Therapeutic Apheresis and Dialysis
9(2):128–136, Blackwell Publishing, Inc.

Effect Over Time of Endotoxin Adsorption Therapy in Sepsis

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Abstract: Despite the use of potent antibiotics and intensive supportive care, the mortality among patients with sepsis and Gram-negative bacteremia remains high. In recent years, endotoxin adsorption therapy (PMX-DHP, polymyxin-direct hemoperfusion) has been widely used in Japan to remove endotoxin, a causative agent of sepsis. In septic patients whose clinical condition may change at any moment, the decision of when to perform blood purification in addition to conventional intensive care is a critical factor in the therapeutic strategy and prognosis. In the present study, we investigated the effect over time of PMX-DHP in sepsis. The subjects were 16 patients with systemic inflammatory response syndrome (SIRS) who required surgical treatment including a surgical operation and drainage. The following six parameters were compared between the first and second PMX-DHP: mean blood pressure and time-restricted urine at four time points – at baseline and at 6, 24 and 72 h after PMX-DHP; and white blood cell count, platelet count, base excess and Septic Severity Score (SSS) at 24 and 72 h after PMX-DHP. Mean blood pressure improved over time up to 24 h after both the first and second PMX-DHP. Time-restricted urine volume improved only at 6 h after the first PMX-DHP. White blood cell count improved over time up to 24 h after both the first and second PMX-DHP. The SSS improved at all time points studied except for 3 days after the second PMX-DHP. We conclude that PMX-DHP is expected to have important implications in terms of (i) correction of clinical conditions (by severity assessment); (ii) improvement of hemodynamics; (iii) possible anti-inflammatory effect; and (iv) possible improvement of oxygen metabolism in tissues.
Key Words: Adsorption, Endotoxin, PMX-DHP, Sepsis, Severity assessment.

Despite the use of potent antibiotics and intensive supportive care, the mortality among patients with sepsis and Gram-negative bacteremia remains high (1). Gram-negative bacteria are often causative agents of sepsis, accounting for 40–50% of cases of septic shock (2,3). Endotoxin, a known causative agent, is a component of the extracellular membrane of Gram-negative bacteria, and is said to be inactivated by polymyxin B (4). Cytokines and various mediators are also known as causative agents, and studies on these agents and development of therapeutic drugs have been actively pursued in the United States, as reported by Ziegler (1), Abraham (5) and Opal (6). In Japan, development of a hemoadsorption column has been in progress since 1983, and has resulted in the current widespread use of endotoxin adsorption therapy (PMX-DHP) utilizing polymyxin-attached fiber for septic shock caused by endotoxin derived from Gram-negative bacteria infection (7). Given that anandamide is another cause of septic shock and PMX-DHP is effective against shock through adsorption of anandamide (8), endotoxin adsorption therapy is expected to find wider applications.

In Japan, treatment with PMX-DHP for endotoxemia caused by Gram-negative bacilli and for suspected Gram-negative bacterial infection is covered by health insurance (Table 1) (9). These clinical conditions may progress to septic shock or multiple organ failure, and are reported to require, as essential therapeutic measures, acute blood purification that includes continuous hemodiafiltration (CHDF), continuous hemofiltration (CHF) and plasma exchange (PE) for the removal of inflammatory cytokines and various mediators (10). In particular, in septic patients whose clinical condition may change at any moment, the decision of when to perform blood purification is a critical factor in the ther-

Received September 2004; revised December 2004.
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TABLE 1. *Criteria of PMX treatment*

1. Endotoxemia or suspected Gram-negative infection
2. Two of the following conditions from (a) to (d):
   (a) Fever with oral temperature >38°C or <36°C
   (b) Tachycardia >90 beats/min
   (c) Tachypnea >24 breaths/min
   (d) Leukocytosis >12 000/mm^3 or leukopenia >4000 mm^3 or 10% bands form
3. Septic shock which necessitates vasopressor therapy

apeutic strategy and prognosis, and requires careful assessment of patients' clinical conditions. As is evident from a report that indicates the importance of introducing PMX-DHP during the hyperdynamic state in the early phase of septic shock (11), prompt intervention and intensive therapy is desirable in treating septic shock and associated clinical conditions. Since the clinical conditions may progress to septic multiple organ failure (MOF) and severe sepsis in some cases, it is important to understand improvement in clinical conditions over time through the introduction of PMX-DHP in the field of intensive care requiring systemic control of patients. We carried out a retrospective study on the effect over time of PMX-DHP on clinical conditions in 16 patients, including five non-survival cases, who underwent two cycles of PMX-DHP.

