J Anesth (2006) 20:11–16
DOI 10.1007/s00540-005-0366-5

Journal of
Anesthesia

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Anandamide absorption by direct hemoperfusion with polymixin B-immobilized fiber improves the prognosis and organ failure assessment score in patients with sepsis

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Abstract
Purpose. Direct hemoperfusion (DHP) with polymixin B-immobilized fiber (PMX) has been reported to be effective for patients with septic shock. The aim of this study was to clarify the mechanism of PMX-DHP effect on septic shock.
Methods. The following parameters were measured in septic shock patients who were treated with PMX-DHP: survival rate, sepsis-related organ failure assessment (SOFA) score, acute physiology and chronic health evaluation II (APACHE-II) score, and plasma concentrations of cannabinoids [anandamide (ANA) and 2-arachidonyl glyceride (2-AG)], cytokines [interleukin (IL)-6, IL-8, IL-10], transforming growth factor β (TGF-β), and calcitonin gene-related peptide (CGRP)]. The primary end point was mortality from all causes at day 28 after intensive care unit (ICU) admission or discharge.
Results. The survival rate of all patients at 28 days after ICU admission was 37.5% (9/24). The survival group showed significantly lower SOFA and APACHE-II scores than the nonsurvival group after PMX-DHP treatment ($P = 0.008$ and 0.028, respectively). The improved SOFA score group showed a better survival rate than the nonimproved SOFA score group (71.4% versus 23.5%, $P = 0.028$). Plasma ANA level significantly decreased after PMX-DHP treatment both in the improved SOFA score group and in the survival group. The level of 2-AG, however, showed no significant change in either group.
Conclusion. ANA, an intrinsic cannabinoid that induces hypotension in septic shock, is inferred to be the main mechanism of the PMX-DHP effect. Removal of ANA by PMX-DHP could be key to successful septic shock treatment.

Key words Direct hemoperfusion · Polymixin B-immobilized fiber · Septic shock · Sepsis organ failure assessment · Anandamide

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Received: July 1, 2005 / Accepted: October 9, 2005

Introduction

In the management of sepsis, previous research focused on the importance of Gram-negative bacteria and endotoxins. Polymixin B-immobilized fiber (PMX) was first developed as a biomaterial for selective adsorption of endotoxin in patients with Gram-negative bacterial infection [1–3]. Endotoxin adsorption using PMX provided some successful results for Gram-negative bacteria-induced sepsis [4].

On the other hand, antilipopolysaccharide (LPS) monoclonal antibodies (HA-IA [5], E5 [6]) have been developed against endotoxin, but clinical trials have not provided reproducible survival benefits in LPS shock patients [7]. Direct hemoperfusion (DHP) with PMX (PMX-DHP) has been reported to be effective for patients with septic shock who are infected not only by Gram-negative bacteria but also by Gram-positive bacteria without endotoxin release [8]. From these facts, it is supposed that the therapeutic effect of PMX-DHP on septic shock would depend on the other mediators, except for endotoxin removal. The aim of this study was therefore to clarify the mechanism of PMX-DHP effect on septic shock.

Cytokines are regarded as important mediators in the pathophysiology of sepsis and septic shock. Several studies have demonstrated an increase in serum levels of inflammatory cytokines in critically ill patients [9]. However, it has also been reported that cytokines are not removed by PMX-DHP [10], and pharmacological antagonism of cytokine effects failed to provide protection from the hypotension of septic shock [11]. It is supposed that cytokines are not a major mechanism of the PMX-DHP effect for septic patients. Both Gram-negative and Gram-positive bacteria have been suggested to release endogenous cannabinoids in animal studies. Recent evidence indicates that during certain shock conditions, platelets and macrophages produce at least two different endogenous cannab-

inoids, anandamide (ANA) and 2-arachidonyl glyceride (2-AG), which may be paracrine mediators of hypotension during shock, acting via CB1, a cannabinoid receptor subtype localized in the peripheral vasculature [12–16]. Several studies have demonstrated that ANA and 2-AG can elicit CB1 receptor-mediated hypotension in rats [12,17,18]. ANA induces cell death, and pretreatment with polymixin B neutralizes its cytotoxicity [14]. Based on these studies, we hypothesized that the mechanism of improvement for septic shock patients by PMX-DHP treatment might be the reduction of blood levels of cannabinoids.

A prospective clinical study was performed, and the several parameters described above were measured in septic shock patients who were treated with PMX-DHP, as well as other parameters for critically ill patients: survival rate, sepsis-related organ failure assessment (SOFA) score, acute physiology and chronic health evaluation II (APACHE-II) score, and catecholamine pressure index (CAPI).

