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Changes in Serum S100A12 and sRAGE Associated with Improvement of the PaO_2/FiO_2 Ratio following PMX-DHP Therapy for Postoperative Septic Shock

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Key Words
PMX-DHP · PaO_2/FiO_2 ratio · Sepsis · Acute lung injury

Abstract
Background: Endotoxin (Et) adsorption therapy with a column of polymyxin B-immobilized fibers (PMX) is effective in improving the partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) and increasing mean arterial blood pressure (MAP) in sepsis. S100A12 and soluble receptor for advanced glycation end product (sRAGE) are useful as early markers of acute lung injury. ***Purpose:*** To investigate the effect of improving the PaO_2/FiO_2 ratio by PMX-direct hemoperfusion (PMX-DHP) on production of S100A12 and sRAGE. ***Subjects and Methods:*** Sepsis patients after surgery for perforation of the lower gastrointestinal tract were adopted as the subjects. We retrospectively reviewed the cases of 20 patients on mechanical ventilation and continuous administration of norepinephrine. We recorded PaO_2/FiO_2 ratio, MAP, and norepinephrine doses. S100A12, sRAGE, and Et levels were measured before and after PMX-DHP. ***Results:*** The PaO_2/FiO_2 ratio and MAP improved significantly after PMX-DHP ($p < 0.05$). S100A12 and Et decreased significantly after PMX-DHP ($p < 0.05$). No differences were observed in sRAGE. ***Conclusion:*** S100A12 is useful as a marker that reflected improvement in the PaO_2/FiO_2 ratio after PMX-DHP. We consider PMX-DHP to be useful as adjunctive therapy for sepsis that reduces the Et and corrects the pathology in the early stage.

Introduction

Sepsis caused by perforation of the lower gastrointestinal tract leads to multiple organ failure, and is sometimes fatal, and endotoxin (Et) is cited as one of the contributing factors [1, 2]. Et activates mediators and causes tissue damage [3, 4]. We consider the removal of Et to be an important treatment as a means of preventing multiple organ failure.

Et adsorption therapy with a column of polymyxin B-immobilized fibers (PMX) is effective as a treatment for sepsis because it reduces blood Et values, improves the

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partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio) and increasing blood pressure [5–8]. The usefulness of PMX-direct hemoperfusion (PMX-DHP) has been reported in many papers in recent years [9–11].

Acute lung injury (ALI) is mentioned as one of the forms of multiple organ failure [12]. ALI develops because various mediators, including cytokines, cause vascular endothelial injury, epithelial cell injury, and neutrophil activation [13], and in recent years S100A12 and soluble receptor for advanced glycation end product (sRAGE) have drawn attention as specific markers of ALI [14, 15].

The treatment of sepsis entails a prolonged length of stay in intensive care and an increase in the cost of treatment. The improvement in PaO_2/FiO_2 ratio in response to PMX-DHP is linked to early recovery from ALI and is of benefit to patients. We think that elucidating changes in mediators in response to PMX-DHP will be useful in terms of the indications for PMX-DHP and in timing the start of treatment.

The purpose of this study was to determine what effects the changes in PaO_2/FiO_2 ratio as a result of performing PMX-DHP in ALI patients with postoperative septic shock have on changes in S100A12 and sRAGE.

Subjects and Methods

The protocol of the study was approved by the institutional review board.

Protocol

The subjects were postoperative sepsis patients who had undergone emergency surgery for perforation of the lower gastrointestinal tract during the 24-month period from January 2008 to December 2009. This study was conducted retrospectively by reviewing 20 cases of postoperative septic shock that met the diagnostic criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [16] and in which mechanical ventilation was performed during continuous administration of norepinephrine.

The subjects were thus postoperative patients in whom the focus of infection had been appropriately resected, adequate drainage had been performed and appropriate antibiotics had been given. Patients were excluded under the following conditions: (1) non-availability of informed consent, (2) history of administration of chemotherapy, radiotherapy or immunotherapy prior to the surgery, (3) age 18 years old or younger, (4) presence of liver cirrhosis, diabetes under treatment with insulin, chronic renal failure or steroid administration, (5) pregnancy, (6) presence of heart failure, and (7) presence of chronic lung disease.