PATIENTS AND METHODS

The study subjects were 16 patients who required surgical treatment including a surgical operation and drainage. All subjects fulfilled the diagnostic criteria for systemic inflammatory response syndrome (SIRS) (12). The 16 patients consisted of 5 males and 11 females with a mean age of 75.2 years. The mean septic severity score (SSS) (13) was 32 and the mean endotoxin level 18.0 pg/mL (Table 2). Thirteen patients received CHDF between the first and second PMX-DHP, and two patients received preoperative PMX-DHP. According to the indication criteria established in our hospital (1. Septic shock suspected of infection by Gram-negative bacteria; 2. Sepsis the cause of which is unknown; 3. Suggestion of a drop in blood pressure or urinary volume or an advance of sepsis in spite of implementation of other acute blood purification) all subjects received PMX-DHP twice. Endotoxin adsorption therapy was performed in 14 patients with suspected sepsis and hypercytokinemia caused by localized peritonitis or diffuse peritonitis, one patient with preoperative septic shock, and one patient with postoperative sepsis, in addition to administration of antibiotics and vasoactive agents, artificial ventilation, and acute blood purification such as CHDF. Informed consent was obtained from all participating subjects or their families. Conditions utilized for blood purification were as follows. A double lumen catheter was inserted by Seldinger's method and maintained in the femoral vein for blood access. Dialyzer ACH-07S (Asahi-Medical Co., Tokyo, Japan) was used for hemodialysis, Toraymyxin (Toray Industries Inc., Tokyo, Japan) for endotoxin adsorption, hemofilter PANFLO APF-06S (Asahi-Medical Co.) for continuous hemofiltration, Hemosorber CH-350 (Asahi-Medical Co.) for hemoadsorption, and Plasma Flow OP-02 (Asahi-Medical Co.) for plasma separation. The anticoagulant used was nafamostat mesilate (Futhan, Torii Pharmaceutical Co., Tokyo, Japan) and the replacement fluid for blood filtration was Sublood-A (Fuso Pharmaceutical Industries, Osaka, Japan). Endot-

TABLE 2. *Cases involved. Concommitant blood purification method, combination therapy with continuous hemodiafiltration (CHDF) or plasma exchange (PE)*

Case	Age	Sex	Diagnosis	Concomitant blood purification/surgical treatment
1	65	Female	Perforation in the sigmoid colon	CHDF
2	81	Female	Perforation in the sigmoid colon	CHDF
3	71	Female	Perforated duodenal ulcer	CHDF
4	73	Male	Strangulated ileus	CHDF
5	52	Female	Perforation in the descending colon	Operation
6	74	Female	Strangulated ileus	CHDF
7	81	Female	Renal abscess	Operation/CHDF
8	91	Female	Strangulated ileus	CHDF/PE/PTGBD
9	63	Male	Strangulated ileus	CHDF
10	85	Male	Strangulated ileus	CHDF
11	84	Female	Acute cholecystitis	CHDF
12	81	Female	Ascending colon cancer	–
13	87	Male	Gastric cancer	CHDF
14	79	Male	Abdominal aortic aneurysm	CHDF
15	72	Female	Perforation in the gallbladder	CHDF
16	64	Female	Pancreatiac head cancer	CHDF

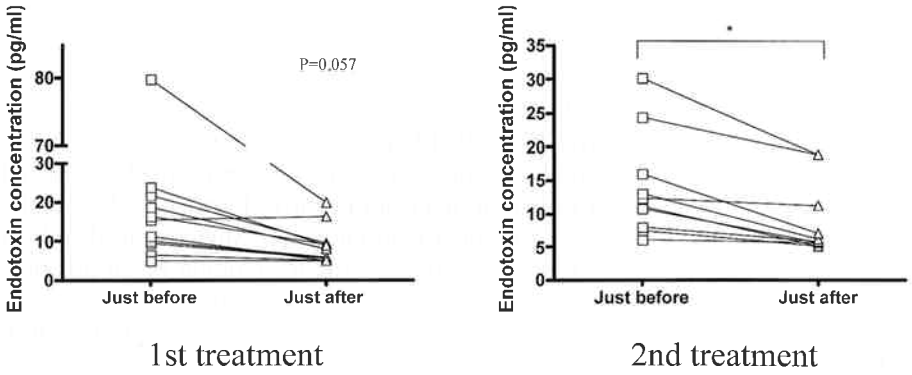


FIG. 1. Changes of endotoxin concentration level in patients by PMX-DHP. PMX-DHP treatment significantly reduced endotoxin levels (second treatment: $^*P < 0.05$).