Patients and methods

Study design

This study was approved by the review board of our institution, and informed consent was obtained from the family members of patients. This prospective consecutive study was conducted at Sapporo Medical University and three community hospitals in Japan from the beginning of January 2000 to December 2002. Standard treatments including regular antibiotic therapy were started before the induction of PMX-DHP treatment.

Patients

Twenty-four patients with a clinical diagnosis of septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [19] were included in this study. Antibiotic therapy was judged to be adequate when the patient received an antibiotic to which each isolated organism was sensitive. Standard treatments for septic shock were continued during and after PMX-DHP. The primary end point was mortality from all causes at day 28 after intensive care unit (ICU) admission or discharge, if patients were discharged from the hospital or transferred to another hospital within the 28 days.

PMX-DHP treatment

The PMX was produced by immobilizing polymyxin B on polystyrene fiber using covalent bonding without its release. The column for DHP contained 53 g of PMX, supplied by Toray Industries (Tokyo, Japan) [20]. During PMX-DHP, the blood flow volume was about 80 to 100 ml·min^{-1} by the venovenous method with a double lumen catheter. The PMX-DHP treatment lasted for 2 h and 20 mg of nafamostat mesilate (Torii Pharmaceutical, Tokyo, Japan), an anticoagulant was administered concurrently.

Clinical and laboratory evaluation

SOFA and APACHE-II scores were calculated before and after DHP-PMX treatment. SOFA is a scoring system that was devised in 1994 to describe the degree of organ dysfunction in sepsis [21]. The system scores the function of six different organ systems: respiratory, cardiovascular, central nervous system, coagulation, hepatic, and renal systems, and each system is scored (1–4) according to the level of physiological derangement. APACHE-II uses a point score based upon initial values of 12 routine physiological measurements, age, and previous health status to provide a general measure of severity of disease [22]. CAPI was measured before/after and 1 day after the PMX treatment. CAPI was calculated by the following equation: {[dopamine (μg·kg^{-1}·min^{-1}) + dobutamine (μg·kg^{-1}·min^{-1}) + 100·adrenaline (μg·kg^{-1}·min^{-1}) + 100·noradrenaline (μg·kg^{-1}·min^{-1})]/systolic blood pressure (mmHg)}. Blood samples were also collected, and serum concentrations of ANA, 2-AG, transforming growth factor β (TGF-β), interleukin (IL)-6, IL-8, IL-10, and calcitonin gene-related peptide (CGRP) were measured before, just after, and 24 h after DHP-PMX treatment. Collected blood samples were centrifuged at 1500 *g* for 10 min, and the plasma samples were stored at −70°C until measurements. All samples were transported to and analyzed at the Department of Laboratory Medicine, Kagoshima University School of Medicine, as previously reported [13].

Statistics

Data are expressed as numbers or means ± SD. All parameters were compared in two sets of two groups, using an unpaired *t* test or a λ^2 test, between survival and nonsurvival groups, and between improved and nonimproved SOFA score groups. The changes in parameters obtained before, just after, and 24 h after PMX-DHP treatment were analyzed by one-way analysis of variance (ANOVA) with Fisher's post hoc test in each group. All P values < 0.05 were considered significant.

Results

Of the 24 patients diagnosed as having septic shock during the study period, 18 patients were men and 6

were women. The mean age was 61.5 ± 19.9 years (range, 14–83). The survival and nonsurvival demographic data and clinical parameters for critically ill patients prior to PMX-DHP treatment are shown in Table 1. The survival rate of all patients at 28 days after ICU admission was 37.5% (9 out of 24 patients). Sex, SOFA scores, and APACHE-II scores before PMX-DHP treatment were indistinguishable between survival and nonsurvival groups; only CAPI showed a small but significant difference between these groups ($P = 0.022$). Figure 1 shows the changes in these parameters in the survival and nonsurvival groups before and after PMX-DHP treatment. Although CAPI did not change by the PMX-DHP treatment, both SOFA and APACHE-II scores in the survival group significantly decreased by PMX-DHP, and these were significant differences between the groups after the PMX-DHP treatment ($P = 0.008$, and 0.028, respectively). The improved SOFA score group showed a better survival rate than the nonimproved SOFA score group (71.4% versus 23.5%, $P = 0.028$).