The Acute Physiology and Chronic Health Evaluation (APACHE) II score [17] was used for evaluation of the severity of sepsis. Sepsis and septic shock were defined according to the definitions of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) [16].

Fluid replacement, blood transfusion and administration of vasopressors during and after the surgery were performed in accordance with the Surviving Sepsis Campaign Guidelines for the management of severe sepsis and septic shock [18]. When patients were unable to recover from the shock despite fluid replacement therapy, a continuous infusion of norepinephrine was started, beginning at the dose of 0.05 μg/kg/min. No concurrent infusion of dopamine was initiated. In addition, echocardiography was performed at the bedside by a cardiovascular physician before and after the surgery.

Definition of Postoperative ALI

ALI was diagnosed according to the definition of the American-European Consensus Conference [19]. The diagnosis was made by a physician certified by the Japan Infection Control Doctor Council, who was independent of the staff managing the patient in the intensive care unit.

PMX-DHP

In regard to the vascular access for this procedure, venous blood was withdrawn from the femoral vein or subclavian vein. PMX-20R (Toray Industries Inc., Tokyo, Japan) was used as the Et adsorption column, and PMX-DHP was performed at the blood flow rate of 80–120 ml/min for 120 min and started within 3 h after surgery.

Blood Sampling and Assay

Blood samples were taken just before and after the PMX-DHP. Samples were immediately centrifuged and the separated plasma specimens were cryopreserved at –80°C until assay. The serum levels of sRAGE were measured by enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, Minn., USA) and those of S100A12 were also measured by an enzyme-linked immunosorbent assay (CircuLex, Nagano, Japan). The minimum detection levels of sRAGE and S100A12 were 4 and 56 pg/ml, respectively. Et was assayed by Endotoxin-Single Wako (Wako Pure Chemical Industries, Osaka, Japan), using a toxinometer for Et assay that measured the intensity of the transmitted light after the *Limulus* reaction of the sample solution [20]. Arterial blood gas analysis was performed at the central clinical laboratory of our hospital.

The Et assay was performed based on the research results of, and under the instruction of, Dr. Yasunori Yaegashi, and was taken over by the staff of our department.

Statistical Analysis

The data are expressed as mean values ± SD and were analyzed by Wilcoxon signed-rank test. A p value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed on a personal computer with the statistical package JMP for Macintosh (SAS Institute Inc., Cary, N.C., USA).

During the 24-month period from January 2008 to December 2009, emergency surgery for perforation of the lower gastrointestinal tract was performed in 52 cases. A total of 32 of those 52

Table 1. Clinical characteristics of the patients

Gender, n	
Male	12
Female	8
Age, years	72.6 ± 13.3
APACHE score II[a]	27.1 ± 4.2
SOFA score[b]	9.7 ± 2.2
Duration of surgery, min	124.3 ± 33.8
Operative blood loss, ml	219.4 ± 194.7
Cause of perforation	
Cancer	7
Ulcer	4
Ischemic	5
Diverticular	4

[a] Acute physiology and chronic health evaluation score II.
[b] Sequential organ failure assessment score.

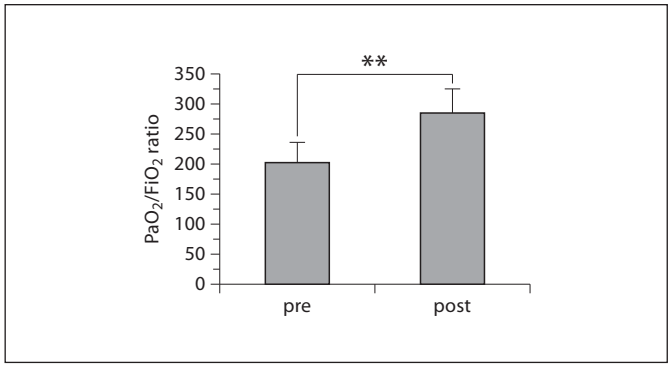

Fig. 1. Changes (±SD) in the PaO_2/FiO_2 ratio. Pre-PMX-DHP (pre) and post-PMX-DHP (post). The PaO_2/FiO_2 ratio post-PMX-DHP was significantly higher than the pre-PMX-DHP ($p < 0.01$). ** $p < 0.01$: pre-PMX-DHP vs. post-PMX-DHP (Wilcoxon signed-rank test).

