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ORIGINAL ARTICLE

EFFECT OF SIVELESTAT SODIUM HYDRATE (ELASPOL) FOR LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME AFTER CARDIOVASCULAR SURGERY

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Abstract Background: Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass were described as severe postoperative complication. Although the incidence of ARDS after cardiopulmonary bypass (CPB) is about 1%, the mortality of ARDS is extremely high. It has been well recognized that CPB is associated with systemic inflammation. This pulmonary dysfunction after CPB is one of those inflammatory responses, activated neutrophil and neurophil elastase play an important role in this injury. **Method:** ELASPOL (Sivelestat sodium hydrate; Ono Pharmaceutical Co., in Japan) is neutrophil elastase inhibitor that was introduced in 2002 for acute lung injury with SIRS. We hypothesized that this drug would reduce lung dysfunction after CPB especially in the patient who had total arch replacement or cardiac surgery with severe preoperative condition. We compared control group and group treated with ELASPOL® group retrospectively. The control group were cases of total arch replacement with severe lung dysfunction before 2002, therapeutic group were cases of total arch replacement with ELASPOL that included a case without operation. Arterial PO_2/FiO_2 as indication of lung injury (The P/F ratio is an index of acute lung injury and ARDS, it is defined as acute lung injury when the P/F ratio is under 300, and the P/F ratio of ARDS is under 200.), platelet count, WBC count, CRP, duration of intubation and ICU stay were evaluated. **Results:** As compared with the control group that had almost same operative procedure with ELASPOL, P/F ratio (arterial PO_2/FiO_2) was increased over 200 at four postoperative days and well maintained after all in therapeutic group. On the other hand it dropped to below 150, and it did not recovered to 200 until 10 days after the operation in the control group ($p<0.05$). Platelet count in ELASPOL group was relatively higher than control, but there is no significance of differences between groups. The other factors such as WBC count, CRP level, duration of intubation and ICU stay were almost equal. **Conclusions:** We conclude that ELASPOL is expected to reduce lung injury after CPB in the case of total arch replacement or cardiac surgery with severe preoperative condition.

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Key words: cardiopulmonary bypass; lung injury; neutrophil elastase; ELASPOL (Sivelestat sodium hydrate).

原 著

心大血管手術後肺障害に対するシベレスタットナトリウム（エラスポール）の効果

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抄録　背景：人工心肺を使用した開心術後の肺障害あるいはARDS（急性呼吸促迫症候群）は重篤な術後合併症であり，発生頻度は1％と低いもののARDSを発症した場合の死亡率は非常に高いことが知られている．このような症例の急性肺障害はSIRSに伴うものとされ，その病態に好中球の動態及び好中球エラスターゼが深く関与している．**対象と方法**：SIRSに伴う肺障害に対して2002年より好中球エラスターゼ阻害剤であるシベレスタットナトリウム（エラスポール）が導入された．我々は，人工心肺を使用した大動脈弓部置換術あるいは開心術で術後に生じる肺障害を軽減できるという仮説をたて，今回その効果について後方視的に検討した．エラスポールと投与したのは6例（1例解離性大動脈瘤の保存的治療例を含む），コントロールとして2002年以前の解離性大動脈瘤手術例のうち肺障害を認めた症例とした．肺障害の指標としてP/F比，術後挿管期間，ICU滞在期間，その他血小板白血球数，CRPの変化を比較した．**結果**：P/F比はエラスポール投与群で術後4日目より改善したのに対してコントロール群では術後2日目に悪化した後改善傾向を認めなかった（$p<0.05$）（P/F比，肺障害＜300，ARDS＜200）．血小板数はエラスポール群でコントロールに比べて高い数値を示したが統計学的には有意差を認めなかった．その他の指標（手術成績，術後挿管期間，ICU滞在期間，白血球）は両群間に有意差は認めなかった．**結語**：特に重症の心大血管手術例に対して術後肺障害を予防する上でエラスポールの有効性が示唆された．