In light of these results, the patients included in this study were then divided into two groups, the improved and nonimproved SOFA score groups, in order to investigate the mechanism of the PMX-DHP effect on septic shock. Figure 2 shows the changes in plasma concentrations in the cannabinoids ANA and 2-AG, both between the improved and nonimproved SOFA score groups and between the survival and nonsurvival groups during the PMX-DHP treatment. Although there were no characteristic changes in 2-AG values, ANA both in the improved SOFA score group and in the survivor group significantly decreased during the PMX-DHP treatment. At 24 h after PMX-DHP treatment, the plasma concentration of ANA in the improved SOFA score group was significantly higher than that in the nonimproved SOFA score group ($P = 0.005$).

The changes in plasma concentrations of TGF-β, cytokines (IL-6, 8, and 10), and CGRP during PMX-DHP treatment are shown in Table 2. Both TGF-β and IL-10 significantly decreased after PMX-DHP treatment in the nonimproved SOFA score group, whereas these parameters in the improved SOFA score group did not change but were stable at low levels during the study period. In neither the survivor nor the nonsurvivor group did any of the parameters show significant changes by the PMX-DHP treatment in this study. However, TGF-β, IL-6, and IL-8 in the survival group were significantly lower than those in the nonsurvival group at each measured point. CGRP did

Table 1. Survival and nonsurvival demographic data and clinical parameters for critically ill patients prior to PMX-DHP treatment

	Survival ($n = 9$)	Nonsurvival ($n = 15$)	P
Sex (female/male)	4/5	2/13	0.088
Age (years)	57.8 ± 23.1	63.2 ± 16.7	0.475
SOFA score	12.0 ± 3.7	14.5 ± 3.4	0.138
APACHE-II score	26.2 ± 10.2	27.5 ± 6.5	0.973
CAPI	0.23 ± 0.23	0.70 ± 0.53	0.022

Data are expressed as numbers or means ± SD.
PMX-DHP, direct hemoperfusion with polymixin B-immobilized fiber; SOFA, septic-related organ failure assessment; APACHE-II, acute physiology and chronic health evaluation II; CAPI, catecholamine pressure index {[(dopamine (μg·kg^{-1}·min^{-1}) + dobutamine (μg·kg^{-1}·min^{-1}) + 100·adrenaline (μg·kg^{-1}·min^{-1}) + 100·noradrenaline (μg·kg^{-1}·min^{-1})]/systolic blood pressure (mmHg)}

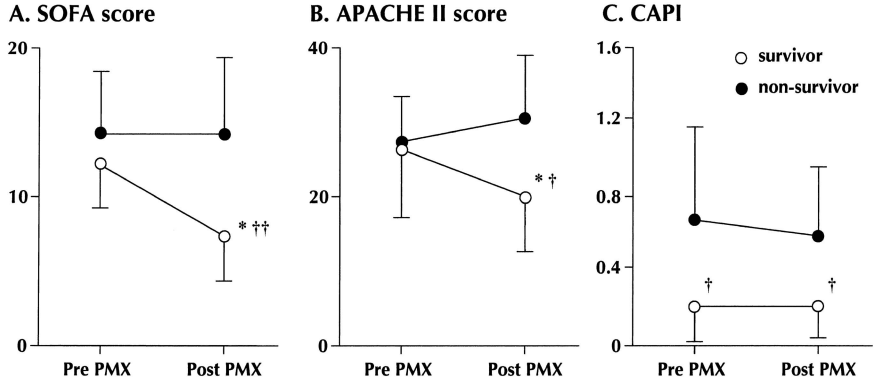

Fig. 1. The changes in the SOFA score (**A**), APACHE-II score (**B**), and CAPI (**C**) in survival and nonsurvival groups before and after PMX-DHP treatment. Data are expressed as means ± SD, and $n = 9$ and 15 in survival and nonsurvival groups, respectively. *SOFA*, sepsis-related organ failure assessment; *APACHE-II*, acute physiology and chronic health evaluation II; *CAPI*, catecholamine pressure index {[dopamine (μg·kg^{-1}·min^{-1}) + dobutamine (μg·kg^{-1}·min^{-1}) + 100·adrenaline (μg·kg^{-1}·min^{-1}) + 100·noradrenaline (μg·kg^{-1}·min^{-1})]/systolic blood pressure (mmHg)}; *PMX-DHP*, direct hemoperfusion with polymixin B-immobilized fiber; *Pre PMX*, before PMX-DHP treatment; *Post PMX*, just after PMX-DHP treatment. Although CAPI did not change by PMX-DHP treatment, both SOFA and APACHE-II scores showed significant differences between the groups after the PMX-DHP treatment ($P = 0.008$, and 0.028, respectively)

