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Study on the Efficacy of Sivelestat on Thrombocytopenia in Cases of Severe Pneumonia

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Abstract

When systemic inflammatory response syndrome (SIRS) takes a protracted course, disseminated intravascular coagulation (DIC) may be induced. Therefore, the efficacy of sivelestat on the reduction of platelet counts as an indicator for DIC in cases of acute lung injury (ALI) associated with SIRS triggered by severe pneumonia was investigated in a retrospective comparative study. Eight patients were treated with sivelestat (0.2 mg/kg/hr) for acute lung injury (ALI/ARDS) associated with SIRS brought on by severe pneumonia (group S, treated with sivelestat), while 6 with similar backgrounds (group C, the untreated group) served as the control. The following clinical parameters of the two groups were compared: 1) platelet counts; 2) P/F (PaO_2/FiO_2) ratio; 3) CRP; and 4) ventilator-free days (VFD). In comparison with group C, the thrombocytopenic tendency of group S appeared to improve on day 5 following the start of ventilator use ($p=0.098$). In comparison with group C, the P/F ratio of group S appeared to improve after 3 days of ventilator use ($P=0.051$). CRP of group S was significantly lower than that of group C after 5 days of ventilator use ($p=0.044$). The mean VFD was 15.8 ± 0.6 for group S and 11.5 ± 2.8 for group C. These results indicated that sivelestat is capable of preventing DIC followed SIRS.

Key Words

sivelestat, thrombocytopenia, systemic inflammatory response syndrome, acute lung injury, severe pneumonia

Introduction

Systemic inflammatory response syndrome (SIRS) is defined as a state in which the systemic inflammatory response is exaggerated due to invasive events such as infection, trauma, thermal burn, and pancreatitis and it may be diagnosed by the presence of three vital signs—body temperature, pulse, and respiratory frequency—and the leukocyte count obtained in clinical tests.[1)] The essential characteristic of SIRS, however, is hypercytokinemia, in which a high blood level of inflammatory cytokines is seen: and increases in the inflammatory cytokine levels (e.g., those of IL-6 and TNF-α) are involved in the changes in the 3 vital signs cited above and in the leukocyte count.[2–3)] It is believed that the severe form of this disease generally meets the criteria of SIRS.

Acute lung injury (ALI), on the other hand, is pulmonary edema with exaggerated permeability of the pulmonary vessels that is caused by inflammation: it represents a syndrome that is characterized by extreme hypoxemia. For its diagnostic criteria, it is defined to meet all 4 of the following conditions—acute onset, P/F ratio (hypoxemic $P/F<300$ mmHg), bilateral moist appearance on thoracic ra-

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diography, and exclusion of cardiogenic etiology.[4]

When the clinical course of SIRS is protracted, vascular endothelial cells may be disturbed due to inflammation, triggering disseminated intravascular coagulation (DIC).[5] It is known that the process results in systemic microvascular dysfunction, followed by dysfunctions of major organs such as the liver and kidneys. Inflammatory cytokines such as TNF-α are also significantly involved in the process.[6]

In the current study, a neutrophil elastase inhibitor (sivelestat sodium hydrate) was administered to patients with ALI associated with SIRS that had been triggered by severe pneumonia and the platelet counts were examined as an indicator for DIC to evaluate the efficacy of the agent on reduction of platelet counts in comparison with the control.

Materials and methods

The subjects consisted of the 14 patients who suffered ALI associated with SIRS triggered by severe pneumonia between June 2001 and May 2003. They were retrospectively stratified into either the group not treated by sivelestat (group C, untreated group, n=6) or the group treated with the drug (group S, treated with sivelestat, n=8). The characteristics of the individuals in both groups are listed in **Table 1**. The concomitant drugs are shown in **Table 2**. For group S, 0.2 mg/kg/hr of sivelestat was continuously infused via intravenous route immediately after the start of ventilator use to improve oxygenation capability.

For the indicator of DIC that follows SIRS, a platelet count was recorded immediately after the start of the ventilator and 3 and 5 days thereafter. For indicators to assess any amelioration in the acute pulmonary dysfunction, the following were observed: 1) P/F ratio, 2) CRP, and 3) VFD.

Table 1. Background

	Sivlestat n=8	Control n=6	p value
Age	75±3. 8	74±6. 6	N.S
Male/female	6:2	5:1	N.S
P/F ratio	122±18	132±20	N.S
CRP (mg/dl)	25±4	21±3. 5	N.S
Plt. ($\times 10^4/\mu l$)	23±3	21±1	N.S

t test mean±SD

Results

There were no significant differences between the 2 groups in age and gender, P/F ratio immediately after beginning of the use of ventilators, CRP, and the backgrounds of the patients at the start of platelet counts (**Table 1**).