oxin adsorption therapy was performed for 2 h at a blood flow rate of 80–100 mL/min. The following parameters were compared between the first and second PMX-DHP: Mean blood pressure and time-restricted urine volume at four time points – at baseline and at 6, 24 and 72 h post PMX-DHP; and white blood cell count, platelet count, base excess, and SSS at 24 and 72 h post PMX-DHP. For statistical analyses, data were compared by the paired *t*-test at a significance level of $P < 0.05$.

RESULTS

Change in endotoxin level after PMX-DHP

Endotoxin level was significantly lower post PMX-DHP than at baseline in both treatments (Fig. 1).

Proportion of bacteria detected

Suspected causative agents of sepsis were Gram-negative bacteria such as Pseudomonas, Klebsiella and Enterobacter with each accounting for 9–13% of all causative agents and all Gram-negative bacteria combined constituting a majority (Table 3).

Rationale for introducing PMX-DHP

The first PMX-DHP was introduced because 12 patients had sepsis caused by Gram-negative bacilli and four patients had septic shock. The second PMX-DHP was introduced in five patients who had decreased blood pressure compared with the level at the first PMX-DHP, eight patients with persistent or progressive septic symptoms such as decreased white blood cell count and platelet count, as well as prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), two patients with septic shock, and one patient who developed acute cholecystitis (Fig. 2).

Effect on hemodynamics

Blood pressure improved over time up to 24 h after both the first and second PMX-DHP, then decreased slightly thereafter, but remained at higher levels than the baseline level on average. However, blood pressure was improved to a higher level after the first than after the second PMX-DHP up to 24 h post therapy.

Urine volume improved up to 6 h after the first PMX-DHP, but did not show definite signs of improvement thereafter, as was the case after the second PMX-DHP.

Differences in treatment effects between survival cases and non-survival cases included a smaller improvement of blood pressure and urine volume after the second PMX-DHP when compared to the first PMX-DHP in non-survival cases. In survival cases, improvement in blood pressure was observed at 6 and 24 h after PMX-DHP in both the first and second cycles compared with baseline ($P < 0.05$). The improvement in blood pressure was significantly greater in survival cases than in non-survival cases at 6 and 24 h after the second PMX-DHP ($P < 0.05$). In survival cases, improvement in urine volume was observed at 6 h after the first cycle and at 6 and 24 h after the second cycle compared with baseline ($P < 0.05$). Comparison with non-survival cases

TABLE 3. *Etiology of infection*

Species	Number of cases
Gram-negative bacteria	12
Pseudomonas	3
Klebsiella	3
Enterobacter	2
Citrobacter freundii	1
Escherichia coli	1
Proteus mirabillis	1
Serratia	1
Gram-positive bacteria	6
Enterococcus	4
Methycillin-resistant *Staphylococcus aureus*	1
Streptococcus pyogenes	1
Not detected/others	5

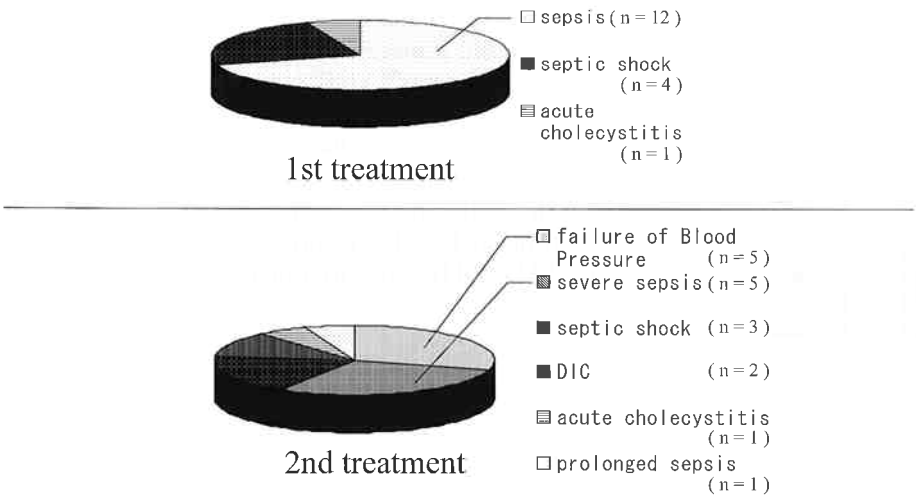


FIG. 2. Rationale for introducing PMX-DHP. All subjects received PMX-DHP twice. The indication may be plural.

showed a significant difference in urine volume improvement at 6 h after the second PMX-DHP ($P < 0.05$) (Figs 3,4).