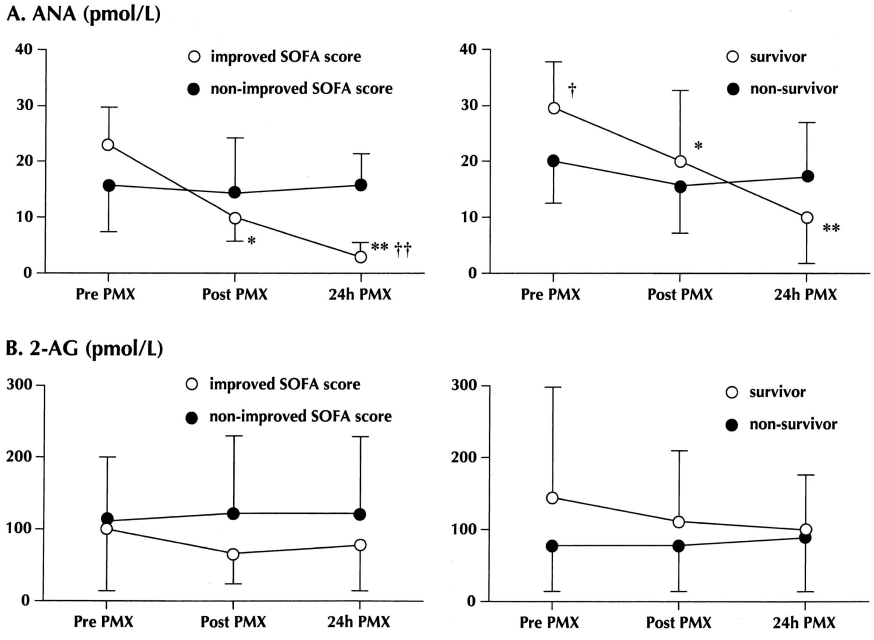

Fig. 2. The changes in plasma concentrations in cannabinoids, ANA (**A**) and 2-AG (**B**), both between improved and nonimproved SOFA score groups and between survival and nonsurvival groups during PMX-DHP treatment. *ANA*, anandamide; *2-AG*, 2-arachidonyl glyceride; 24h PMX, 24 h after PMX-DHP treatment. Although there were no characteristic changes in 2-AG values, ANA significantly decreased both in the improved SOFA score group and in the survivor group during the PMX-DHP treatment. At 24 h after PMX-DHP treatment, the plasma concentration of ANA in the improved SOFA score group was significantly higher than that in the nonimproved SOFA score group ($P = 0.005$)

not show distinct changes by the PMX-DHP treatment in any group.

Discussion

It has been widely accepted that the mechanism of progression from septic shock to multiple organ failure (MOF) is explained by an imbalance in tissue oxygen metabolism, and by the influence of various humoral mediators and toxins, for example, endotoxin, exotoxin, cytokines, and cannabinoid. Various new technologies, including plasma exchange, continuous hemofiltration, continuous hemodiafiltration, and PMX-DHP, have been reported to be useful methods for removal of these humoral mediators from blood, resulting in the improvement of prognosis [1,10,23–25].

PMX-DHP was originally developed for selective adsorption of endotoxin in patients with Gram-negative bacterial infection [1–3]. PMX-DHP treatment of severe sepsis patients has a beneficial effect on the outcome and clinical symptoms [1,8]. Polymyxin B is known to absorb not only endotoxin but also ANA, which induces hypotension during endotoxin shock [14,17,26]. We hypothesized that the mechanism of improvement in septic shock patients by PMX-DHP treatment is the reduction of blood levels of cannabinoids, important factors contributing to the induction of septic shock and influencing prognosis [12–16]. There has been no reported study of the relation between changes in plasma cannabinoid levels and clinical parameters or outcome.

In this study, in both the improved SOFA score group and the survival group, plasma ANA concentrations decreased after PMX-DHP treatment, but not in either the nonimproved SOFA score group or the nonsurvival group. It is suggested that ANA removal plays an important role in the mechanism of the acute phase PMX-DHP effect and outcome. Furthermore, from our data, this rapid decrease in ANA concentration and SOFA score improvement might also play an important part in prognosis, because the survivor group showed a significant decrease in SOFA score.

In the present study, it is still unclear why ANA was successfully removed from some patients but not from others. We speculate that uncontrollable bacterial infection contributes to the production of mediators [27]. Both removal of cytotoxic mediators and elimination of infection are key to the successful treatment of septic shock patients.

Tani et al. [28] reported that plasma endotoxins are the major cause of severe sepsis, and that reduction of their levels contributes to a decrease in mediator levels; it alleviates the clinical symptoms and abnormalities in blood pressure, body temperature, and the Pa_{O_2}/FI_{O_2} ratio associated with sepsis. In the present study, we recruited not only Gram-negative but also Gram-positive bacteria-infected septic shock patients, and there was no significant relationship between species of infecting bacteria and the effect of PMX-DHP. These results are consistent with a previous report that PMX-DHP is effective for both Gram-positive and Gram-negative bacteria-infected patients [8]. It is suggested that the main mechanism of PMX-DHP treatment is not endotoxin removal per se.