Table 2. Bacterial culture of the ascetic fluid collected during the operation

Escherichia coli	6
Enterobacter spp.	3
Bacteroides spp.	4
Klebsiella spp.	5
Pseudomonas spp.	4
Morganella spp.	1
Staphylococcus spp.	1
Streptococcus spp.	1
Enterococcus spp.	2
Peptostreptococcus spp.	1
Bacillus spp.	1
Candida spp.	3
Negative	4

cases, consisting of 19 cases in which NE was not administered, 3 cases on oral steroid therapy, 3 cases of chronic renal failure, and 7 cases that did not fulfill the ACCP/SCCM diagnostic criteria, were excluded from the study.

Results

Background Factors

Twenty patients with septic shock developing after surgery were investigated; the patients had undergone emergency surgery for peritonitis caused by lower gastrointestinal tract perforation and underwent PMX-DHP after the surgery. All the patients underwent PMX-DHP for the first time after the surgery. Table 1 shows the patient background factors. Table 2 shows the detailed results of cultures of the ascitic fluid specimens obtained during the surgery.

Changes in the PaO_2/FiO_2 Ratio (fig. 1)

The PaO_2/FiO_2 ratio pre- and post-PMX-DHP was 202.9 ± 65.1 and 284.5 ± 83.1, respectively ($p < 0.01$).

Changes in the Serum Levels of S100A12 and sRAGE (fig. 2)

The serum S100A12 levels post-PMX-DHP 1,250.8 ± 920.0 pg/ml were lower than the levels pre-PMX-DHP 1,905.9 ± 1,062.9 pg/ml ($p < 0.05$). The sRAGE levels pre- and post-PMX-DHP were 1,167.7 ± 793.8 and 1,095.1 ± 712.2, respectively. No differences were found in the sRAGE levels.

Changes in the Mean Arterial Pressure and the Norepinephrine Dose (fig. 3)

The mean arterial pressure post-PMX-DHP 85.5 ± 17.4 mm Hg was higher than that recorded pre-PMX-DHP 63.4 ± 13.5 mm Hg ($p < 0.01$). The norepinephrine dose pre- and post-PMX-DHP was 0.28 ± 0.23 and 0.20 ± 0.18, respectively. No difference was found in the norepinephrine dose.

Changes in the Et Levels (fig. 4)

The serum Et levels post-PMX-DHP 0.9 ± 1.6 pg/ml were lower than the levels pre-PMX-DHP 3.1 ± 4.3 pg/ml ($p < 0.01$).

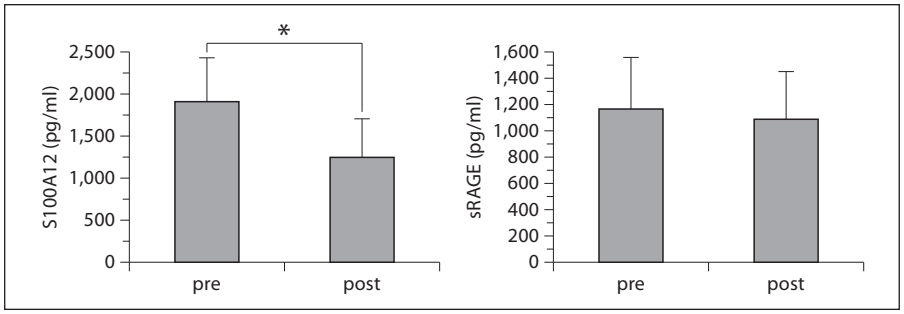

Fig. 2. Changes (±SD) in the serum S100A12 and the sRAGE levels. Pre-PMX-DHP (pre) and post-PMX-DHP (post). The serum S100A12 levels post-PMX-DHP was significantly lower than the levels pre-PMX-DHP ($p < 0.05$). There were no marked differences in the changes in serum sRAGE. * $p < 0.05$: pre-PMX-DHP vs. post-PMX-DHP (Wilcoxon signed-rank test).