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Introduction

Pulmonary dysfunction after cardiopulmonary bypass (CPB) was described 40 years ago[1]. In a patient with ruptured abdominal aortic aneurysm or dissected aortic aneurysm type B, the CPB is not required for surgical treatment. However, lung injury is one of the major complications in the treatment of those patients without CPB. The clinical significance of this CPB and dissected aortic aneurysm or ruptured abdominal aortic aneurysm-related pulmonary injury varies widely, ranging from a clinically undetectable condition to very severe pulmonary failure. These varieties of lung dysfunction probably depend on the level of hole body inflammatory responses, but these varieties of clinical course have not as yet well studied. This lack of outcome predictability in the CPB and other cardiovascular patients is probably because the exact mechanisms leading to acute lung injury and acute respiratory distress (ARDS) are not yet fully clarified on a molecular and cellular level[2].

Under the condition of Systemic inflammatory response syndrome (SIRS), neutrophil is activated and release various cytotoxic contents. One of these cytotoxic contents is elastase, which plays an important role in the lung injury.

Sivelestat sodium hydrate (ELASPOL®; Ono Pharmaceutical Co., Osaka, Japan) is a neutrophil elastase inhibitor that was introduced in 2002 for acute lung injury with SIRS. We have used this drug for lung injury after CPB especially in the patient who had total arch replacement or cardiac surgery with severe preoperative condition since April 2002. We reported our clinical experiences of Sivelestat sodium hydrate as compared to the cases of total arch replacement without Sivelestat sodium hydrate before 2002.

Methods

Six patients undergoing cardiovascular surgery from April, 2002 to September, 2004 were induced with Sivelestat sodium hydrate because of severe respiratory dysfunction after the operation (ELASPOL® group). Two had aortic operation for dissected aortic aneurysm type A, one had mitral and tricuspid valve surgery, two had abdominal aorta operation for ruptured abdominal aortic aneurysm, and one had conservative therapy to control hypertension for management of dissected aortic aneurysm type B. Nine patient undergoing total aortic arch replacement for dissected aortic aneurysm type A before 2002 (before introduction of ELASPOL®) were enrolled in this study as control group. These nine patients all had lung injury after the operation. During the same period 8 other patients had total arch replacement for dissected aortic aneurysm, but they were excluded from this study because they had no lung injury following the operation. The clinical and operative profiles of the patients are summarized in Table 1. Operation time was 9±6 hours in the ELASPOL® group and 11±6 hours in the control group, PaO_2 after the operation was 128±87 mmHg in ELASPOL® group and 184 ±76 in the control group. These two groups were considered similar for surgical damage to the lung, e.g., systemic inflammatory response, lung dysfunction. As there was no significant difference between groups, the randomization scheme could achieve uniformity between the two patient groups.

In the ELASPOL® group, infusion of ELASPORL® (0.2mg/kg/h) was started before the operation in one patient, on the first postoperative day in one patient, and on the second postoperative day in 3 patients. Infusion of drug was discontinued when the

P/F ratio (arterial PO_2/FiO_2) recovered over 200 and respiratory function became stable, duration of infusion were 2 to 12 days (7.8± 3.8 days). The P/F ratio is an index of acute lung injury and ARDS, it is defined as acute lung injury when the P/F ratio is under 300, and the P/F ratio of ARDS is under 200. A case of dissected aortic aneurysm type B was initially treated in another hospital with conservative therapy. Five days after onset of the disease, he transferred to our hospital because of respiratory dysfunction. After admission to our hospital, treatment with ELASPOL® was initiated immediately.

Arterial PO_2, platelet count, white blood cell count (WBC) and C reactive protein (CRP) were measured every morning from before operation to 10days after operation, then P/F ratio was calculated using arterial PO_2 and FiO_2. These data, the ICU stays and duration of intubation were compared between the ELASPOL® group and control group.

All values are reported as mean±STD. Two-way ANOVAs between the control group and ELASPOL® were used to analyze group and time effects and establish significant differences (Stat View 4.0 for Macintosh). The unpaired t statistic was used for comparing the ICU stay and duration of intubation between the groups. Differences were considered significant at a probability level of p less than 0.05.