1) Changes in platelet count

Compared with data recorded immediately after ventilator use, significant reductions in the platelet count were noted for all 14 patients 3 days later (p=0.0002) (**Fig. 1**). Compared with group C, group S showed a tendency for improvement in the reductions in platelet counts 5 days after the ventilator use started (p=0.098) (**Fig. 2**).

Table 2. Concomitant Drugs

Siveleatat	1	imipenem/cilaatatin sodium(IPM/CS)	mimocycline hydrochloride(MINO)	
	2	sultamicillin tosilate hydrate(SBTPC)	imipenem/cilastatin sodium(IPM/CS)	
	3	cefogopram hydrochloride(CZOP)	panipenem/betamipron(PAPM/BP)	clindamycin(CLDM)
		ciprofloxacim hydrochloride(CPFX)	micafungin sodium(MCFG)	teicoplanin(TEICO)
		methylpredmisolone sodium succinate		
	4	methylpredmisolone sodium succinate	imipenem/cilastatin sodium(IPM/CS)	mimocycline hydrochloride(MINO)
		Kenketsu Venilon-I		
	5	panipenem/betamipron(PAPM/BP)	mimocycline hydrochloride(MINO)	
	6	imipenem/cilastatin sodium(IPM/CS)	mimocycline hydrochloride(MINO)	
	7	cefogopram hydrochloride(CZOP)	mimocycline hydrochloride(MINO)	methylpredmisolone sodium succinate
	8	imipenem/cilastatin sodium(IPM/CS)	mimocycline hydrochloride(MINO)	
Control	1	imipenem/cilastatin sodium(IPM/CS)	gadexate mesilate	
	2	imipenem/cilastatin sodium(IPM/CS)	vancomycin hydrochloride(VCM)	
	3	panipenem/betamipron(PAPM/BP)	ulinastatin	hydrocortisome sodium succinate
	4	meropenem hydrate(MEPM)	clindamycin(CLDM)	methylpredmisolone sodium succinate
	5	cefogopram hydrochloride(CZOP)		
	6	meropenem hydrate(MEPM)	mimocycline hydrochloride(MINO)	

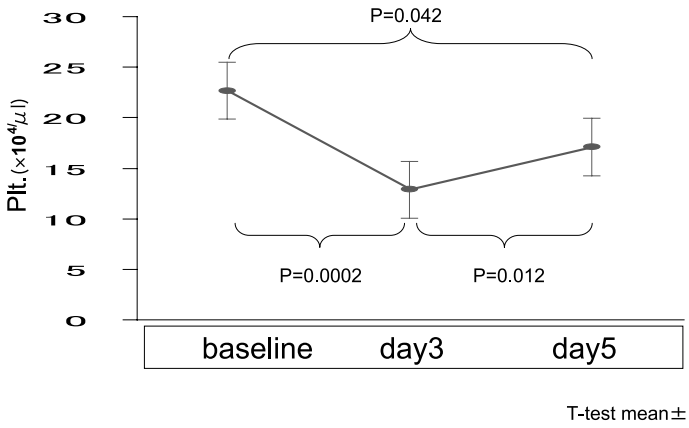

Fig. 1. Compared with the control, the sivelestat-treated group showed a trend towards improvement in the P/F ratio 3 days after ventilator use was started (P=0.051).

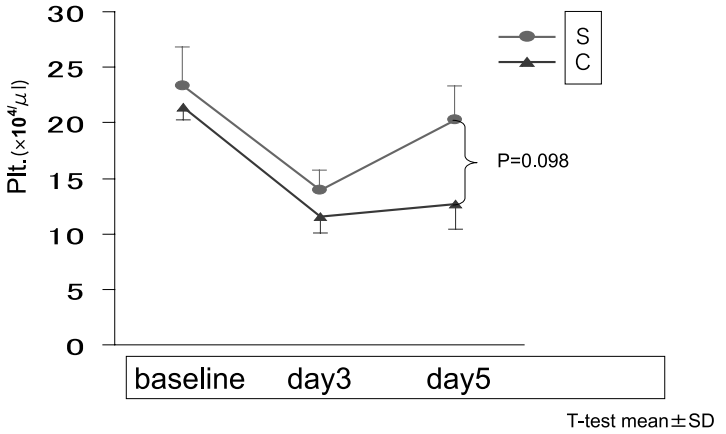

Fig. 2. CRP improved significantly 5 days after the start of ventilator use in group S in comparison with group C (P=0.044).

