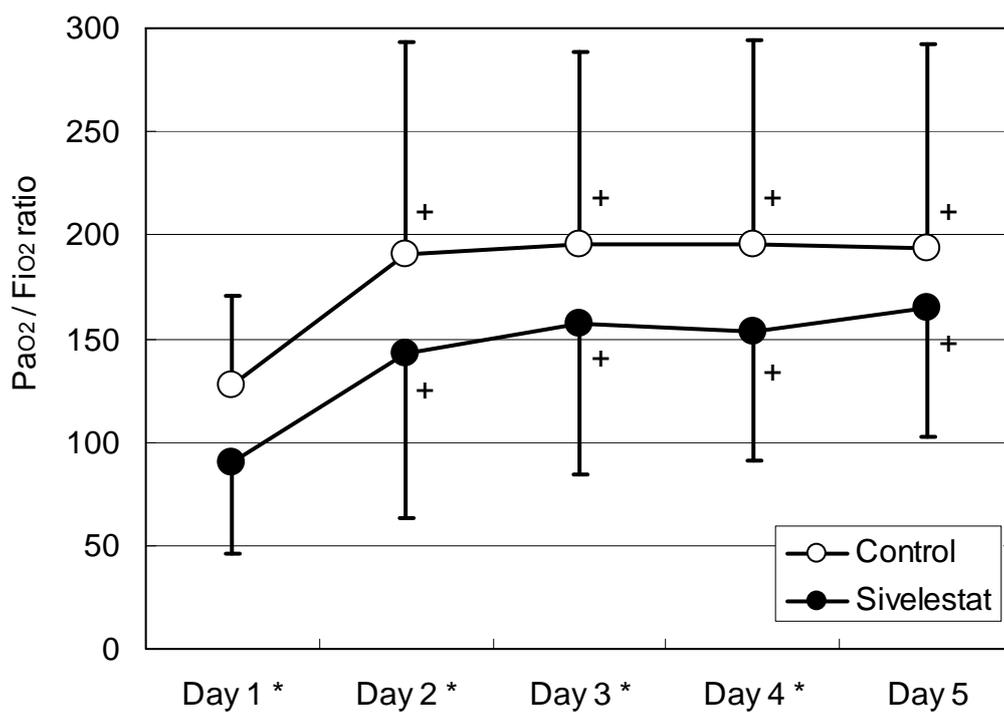


FIG. 3

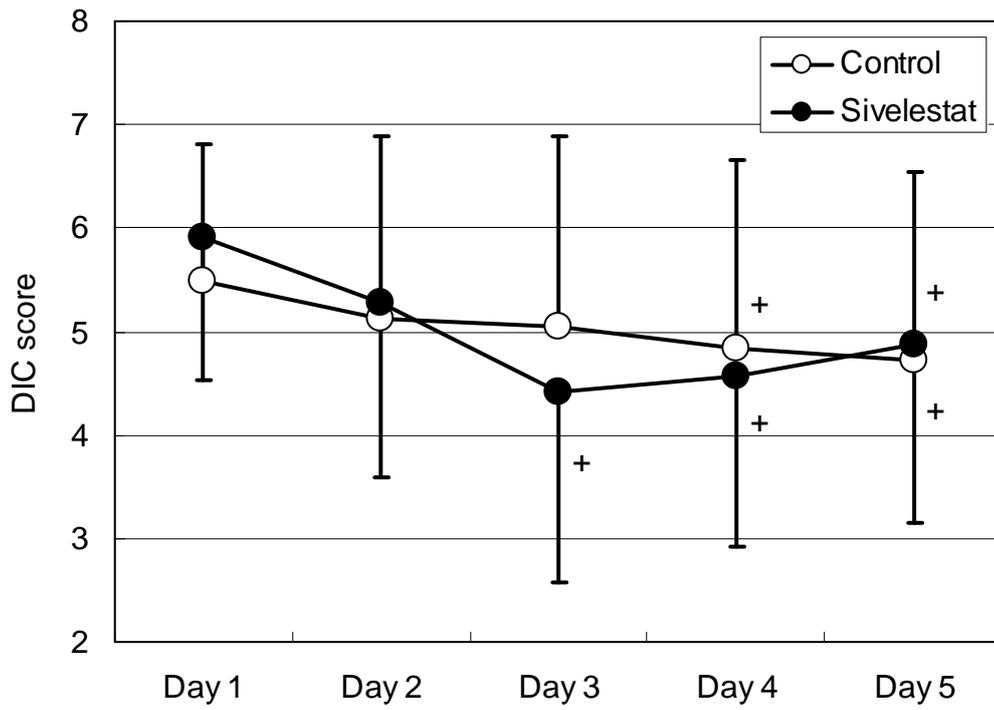


FIG. 4

