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Direct Hemoperfusion Using Polymyxin-B Immobilized Fiber for Septic Shock After Cardiac Surgery

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Background: The factors contributing to the efficacy and outcome of direct hemoperfusion using polymyxin-B immobilized fiber (PMX-DHP) after cardiac surgery were investigated.

Methods and Results: In 23 patients who received PMX-DHP for shock related to infection after cardiac surgery, there were no differences in the pre- and intraoperative clinical data of survivors (n=14) and non-survivors (n=9). Before the PMX-DHP treatment, the clinical assessment values of the survivors and non-survivors, respectively, showed the following significant differences: sepsis-related organ failure assessment score, 9.46±2.84 vs 12.89±3.37 (P<0.05); number of failed organs, 1.8±0.9 vs 3.1±1.1 (P<0.05); partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio, 194±118 vs 102±29 (P<0.05); and total bilirubin, 2.7±2.8 vs 8.7±6.5 mg/dl (P<0.05). The systolic blood pressure and catecholamine index in the survivors improved significantly 12 h after PMX-DHP treatment, from 83±19 mmHg to 118±14 mmHg (P<0.01), and from 20.7±11.5 to 14.9±8.0 (P<0.05). Conversely, in the non-survivors, only the systolic blood pressure improved significantly, from 74±17 mmHg to 118±33 mmHg (P<0.001).

Conclusions: Prompt initiation of PMX-DHP with drug treatment during the postoperative course of patients with septic shock caused by systemic inflammatory response syndrome related to infection and who are refractory to vasopressor treatment, can improve the disease state before multiple organ failure develops. (*Circ J* 2009; **73:** 658–661)

Key Words: Hemodynamics; Infection; Inflammation; Shock; Surgery

Endotoxin adsorption treatment (direct hemoperfusion using polymyxin-B immobilized fiber: PMX-DHP) was first described in 1994[1] and is now performed in many institutions. At present, PMX-DHP is generally used to treat severe sepsis and improve survival rates, but there are few reports that describe its use after cardiac surgery. We reported previously that PMX-DHP dramatically improved the hemodynamics of patients with systemic inflammatory response syndrome (SIRS; severe shock defined as systolic blood pressure (BP) <80 mmHg) caused by postoperative infection and who were unresponsive to a vasopressor[2] In the present study, we investigated the factors contributing to the efficacy and outcome of PMX-DHP instituteded after cardiac surgery.

Methods

Patients

The subjects of this study were 23 patients who suffered severe septic shock caused by SIRS precipitated by infection after cardiac surgery performed under extracorporeal circulation between November 2001 and March 2006. There were 14 survivors, who were discharged from hospital, and 9 non-survivors, who died during hospitalization. The survivor group comprised 5 patients who underwent aortic surgery, 5 who underwent coronary artery bypass grafting (CABG), 3 who underwent valve replacement, and 1 who underwent repair of a cardiac rupture. Of these 14 patients, 6 underwent emergency surgery and 1 was treated with hemodialysis (HD) for chronic renal failure. The non-survivors comprised 2 who underwent aortic surgery, 3 who underwent CABG, 3 who underwent valve replacement, and 1 who underwent resection of a cardiac tumor. Of these 9 patients, 2 underwent emergency surgery and 2 were treated with HD for chronic renal failure (**Table 1**).

PMX-DHP comprised a direct blood perfusion at 80–100 ml/min, using a polymyxin B immobilization column (TORAYMYXIN Toray Co, Tokyo, Japan), for periods

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Table 1. Operative Data

	Survivors	Non-survivors
Aortic disease	5	2
Coronary disease	5	3
Valvular disease	3	3
Cardiac rupture	1	0
Cardiac tumor	0	1
Total	14	9
Emergency surgery	6/14	2/9
Pre-existing renal failure (CHD)	1/14	2/9

CHD, chronic hemodialysis.

Table 2. Background Clinical Data Before PMX-DHP

	Survivors	Non-survivors	P value
Age (years)	63.4±13.6	69.7±2.7	0.112
Operation time (min)	632.7±345.7	655.3±493.2	0.908
ECC time (min)	263.9±151.5	266.9±176.2	0.967
PMX-DHP performed (POD)	10.4±5.5	10.9±6.0	0.855
Shock state before PMX-DHP (h)	6.2±4.6	11.9±12.6	0.227
PMX-DHP time (min)	260.5±319.1	430.6±451.1	0.343
SOFA score	9.46±2.84	12.89±3.37	0.03
No. of failed organs	1.8±0.9	3.1±1.1	0.018
Body temperature (°C)	37.8±1.4	37.2±0.9	0.21
P/F ratio	194±118	102±29	0.014
Heart rate (beats/min)	110±17	104±20	0.45
Systolic blood pressure (mmHg)	83±19	74±16	0.23
CaI	20.7±11.5	23.2±8.6	0.56
pH	7.39±0.07	7.40±0.05	0.55
Hematocrit (%)	28.0±4.5	26.9±6.7	0.67
Platelet count (10^{10}/L)	17.2±16.1	15.7±17.4	0.85
Leukocyte count (10^6/L)	17,938±9,811	12,832±6,111	0.14
C-reactive protein (mg/dl)	22.5±7.8	23.3±8.9	0.83
Total bilirubin (mg/dl)	2.7±2.8	8.7±6.5	0.027
Creatinine (mg/dl)	2.1±1.6	2.6±1.6	0.53
Sodium (mmol/L)	135.1±4.6	133.6±4.0	0.39
Potassium (mmol/L)	4.7±0.8	4.9±1.0	0.56