Hematology

White blood cell counts improved at 24 h after both the first and second PMX-DHP, and continued to increase thereafter. Platelet counts decreased at 24 h after PMX-DHP, but improved slightly after 3 days in both the first and second cycles. Base excess improved at 24 h after the first cycle, but otherwise showed no significant changes, either in the first or second cycles.

In non-survival cases, white blood cell counts did not tend to improve after the second PMX-DHP and tended to increase over time. In survival cases, platelet counts showed a tendency to decrease at 24 h after the first PMX-DHP, but remained unchanged at other time points. In contrast, platelet counts in non-survival cases remained at a low level of around $10 \times 10^4/mm^3$ on average (Figs 5–7).

Effect on severity assessment

The severity assessment score improved over time after both the first and second PMX-DHP, but not after 3 days in the second cycle, compared with the score at 24 h after PMX-DHP. In survival cases, the severity assessment score improved over time after both the first and second cycles, whereas in non-survival cases the score did not improve after the second PMX-DHP. In survival cases, the severity assessment score was significantly better at 24 h and 3 days after the second PMX-DHP ($P < 0.05$) relative to baseline and to the non-survival cases ($P < 0.05$) (Fig. 8).

DISCUSSION

Despite advances in intensive supportive care, the survival rate of patients with septic shock remains low, at about 50% in the United States and Europe, where PMX-DHP is not performed (14). The therapeutic strategy of using PMX-DHP has been widely utilized in Japan and it's usefulness has almost been established (15,16). Since prompt decision-making is a critical factor that determines the success or failure of life-saving therapy, particularly in patients with severe sepsis that requires intensive care, we reported the importance of severity assessment (17).

For severity assessment, we performed serial measurements of SSS, which was reported to be useful in the severity assessment of sepsis (13), hemodynamics, which was reported to be improved by PMX-DHP (18,19,20), and three hematology parameters, white blood cell counts, platelet counts, and base excess. The acute physiology and chronic health evaluation II score (APACHE II) and sepsis-related organ failure assessment (SOFA) are commonly used to assess severity in patients with severe sepsis (21,22). The SSS, which we used in the present study, is the only severity assessment measure that includes the gastrointestinal tract as one of the target organs, and we have reported the usefulness of SSS in monitoring patients undergoing acute blood purification (17). In the present study, the severity score improved in all patients after the first PMX-DHP, but the score failed to improve after the second PMX-DHP in non-survival cases, showing a significant difference between survival and non-survival cases. These results suggested that patients who do not