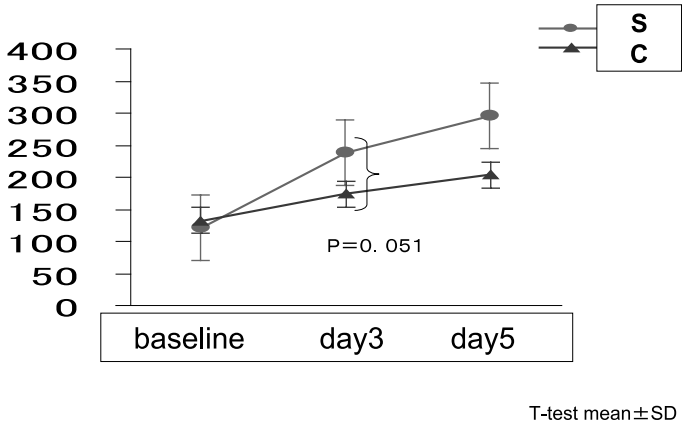

Fig. 3. The mean VFD was 11.5±2.8 for group C and 15.8±0.6 for group S. No significant difference was noted between these groups.

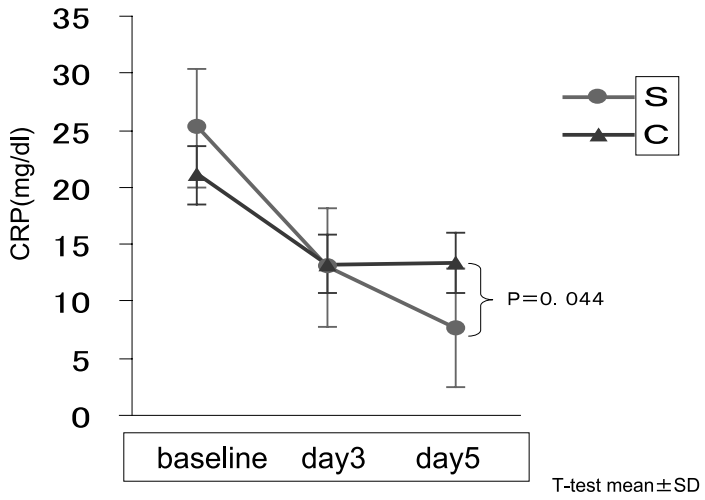

Fig. 4. Compared with the data recorded immediately after ventilator use, significant reductions in the platelet count were noted for all 14 patients 3 days later (P=0.0002).

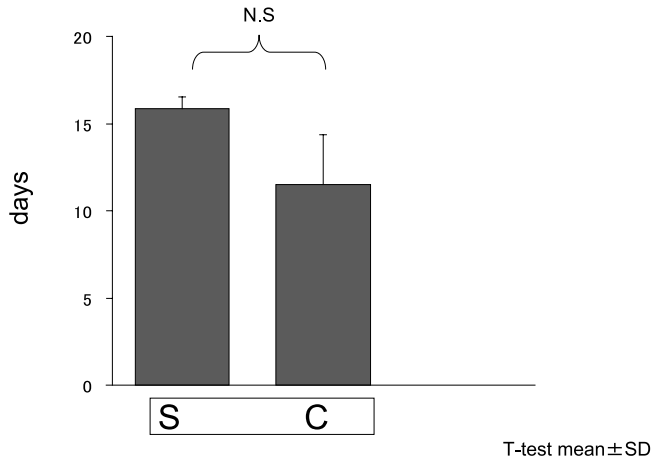

Fig. 5. Compared with group C, group S showed a tendency for improvement in the reductions in platelet counts 5 days after the ventilator use started (P=0.098).

2) P/F ratio

Compared with the control, the sivelestat-treated group showed a trend towards improvement in the P/F ratio 3 days after ventilator use was started (P=0.051) (**Fig. 3**).

3) CRP

CRP improved significantly 5 days after the start of ventilator use in group S in comparison with group C (p=0.044) (**Fig. 4**).

4) VFD

The mean VFD was 11.5±2.8 for group C and 15.8±0.6 for group S. No significant difference was noted between these groups (**Fig. 5**).