PMX-DHP, direct hemoperfusion using polymyxin-B immobilized fiber; SOFA score, Sepsis-related organ failure assessment score (excluding the Glasgow Coma Score for most patients under sedation); P/F ratio, partial pressure of oxygen in arterial blood/fraction of inspired oxygen ratio; CaI, catecholamine index.

Table 3. Clinical Data Before and After PMX-DHP Therapy in Survivors and Non-Survivors

	Before PMX-DHP	After PMX-DHP	P value
Survivors			
SOFA score	9.46±2.84	8.69±3.32	0.14
Failure organs (n)	1.8±0.9	1.5±1.3	0.08
Body temperature (°C)	37.8±1.4	36.9±0.7	0.035
P/F ratio	194±118	233±147	0.067
Heart rate (beats/min)	110±17	104±11	0.038
Systolic blood pressure (mmHg)	83±19	118±14	<0.01
CaI	20.7±11.5	14.9±8.0	0.012
pH	7.39±0.07	7.40±0.07	0.58
Hematocrit (%)	28.0±4.5	28.5±2.5	0.58
Platelet count (10^{10}/L)	17.2±16.1	17.4±14.9	0.06
Leukocyte count (10^6/L)	17,938±9,811	16,736±9,843	0.34
C-reactive protein (mg/dl)	22.5±7.8	22.2±8.3	0.87
Total bilirubin (mg/dl)	2.7±2.8	2.9±3.1	0.49
Creatinine (mg/dl)	2.1±1.6	2.1±1.6	0.69
Sodium (mmol/L)	135.1±4.6	136±4.4	0.3
Potassium (mmol/L)	4.7±0.8	4.6±1.0	0.76
Non-survivors			
SOFA score	12.89±3.37	12±3.04	0.035
Failure organs (n)	3.1±1.1	2.9±1.1	0.17
Body temperature (°C)	37.2±0.9	36.2±0.7	<0.01
P/F ratio	102±29	138±73	0.09
Heart rate (beats/min)	104±20	101±22	0.41
Systolic blood pressure (mmHg)	74±16	118±33	<0.01
CaI	23.2±8.6	20.8±7.2	0.08
pH	7.40±0.05	7.39±0.06	0.39
Hematocrit (%)	26.9±6.7	25.9±4.1	0.48
Platelet count (10^{10}/L)	15.7±17.4	14.6±16.0	0.17
Leukocyte count (10^6/L)	12,832±6,111	13,196±5,207	0.8
C-reactive protein (mg/dl)	23.3±8.9	21.9±9.3	0.56
Total bilirubin (mg/dl)	8.7±6.5	10.3±8.0	0.06
Creatinine (mg/dl)	2.6±1.6	2.6±1.6	0.59
Sodium (mmol/L)	133.6±4.0	135.0±4.2	0.29
Potassium (mmol/L)	4.9±1.0	4.6±0.9	0.16

Abbreviations see in Table 2.

Table 4. SVR and CO Before and After PMX-DHP Therapy

	Before PMX-DHP	After PMX-DHP	P value
SVR (dynes·s^{-1}·cm^{-5})	835.5±418.8	1,004.1±323.2	0.033
CO (L/min)	5.5±1.6	5.6±1.3	0.89

SVR, systemic vascular resistance; CO, cardiac output. Other abbreviation see in Table 2.

ranging from 90 to 1,350 min (327±376 min). We gave nafamostat mesilate as an anticoagulant and maintained the activated clotting time within the range of 180–220 s. We defined life-support devices as percutaneous cardiopulmonary support (PCPS), intra-aortic balloon pumping, continuous hemodiafiltration (CHDF), and HD, and organ failure as a sepsis-related organ failure assessment (SOFA) score of 3 or higher. We defined the catecholamine index (CaI) as the total gamma dosage of dopamine and dobutamine and 100-fold the gamma dosage of adrenaline and noradrenaline. The amounts of catecholamine were compared as the CaI. We compared the patients' age at operation, operation time, extracorporeal circulation time, postoperative course days, PMX-DHP induction time from the beginning of the severe shock state (defined as systolic BP <80 mmHg), the PMX-DHP time, and the number of life-support devices in each group.