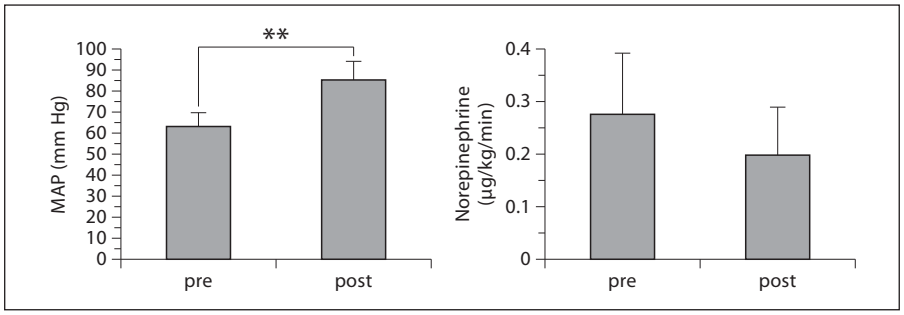

Fig. 3. Changes in the mean arterial pressure (MAP) and the norepinephrine dose. Pre-PMX-DHP (pre) and post-PMX-DHP (post). The MAP post-PMX-DHP was significantly higher than the pre-PMX-DHP ($p < 0.01$). There were no marked differences in the changes in the norepinephrine dose. ** $p < 0.01$: pre-PMX-DHP vs. post-PMX-DHP (Wilcoxon signed-rank test).

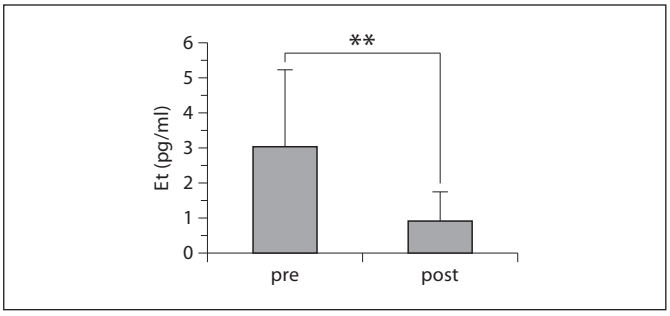

Fig. 4. Changes in the Et levels. Pre-PMX-DHP (pre) and post-PMX-DHP (post). The serum Et levels post-PMX-DHP was significantly lower than the levels pre-PMX-DHP ($p < 0.01$). ** $p < 0.01$: pre-PMX-DHP vs. post-PMX-DHP (Wilcoxon signed-rank test).

Discussion

Evidence regarding the treatment of sepsis has been organized in recent years, and guidelines have been drawn up [21]. However, the treatment of sepsis is often very difficult. Various intensive therapies are performed in cases that have undergone the transition from sepsis to multiple organ failure, and treatment is performed with the goal of improving the pathology. However, because of the excessive invasiveness experienced by sepsis patients who require surgery, correcting the pathology takes time. Early recovery from such invasiveness is most important in terms of treatment.

We have reported that PMX-DHP decreases blood Et levels and brings about an improvement in the clinical manifestations, and shows an improvement in ability to produce cytokines [6]. A recent study has corroborated that PMX-DHP leads to an improvement in circulatory dynamics and improvement in 28-day mortality rate in septic shock, and is useful in the treatment of sepsis [11]. It is highly likely that improvement of the PaO_2/FiO_2 ratio is linked to early recovery from ALI.

The principal site of S100A12 expression is neutrophils [22], and its expression increases in the presence of lipopolysaccharide stimulation and in inflammatory states [23, 24]. The receptor for advanced glycation end products (RAGE), which is the receptor for advanced glycation end products (AGE), has been described as a receptor for S100A12 [25]. The intracellular signaling as a result of the interaction between S100A12 and RAGE causes activation of nuclear factor-κB and production of tumor necrosis factor-α and interleukin-6, and because of the cell response, it contributes to the pathology of the cell injury. S100A12 increases in the early stage of ALI as a result of postoperative sepsis. sRAGE, on the other hand, increases in non-ALI as a result of postoperative sepsis [15]. sRAGE, the soluble form of RAGE, is secreted by vascular endothelial cells and is also present in the blood [26]. Zhang et al. [23] showed that the lipopolysaccharide-in-

duced inflammatory events (neutrophil infiltration, increased pulmonary permeability, edema, pro-inflammatory cytokine production, nuclear factor-κB activation) were inhibited by administering of sRAGE.