Result

Hospital mortality occurred in two patients (one patient in each group). In the ELSPOL® group, one patient died as result of MRSA mediastinitis 30 days after surgery. Another patient in the control group died as a result of MRSA pneumonia 170 days after surgery. The patients had a tracheostomy at 13 days and 25 days respectively after operation because of respiratory dysfunction. One more patient in the control group required a tracheostomy at 26 days.

Arterial PO_2/FiO_2 of the control group before operation was relatively higher than the ELASPOL® group, but there were no significant differences between groups (p=0.2). Two days after the operation, arterial PO_2/FiO_2 dropped to below 150 and it did not recovered to 200 until 10 days after the operation in the control group. On the other hand, in the ELASPOL® group, the

Table 1 Patient's characteristics

	ELASPOL	Control
No.of patients	6	9
age±SD(y)	64±12	64±9
male :female	6 : 0	5 : 4
diagnosis	DAA type A:2 MR, TR:1 ruptured AAA:2 DAA type B:1	DAA type A:8 DAA type B:1
operation	Total arch replacement:2 MVR+TAP:1 Graft replacement:2 (Abdominal aorta)	Total arch replacement:8 Des.Ao graft replacement:1
operation time (hours)	9±6	11±6
CPB	2	all
PaO_2 (mmHg)	128±87	184±76
mortality	1 (30 POD)	1 (170 POD)
tracheostomy	1	2

DAA: dissected aortic aneurysm, MR: mitral regurgitation, TR: tricuspid valve regurgitation, AAA: abdominal aortic aneurysm, MVR: mitral valve replacement, TAP: tricuspid valve plasty, POD: post operative day.

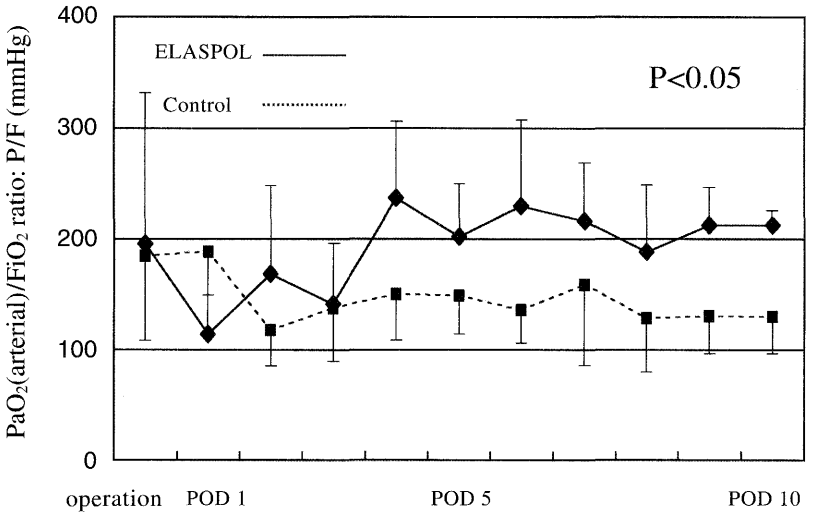

Figure 1 PaO_2 (arterial)/FiO_2 ratio: P/F (mmHg) (Raw data)
Arterial PO_2 was measured every morning from before operation to 10 days after operation, and then P/F ratio was calculated using arterial PO_2 and FiO_2. Filled diamonds indicate ELASPOL® group; filled squares indicate control group. Values are the mean±standard deviation (STD).