Cytokines have been thought to be involved in the induction of hemodynamic abnormalities observed in sepsis and septic shock. The presence of cytokines in the

Table 2. The changes in plasma concentrations of cytokines and CGRP during PMX-DHP treatment both in improved/non-improved SOFA score groups and in survival/nonsurvival groups

	Pre PMX	Post PMX	24h PMX
TGF-β (ng·ml^{-1})			
SOFA score			
Improved (n = 7)	15.6 ± 5.1†	12.2 ± 4.6*†	12.0 ± 5.4
Nonimproved (n = 17)	18.1 ± 9.0	15.1 ± 7.2*	12.6 ± 4.6**
Survival at 28 days			
Survival (n = 9)	12.1 ± 2.5†	9.5 ± 1.2*†	8.6 ± 3.1†
Nonsurvival (n = 15)	18.8 ± 8.5	16.8 ± 9.2	14.2 ± 3.8*
IL-6 (pg·ml^{-1})			
SOFA score			
Improved (n = 7)	395 ± 287	362 ± 365	215 ± 326
Nonimproved (n = 17)	435 ± 224	401 ± 215	285 ± 345
Survival at 28 days			
Survival (n = 9)	215 ± 256†	198 ± 289†	136 ± 254†
Nonsurvival (n = 15)	442 ± 221	408 ± 225	308 ± 298
IL-8 (pg·ml^{-1})			
SOFA score			
Improved (n = 7)	213 ± 156	186 ± 142	175 ± 125
Nonimproved (n = 17)	251 ± 123	243 ± 115	235 ± 142
Survival at 28 days			
Survival (n = 9)	185 ± 112†	162 ± 129†	129 ± 125††
Nonsurvival (n = 15)	300 ± 156	308 ± 125	304 ± 45
IL-10 (pg·ml^{-1})			
SOFA score			
Improved (n = 7)	85 ± 54†	52 ± 42†	68 ± 51
Nonimproved (n = 17)	325 ± 185	154 ± 54**	64 ± 21**
Survival at 28 days			
Survival (n = 9)	128 ± 101	89 ± 54	95 ± 75
Nonsurvival (n = 15)	168 ± 187	129 ± 108	115 ± 187
CGRP (ng·ml^{-1})			
SOFA score			
Improved (n = 7)	92 ± 112	84 ± 97	62 ± 65
Nonimproved (n = 17)	80 ± 88	85 ± 89	88 ± 102
Survival at 28 days			
Survival (n = 9)	54 ± 54	58 ± 80	56 ± 64
Nonsurvival (n = 15)	89 ± 131	78 ± 88	76 ± 100

Data are expressed as means ± SD.
TGF, transforming growth factor; IL, interleukin; CGRP, calcitonin gene-related peptide; Pre PMX, before PMX-DHP treatment; Post PMX, just after PMX-DHP treatment; 24h PMX, at 24 h after PMX-DHP treatment
* $P < 0.05$; ** $P < 0.01$ versus values before PMX-DHP treatment, $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ versus values at the same points in nonimproved or nonsurvival group.

circulation is often considered to be the tip of the iceberg, and for this reason cytokine removal influences only a small fraction of the abnormalities, and is therefore not considered clinically relevant [29]. As shown in our data (Table 2), some cytokines levels in the nonsurvival group were higher than in the survival group, but the relationship between cytokine level and PMX-DHP is not clear, suggesting that these cytokines play important roles in the clinical condition or outcome of septic shock patients, although cytokine removal is not the direct mechanism of the PMX-DHP effect.

CGRP is an intrinsic peptide that is colocalized in sensory nerve endings and acts as a neurotransmitter in nonadrenergic, noncholinergic vasodilator nerves scattered throughout most arterial beds, including heart, kidney, mesenteric, and skeletal muscle vessels [30]. CGRP has also been reported to be an important mediator of hypotension in sepsis and septic shock [31], and to be involved in the pathogenesis of sepsis [32]. In the present study, there was no significant relationship between CGRP concentration and outcome (Table 2). These results suggest that CGRP is not a main or direct mechanism of the PMX-DHP effect on septic shock.

In conclusion, ANA, an intrinsic cannabinoid that induces hypotension in septic shock, is inferred to be the main mechanism of the PMX-DHP effect. Removal of

ANA as well as the control of bacterial infection is key to successful septic shock treatment.

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