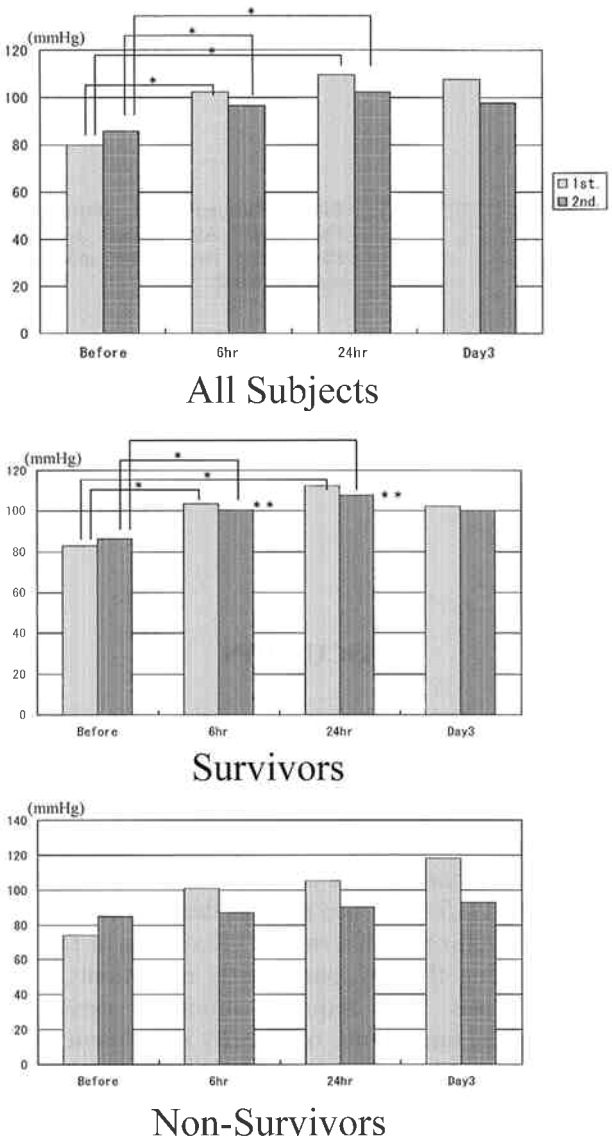


FIG. 3. Changes in hemodynamics: mean blood pressure. Changes in mean blood pressure produced a significant elevation up to 24 h after both the first and second PMX-DHP. In survival cases, improvement was observed at 6 and 24 h after PMX-DHP in both the first and second treatment compared with baseline (*$P < 0.05$). The improvement was significantly greater in survival cases than in non-survival cases at 6 and 24 h after the second PMX-DHP (**$P < 0.05$).

show improvements in the score after the second PMX-DHP are at a high risk of poor prognosis.

With regard to the therapeutic effect of PMX-DHP on hemodynamics, for which there is now a general consensus, improvement in blood pressure was observed in all patients within 3 days following PMX-DHP compared with baseline. In survival cases in particular, blood pressure significantly improved within a short period of 6 or 24 h after PMX-DHP compared with baseline. Coupled with a report that the time from the first blood pressure drop is associated with the prognosis of sepsis (23), these findings suggested that PMX-DHP is a useful therapy for sepsis. Furthermore, the results suggest the usefulness of PMX-DHP as one of the bridging antishock therapies until surgical operations can be performed. Even in four of the five patients who died, a sufficient elevation of blood pressure was observed after the first PMX-DHP. (first treatment, 6 h $P = 0.082$, 24 h

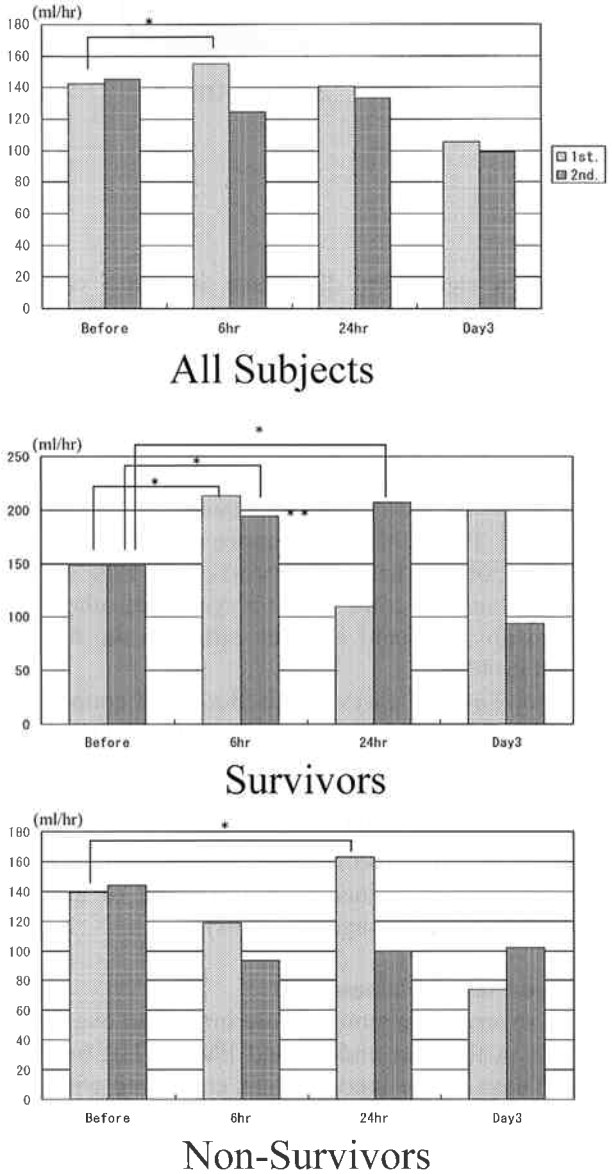


FIG. 4. Changes in hemodynamics: urinary volume per hour. Urine volume improved only at 6 h after the first PMX-DHP. In survival cases, improvement was observed at 6 h after the first treatment and at 6 and 24 h after the second treatment compared with baseline (*$P < 0.05$). Comparison with non-survival cases showed a significant difference in improvement at 6 h after the second PMX-DHP (**$P < 0.05$).