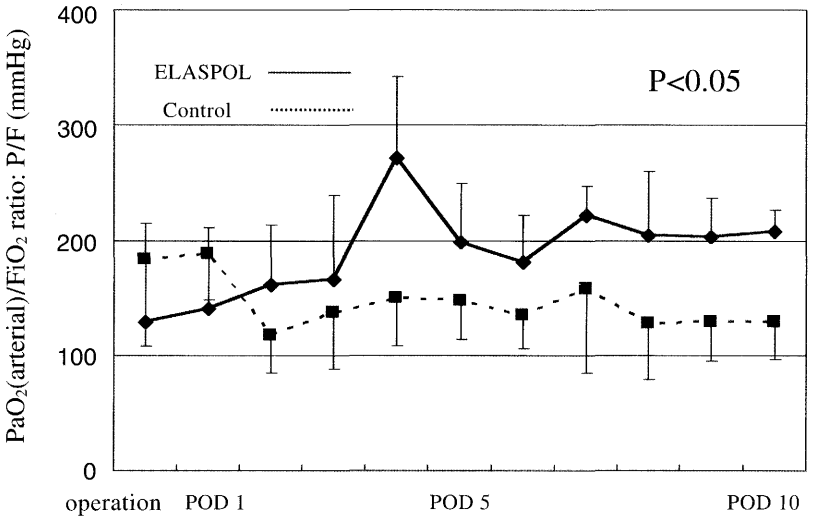

Figure 2 PaO_2 (arterial)/FiO_2 ratio: P/F (mmHg) (adjusted by started day of ELASPOL®)
In the ELASPOL® group, infusion of ELASPORL® (0.2mg/kg/h) was started at before the operation, on the first postoperative day, and the second postoperative day. This figure shows that time course is adjusted, as started day of ELASPOL® is day 1.

P/F ratio had increased to over 200 on the fourth postoperative day and well maintained thereafter ($p<0.05$) (Figure 1, 2).

The duration of intubation was 11±10 days in the ELASPOL® group and 34±56 days in the control group. It was relatively shorter in the ELASPOL® group than in the control group, however there were no significant differences between groups.

The platelet count in ELASPOL® group was relatively higher than control at every time point except baseline, but there were no significant of differences between the groups (Figure 3).

The WBC count in the ELASPOL® group was slightly higher than control from

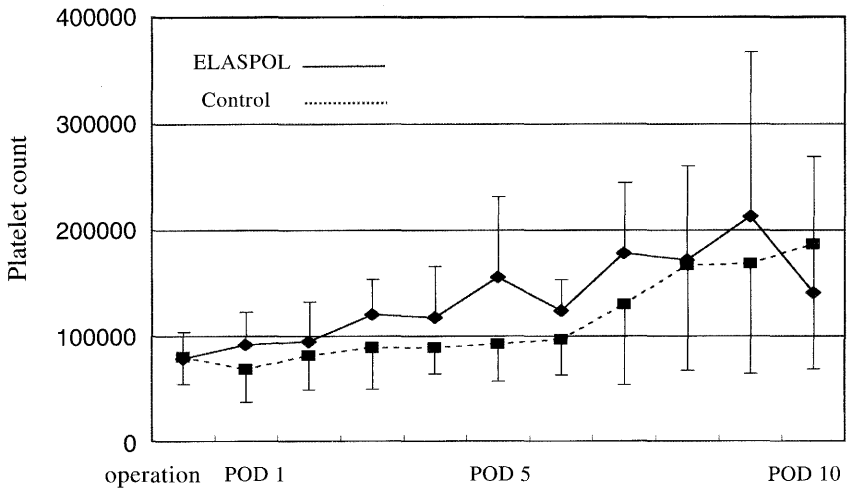

Figure 3 Platelet counts
Platelet counts were measured every morning from before operation to 10 days after operation. Symbols as in Figure 1.