Discussion

The concept of SIRS was first proposed in 1991 at the joint conference by the American Thoracic Society and the Society of Critical Care Medicine: according to this definition, sepsis meets the conditions for SIRS where the existence of an infection is evident.[1] The diagnostic criteria for SIRS is that the condition satisfies two or more of the four diagnostic features—body temperature, pulse, respiratory frequency, and leukocyte count, which are often criticized as being loose. What is important here, however, is prolongation of the state of SIRS.

It has been reported that the protracted state of SIRS increases the incidence of multiple organ failure and provokes postoperative complications or infections.[6] The sustained course of SIRS leads to an increase in the levels of inflammatory cytokines, such as IL-6 and TNF-α, and results in the development of ALI/ARDS and eventually shock and DIC.[2] In other words, one can postulate that pneumonia, when it becomes severe, prolongs the state of SIRS, developing into ALI/ARDS and DIC.

With the advances in systemic inflammatory reactions, inflammatory cytokines form a network and neutrophils are activated.[2] The elastase that is released from the activated neutrophils exaggerates the damage to the vascular endothelial and alveolar epithelial cells, as well as vascular permeability of the lung, through the breakdown of protein of the pulmonary connective tissue: the process culminates in ALI/ARDS.[7] It has been known that there are both direct and indirect factors responsible for the development of ALI/ARDS. It is believed that this difference in the causative conditions poses a considerable problem in designing the therapeutic approach to ALI/ARDS. Specifically, ALI/ARDS is not a single disease: instead, it is a syndrome and different mediators exert their effects depending on the etiology. It has been reported that neutrophil elastase has a significant involvement in the development of ALI/ARDS associated with inflammation. The involvement of this elastase is readily conceivable in ALI/ARDS that has been triggered by severe pneumonia.[7, 8] When the clinical course of SIRS is protracted, vascular endothelial cells may be disturbed due to inflammation, triggering disseminated intravascular coagulation (DIC).[5] It is known that the process results in systemic microvascular dysfunction, followed by dysfunctions of major organs such as the liver and kidneys. Inflammatory cytokines such as TNF-α are also significantly involved in the process.[6]

Sivelestat was developed as an agent for selective suppression of this neutrophil elastase. Because of its small molecular weight, this agent is capable of inhibiting the elastase in an area where a1-protease inhibitor (α1PI), an endogenous elastase inhibitor, cannot reach.

With the background described above, the current retrospective comparative study was conducted on the efficacy of sivelestat on reduction of platelet counts in cases of ALI associated with SIRS triggered by severe pneumonia.

Fluctuations in platelet counts in all the cases observed in the present study were illustrated as follows: $22.6\times10^4/\mu$l when treatment was started, with a significant reduction to $12.8\times10^4/\mu$l on the 3 rd day. The finding suggests that SIRS triggered by severe pneumonia is also a factor responsible for the development of DIC. The platelet count of the group not treated with sivelestat (group C) was 21.3×10^4 at the start of the treatment and 12.7×10^4 five days later, while that of the group treated with sivelestat (group S) was 23.3×10^4 and 20.2×10^4 at the respective time point, showing a tendency for improvement.

One may expect that the early administration of sivelestat will be effective against coagulation disorders in cases of ALI with SIRS triggered by severe pneumonia.

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シベレスタットナトリウムの重症肺炎による血小板減少への有効性の検討

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抄　録

全身性炎症反応症候群（SIRS: systemic inflammatory response syndrome）が遷延すると，汎血管内凝固症候群（DIC: disseminated intravascular syndrome）が誘発されることがある。そこで，重症肺炎を契機としたSIRSに伴うALIで誘発されたDICの指標としての血小板減少へのシベレスタットナトリウムの有効性をレトロスペクティブに検討した。重症肺炎を契機とした SIRS に伴う急性肺障害（ALI/ARDS）をきたした8症例にシベレスタットナトリウム(0.2 mg/kg/hr)を投与し（S群: シベレスタットナトリウム投与群），同様の背景を持つ6例を対照群とし（C群: 非投与群），① 血小板数 ② P/F 比（PaO_2/FiO_2）③ CRP ④ VFD（ventilator free days）を検討した。S群はC群に比べ，人工呼吸器装着5日後の血小板減少の改善傾向がみられた（P＝0.098）。P/F比は，人工呼吸器装着3日後で，S群はC群に比べ改善傾向を認めた（P＝0.051）。CRP は人工呼吸器装着5日後で。S群は C 群に比べて有意に低下した（P＝0.044）。VFD の平均日数はS群15.8±0.6日。C群11.5±2.8日であった。これらの結果よりシベレスタットナトリウムはSIRSに続発するDICの発症を予防しうることが示唆された。

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