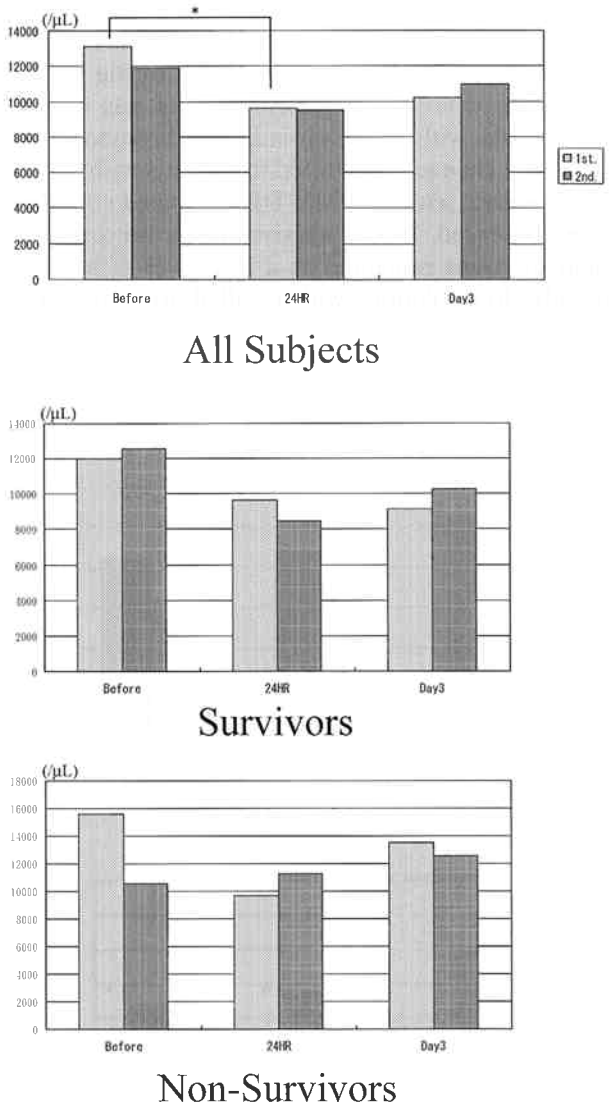


FIG. 5. Changes in leukocytes. White blood cell counts improved over time up to 24 h after both the first and second PMX-DHP (*$P < 0.05$).

$P = 0.124$; second treatment, 6 h $P = 0.739$, 24 h: $P = 0.250$; day 3: $P = 0.239$). However it is clearly showed that the improvement in blood pressure was significantly greater in survival cases than in non-survival cases after the second PMX session. These results may suggest the indication for the second session of PMX-DHP.

Urine volume, another measure of hemodynamics, is said to increase after PMX-DHP, and similar results were observed in our patients within the short period of 6 h after PMX-DHP. However, most of the patients maintained a time-restricted urine volume of ≥1 mL/kg at baseline, which was probably the reason why no definite increase in urine volume was observed after PMX-DHP. During the period after surgery, there was concern about development of renal failure due to oliguria caused by an imbalance of the third space fluid, but this did not occur because most of the patients received continuous blood purification (CBP) including CHDF or CHF even after PMX-DHP. This result provides renewed recognition of the importance of combination therapy with PMX-DHP and CBP. The urine volume of non-survival cases after the second PMX-DHP did not show