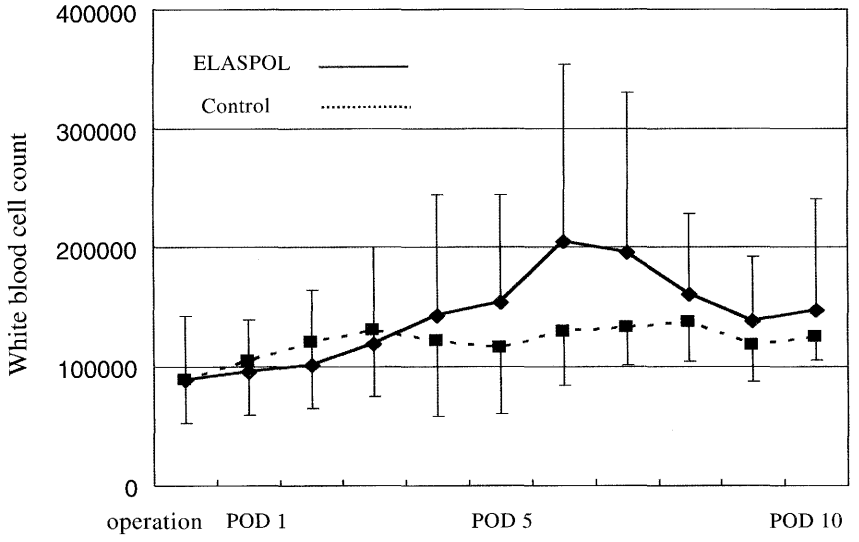

Figure 4 White blood cell counts
White blood cell counts were measured every morning from before operation to 10 days after operation. Symbols as in Figure 1.

postoperative day (POD) 4 to POD 10, but there were no significant differences between the groups (Figure 4). CRP in the ELASPOL® group was almost the same as the control group (date is not shown).

The ICU stay was 8.2±4.2 days in the ELASPOL® group and 8.2±6.7 days in the control group. These data are almost equal.

Discussion

It has been recognized that cardiopulmonary bypass (CPB) is associated with systemic inflammation, and this occasionally leads to major organ dysfunction. Lung injury and acute respiratory distress are one of these[3]. This lung injury is assessed by measuring the alveolar-arterial oxygenation

gradient, intrapulmonary shunt, degree of pulmonary edema, pulmonary compliance, and pulmonary vascular resistance[4].

On the other hand, in the case of dissected aortic aneurysm type B that is treated conservatively to manage hypertension and ruptured abdominal aortic aneurysm that needs emergency operation for treatment of shock, even though CPB is not necessary, pulmonary complications often occur after the operation and during hospitalization. In a recent study of 400 cases undergoing a variety of cardiac surgical procedures, there was a 40% decrease in dynamic pulmonary compliance within the first 4 hours and in alveolar-arterial oxygenation gradient within 24 hours postoperatively[5]. The clinical significance of this CPB and dissected aortic aneurysm or ruptured abdominal aortic aneurysm-related pulmonary injury varies widely, ranging from a clinically undetectable condition to very severe pulmonary failure. In this study, according to the control group, although 17 patients underwent total arch replacement for dissected aortic aneurysm type A before 2002, 8 patients were excluded from this study because they had no lung injury following the operation. Usually dissected aortic aneurysm type A needs total arch replacement using CPB and deep hypothermic circulation, and this operation is done on a emergency basis. The patients with dissected aortic aneurysm type A have more inflammatory responses than patients who have undergone simple cardiac surgery because there are CPB effects, dissected aorta and hypothermic circulation. But in this condition, some patients have severe lung injury that requires long respirator support, and some patients have no pulmonary complication and are easily weaned from the respirator quickly. However, these varieties of clinical course have not as yet well studied. This lack of outcome predictability is probably because the exact mechanisms leading to acute lung injury and acute respiratory distress (ARDS) are not yet fully clarified on a molecular and cellular level[2].

CPB and some severe diseases such as dissected aortic aneurysm and ruptured abdominal aortic aneurysm are associated with a whole body inflammatory response. At an early stage of the inflammatory response, complement is activated and membrane attacking complex (MTA:C5b-C9) is the final product in the reaction[6]. This MTA or complement-independent mechanical mechanism probably activates neutrophils. This activated neutrophils release various cytotoxic contents. One of these cytotoxic contents is elastase, and elastase plasma concentration after CPB is correlated positively with postoperative respiratory dysfunction as shown by changes in the respiratory index and increase in the intrapulmonary shunt[7]. Now neutrophil elastase is said to play an important role in lung injury after cardiovascular surgery with CPB. And this elastase is also a strong stimulator of neutrophil, and creates a vicious circle in the inflammatory cascade.