The present study investigated the effect of the improvement in PaO_2/FiO_2 ratio by PMX-DHP in postoperative septic shock on changes in the ALI markers, S100A12 and sRAGE.

In this study we demonstrated the following: (1) S100A12 decreases as the PaO_2/FiO_2 ratio improves in response to PMX-DHP, and (2) there are no changes in sRAGE between before and after PMX-DHP.

The early ALI marker S100A12 also seems to be effective as a marker of improvement in the PaO_2/FiO_2 ratio by PMX-DHP. We think the reason for the significant decrease in S100A12 in response to PMX-DHP was strongly associated with the significant decrease in Et values, which were measured at the same time. That was the result of S100A12 and other mediators that are stimulated by Et being modified due to the decrease in Et in response to PMX-DHP. The cell walls of Gram-negative bacteria are composed of lipopolysaccharide [2, 27, 28]. In sepsis secondary to perforation of the small intestine, as in our patient, Et is the first stimulating substance that upregulates a variety of mediators [3, 4]. The fact that the removal of Et, which is first in the mediator network, caused a decrease in the upregulation of pro-inflammatory cytokines appears to have contributed to the decrease in S100A12 and the improvement in the PaO_2/FiO_2 ratio.

sRAGE was not effective as a marker of improvement in the PaO_2/FiO_2 ratio by PMX-DHP. The following are possible reasons why no significant difference was found in the sRAGE levels. First, having measured sRAGE at only two points in this study, i.e. before and after PMX-DHP, may have been a contributing factor. It is possible that if chronological changes were examined at several points after PMX-DHP, differences in sRAGE might be seen, because no significant increase in the sRAGE concentration in BALF compared to healthy controls was described in a report by Wittkowski et al. [14] either. Even the results of our own study [15] investigating changes in sRAGE in postoperative ALI showed no significant difference between the ALI cases and the non-ALI cases immediately after surgery, and showed a significant increase for the first time on hospital day 1. It may be necessary to evaluate sRAGE over time. Second, since sRAGE acts as an inhibitor of S100A12 and RAGE, there is also the possibility that as a result of sRAGE having acted as an inhibitor in the patients who developed ALI, it may have tended not to undergo any changes.

Mean arterial blood pressure increased in response to PMX-DHP, and the increase was consistent with many other reports. As stated above, we think that this was the result of the decrease in Et preventing upregulation of the mediators. On the other hand, no differences were observed in the dose of norepinephrine administered. This may have been because there is no scale for tapering the dose of norepinephrine as blood pressure rises. The possibility that decreasing the norepinephrine dose may instead destabilize blood pressure may have caused hesitation to reduce the dose.

The subjects had undergone a surgical intervention (resection, drainage) and been treated with antimicrobial agents, and PMX-DHP was not the only factor that contributed to the decrease in Et or the changes in cytokines. Thus, there was a limitation to this study, which was retrospective. A study in which the subjects are non-surgical patients and a randomized controlled trial will be necessary to be able to reason strongly that PMX-DHP caused the changes in mediators as a result of removing Et.

The method of measuring Et also needs to be considered. Because Et itself is very labile, difficulties may arise with each of the methods of analysis. We consider the evaluation of PMX-DHP, whose principle is adsorption of Et, to be closely related to the Et measurements.

There is also a report that PMX-DHP improves the pathology of other types of sepsis besides the sepsis caused by Gram-negative bacteria [29]. However, in order to draw any conclusions about this, sepsis due to Gram-negative mixed infections would need to be completely excluded. Et measurements and microbiological evaluations by highly accurate cultures would be absolutely essential, but under the present circumstances it is difficult to rule out the possibility from the standpoint of accuracy [30, 31]. Sometimes no Gram-negative bacteria are detected even by ascitic fluid cultures in cases of clear perforation of the lower gastrointestinal tract as in our study.

PMX-DHP in septic shock appears capable of serving as adjunctive therapy for the treatment of sepsis. It is definitely adjunctive therapy, and it would be difficult to improve sepsis by PMX-DHP alone. We regard it as one element of intensive therapy, the same as surgical treatment of the primary focus and antimicrobial therapy are.

Acknowledgments

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