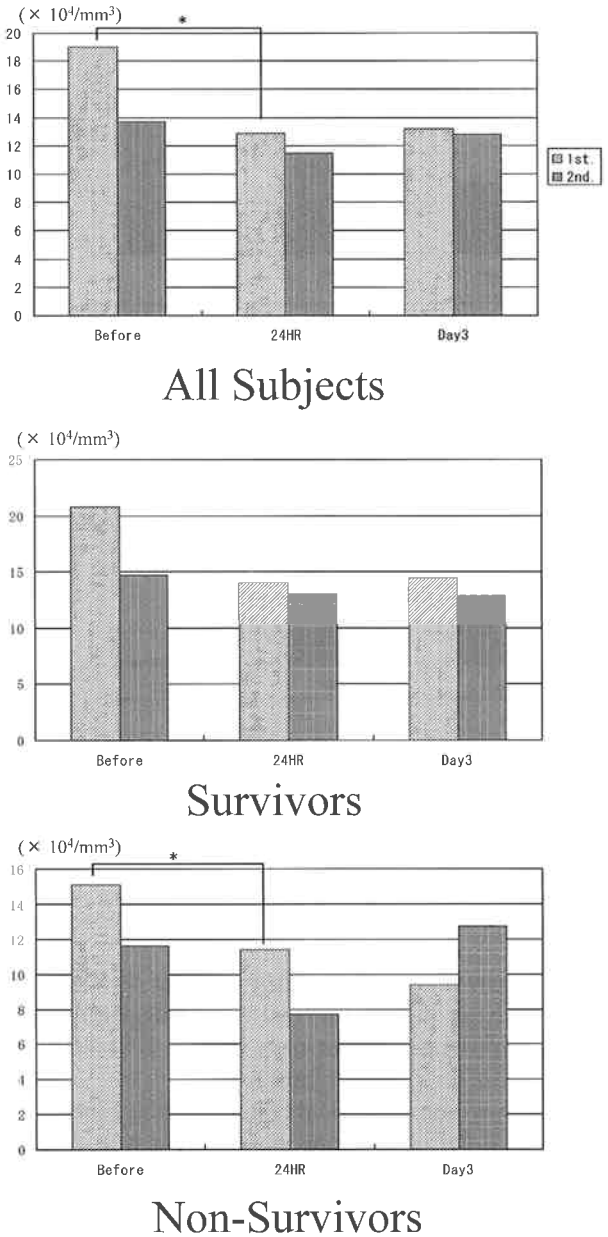
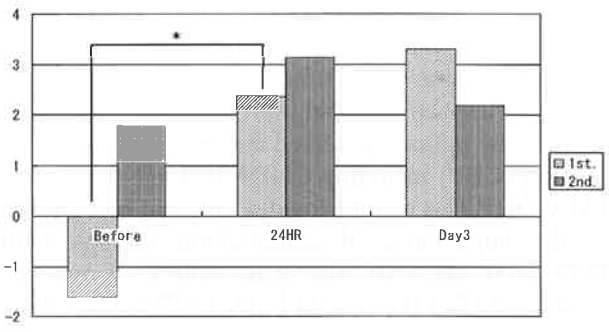
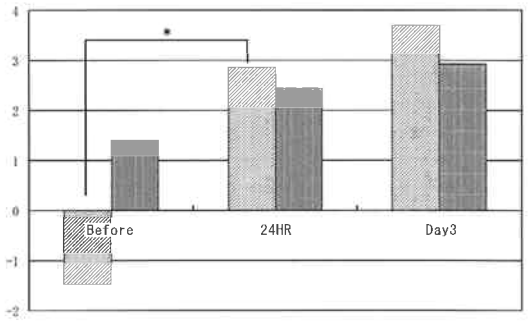


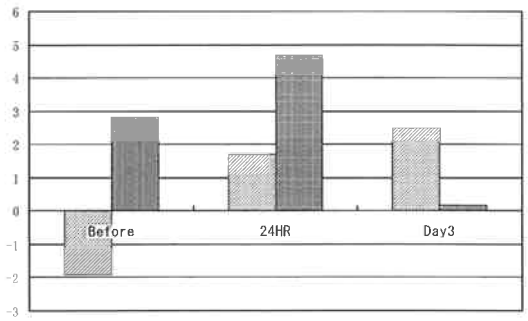
FIG. 6. Changes in platelets. In non-survival cases, platelet counts decreased significantly 24 h after the first treatment compared with baseline (*$P < 0.05$).



All Subjects



Survivors

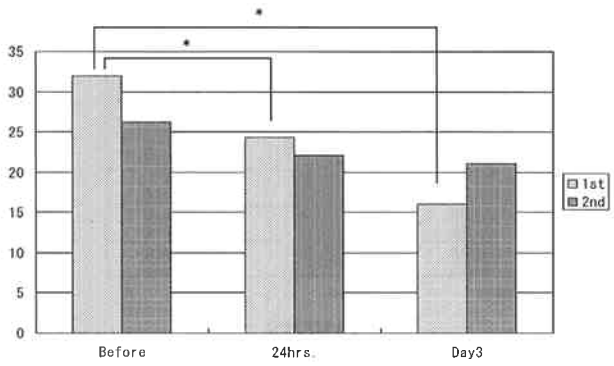


Non-Survivors

FIG. 7. Changes in base excess. In survival cases, base excess improved only at 24 h after the first PMX-DHP (*$P < 0.05$).

clear improvement, although it was not significantly different from that of survival cases, suggesting that lack of improvement in urinary volume is likely to be a risk factor for poor prognosis.