Sivelestat sodium hydrate (ELASPOL®; Ono Pharmaceutical Co., Osaka, Japan) is a neutrophil elastase inhibitor that was introduced in 2002 for acute lung injury with SIRS. It is expected to reduce lung injury after cardiovascular surgery with CPB and lung dysfunction with SIRS[8-10]. After introduction of this drug, we administrated it to patients undergoing cardiovascular surgery if the patient had severe lung dysfunction after the operation or already had an alveolar-arterial oxygenation gradient before operation. In this study, arterial PO_2/FiO_2 had increased over 200 on the fourth postoperative day and was well maintained after that in the

ELASPOL® group ($p<0.05$). On the other hand, in the control group, P/F ratio dropped below 150 at two days after operation, and thereafter did not recovered to over 200 until 10 days after the operation. This change of P/F ratio in the control group is almost same as that described by Gott JP et al[5]. During the operation, neutrophils were activated and adhered to endothelial cell, where they then released elastase that attacked endothelial cells and also activated other neutrophils. Its reaction takes almost 24 hours to 48 hours because in the endotoxin-induced intestinal model neutrophil infiltration into the intestinal space occurred 48 hours after treatment, whereas neutorphils and monocytes were recruited from blood to alveoli at a much earlier stage. In the ELASPOL® group, P/F ratio was well recovered at 4 days after administration of drug and was maintained for 10days after the induction. In the phase III clinical study of Sivelestat sodium hydrate, this drug was continuously given intravenously for 14 days to the patient with lung injury associated with SIRS. In this report, P/F ratio was markedly improved within 5 days from onset caused by lung injury, and then it became plateau level after 10 days. Although the phase III clinical study was done for lung injury associated with SIRS, not included lung dysfunction after cardiac surgery using cardiopulmonary bypass, this data of P/F ratio was almost same as our data[11]. ELASPOL® significantly inhibited lung injury and also elastase, which is a potent activator of neutrophils, and then it broke down the vicious circle of inflammatory cascade.

The role of platelets in acute lung injury is not completely known[12]. Platelet sequestration in pulmonary capillaries occurs during severe lung injury. These platelets may contribute to endothelial injury and tissue edema by secretion of cytotoxic metabolites. Usually during the cardiovascular surgery with CPB, platelets are activated and consumed; and the platelet count is reduced to almost 60% of before operation. In this study there is no data concerning platelet sequestration in pulmonary capillaries by microscopic investigation. So the effect of ELASPOL® on pulmonary capillaries and endothelial cells is not known. Although there was no significant difference between our two groups, platelet count in the ELASPOL® group were relatively higher than control at each time point except baseline. Coagulation system and platelet function are in close connection with systemic inflammatory response. ELASPOL® probably has some kind of role for reduction of platelet consumption and activation that are caused by activated neutrophils.

As increased concentrations of elastase in plasma and in bronchoalveolar lavage fluid of patients correlated directly with the severity of lung injury[13,14], a limitation in this study is that the concentration of neutrophil-derived proteases and neurtophil elastase, in plasma and in bronchoalveolar lavage fluid were not measured. Furthermore, the importance of mechanisms suggestive of systemic inflammation has been demonstrated by descriptive studies showing that plasma and lavage fluid levels of inflammatory mediators, such as TNF-α, IL-1β, IL-6, and IL-8, increase during lung injury and correlate with adverse outcome[12,15]. These inflammatory mediators were also not measured in this study. Further research will be helpful to show the relationship between the effect of ELASOPL® and neutrophil elastase in plasma and in bronchoalveolar lavage fluid. Although we introduced retrospective case-control study, randomized double blind placebo-controlled

design should be needed to evaluate efficacy of ELASPOL® more precisely.

Conclusions

Sivelestat sodium hydrate (ELASPOL®; Ono Pharmaceutical Co., Osaka, Japan) contributed to the recover of P/F ratio in patients who underwent cardiovascular surgery in a severe condition. We conclude that Sivelestat sodium hydrate is expected to reduce lung injury after CPB in the case of total arch replacement or cardiac surgery with severe preoperative condition.

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