Results of hematological tests on white blood cell counts, platelet counts, and base excess were evaluated as follows. Based on changes in white blood cell counts, the anti-inflammatory effect of PMX-DHP was more potent and persisted longer after the first cycle than after the second cycle. Patients who showed an increase in white blood cell count over time after the second cycle appeared to be at a high risk of poor prognosis. The platelet count is reported to decrease after PMX-DHP (24,25). In the present study, the decrease in platelet counts was marked in patients with infection-induced thrombocytosis, while the change was limited in patients with thrombocytopenia, with no PMX-DHP-induced complications observed. In non-survival cases, however, the platelet count remained at a low level of approximately $10 \times 10^4/mm^3$, which called for caution in



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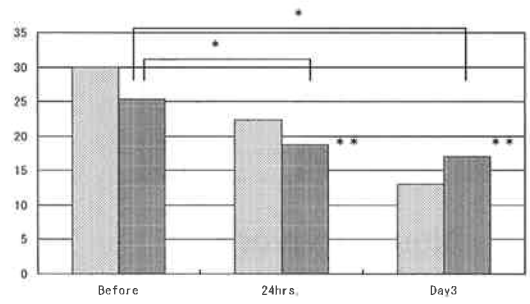
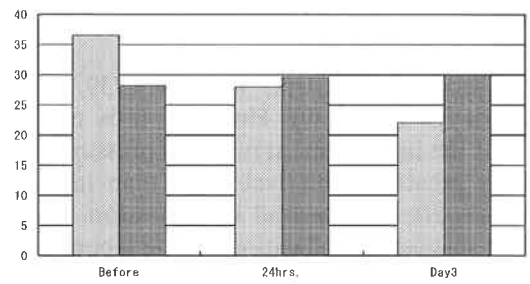


Survivors



Non-Survivors

FIG. 8. Effect on severity assessment. The SSS improved at all time points studied except for 3 days after the second PMX-DHP. In survival cases, the score was significantly better at 24 h and 3 days after the second PMX-DHP (*$P < 0.05$). Comparison with non-survival cases showed a significant difference in the score improvement at 24 h and 3 days after the second PMX-DHP (**$P < 0.05$).

selecting anticoagulants by taking the activated coagulation time into consideration. Base excess is a measure of tissue metabolism. Oxygenation is improved by PMX-DHP, as reported in a sepsis model (26), which suggests that PMX-DHP is also effective in correcting hypoxic conditions such as those found in sepsis. Improvement in pulmonary function, one of the parameters for SSS assessment, was also observed (data not shown).

The above results demonstrated that PMX-DHP elicited the following four effects: (i) correction of clinical conditions (by severity assessment); (ii) improvement of hemodynamics; (iii) a possible anti-inflammatory effect; and (iv) possible improvement of tissue oxygen metabolism. Patients with poor prognosis included (i) those who did not show improvement in SSS over time after the second PMX-DHP; (ii) those with little improvement in blood pressure after the second PMX-DHP; and (iii) those who showed an increase in white blood cell counts over time after the second PMX-DHP.

In Japan, indications for PMX-DHP are still a matter of debate. In recent years, however, favorable results with PMX-DHP have been reported, including a multicenter evaluation by Tani et al. (27) and a randomized controlled trial (RCT) by Nemoto, Suzuki et al. (15). In Europe, a pilot RCT was conducted with six medical institutions in five countries (reported by J-L Vincent et al. 23rd ISICEM, 2002) and ongoing data analyses are producing results that are consistent with the clinical findings in Japan. PMX-DHP is expected to have important implications in patients with sepsis that often remain intractable to treatment.

Several problems remain for future studies. In clinical sites, sepsis is rarely improved by only one or two cycles of PMX-DHP, and often requires CBP such as CHDF or CHF, or multiple PMX-DHP cycles depending on clinical conditions. In this study we mainly used combination therapy with PMX-DHP and CHDF, and we need to evaluate the effect of PMX-DHP alone. Further studies should be carried out in multiple centers on the effective time period and number of PMX-DHP cycles, as well as on mediators.

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