We also compared the SOFA score, excluding the Glasgow Coma Score, for most patients under sedation, the number of failed organs, body temperature, partial pressure of oxygen in the arterial blood/fraction of inspired oxygen ratio (P/F ratio), pH, leukocyte count, C-reactive protein (CRP), hematocrit, platelet count, total bilirubin, creatinine, heart rate, systolic BP, and CaI, immediately before, and 12 h after the PMX-DHP therapy. In those patients who were treated with PMX-DHP more than once, we only studied the data from the first time that PMX-DHP was given. We compared systemic vascular resistance and cardiac output, before and after PMX-DHP, in 12 patients (11 survivors and 1 non-survivor) who had a Swan-Ganz catheter inserted.

Statistical Analysis

All values are expressed as means±standard deviation (SD). For normally distributed data, a paired or an unpaired t-test was used. Analyses were performed using the statistical software, Statview 5.0 (SAS Institute, Inc, Cary, NC, USA). A P-value less than 0.05 was considered significant.

Results

There were no significant differences between the survivors and non-survivors in the background factors, age, operation time, extracorporeal circulatory time, postoperative days, PMX-DHP time, time from shock to PMX-DHP induction, or the number of life-support devices (**Table 2**). Just before PMX-DHP was initiated, there were significant differences between the survivors and non-survivors in the SOFA score (9.46±2.84 vs 12.89±3.37; P=0.030, P<0.05, respectively), number of failed organs (1.8±0.9 vs 3.1±1.1; P=0.018, P<0.05), P/F ratio (194±118 vs 102±29; P=0.014, P<0.05), and total bilirubin value (2.7±2.8 mg/dl vs 8.7±6.5 mg/dl; P=0.027, P<0.05). There were no significant differences in body temperature, pH, leukocyte count, CRP, hematocrit, blood platelet, creatinine, heart rate, systolic BP or CaI (**Table 2**).

By 12 h after PMX-DHP, the survivors showed significant improvement in their heart rate (from 110±17 beats/min to 104±11 beats/min; P=0.038, P<0.05), systolic BP (from 83±19 mmHg to 118±14 mmHg; P=1.85E-05, P<0.001), CaI (from 20.7±11.5 to 14.9±8.0; P=0.012, P<0.05), and body temperature (**Table 3**). Non-survivors showed significant improvement in the SOFA score (from 12.89±3.37 to 12±3.04; P=0.035, P<0.05), systolic BP (from 74±17 to 118±33 mmHg; P=0.99E-03, P<0.001), and body temperature, but not in CaI (**Table 3**). In 12 patients whose cardiac index and systemic vascular resistance were measured before and after PMX-DHP therapy, the cardiac index did not improve, whereas systemic vascular resistance improved significantly (from 835.5±418.8 dynes·s^{-1}·cm^{-5} to 1,004.1±323.2 dynes·s^{-1}·cm^{-5}; P<0.05) (**Table 4**). Blood cultures were performed for 13 blood samples: 9 from survivors and 4 from non-survivors: 3 samples were positive for *Acinetobacter baumannii* in 2, and for *Staphylococcus epidermidis* in 1.

Discussion

Despite remarkable advances in intensive care, the mortality rate associated with septic shock remains high.[3] PMX-DHP is a form of blood purification therapy, initially developed to adsorb blood endotoxins in serious infectious disease states caused by Gram-negative bacteria. Since Aoki et al's report in 1994,[1] PMX-DHP has been used increasingly in Japan for sepsis and septic shock caused by Gram-negative bacterial infections. The adsorption of endotoxin by the polymyxin-B immobilized fiber improves the hemodynamics and prognosis of these patients, but there have been cases of no relationship being found between the endotoxin value and clinical hemodynamics, suggesting the possibility of another mediator. There is also a report of this treatment being used effectively for Gram-positive bacterial infections.[4] Currently, PMX-DHP is initiated to achieve hemodynamic improvement when SIRS caused by infection is diagnosed, regardless of the causative organism. Various theories have been proposed to explain the mechanism of this disease process, and although a consensus has not been reached, it is assumed that a cannabinoid, such as anandamide (ANA), released by monocytes, as well as macrophages, and 2-arachidonyl glycerol (2-AG) produced by the platelets, are all mediators leading to the shock state induced by Gram-negative bacterial infections.[5] In turn, these mediators induce cytokines such as TNF-α and IL-1, resulting in the release of high-mobility group box 1 (HMGB-1), which is a lethal mediator. PMX-DHP adsorbs the early mediators such as ANA and 2-AG, and the patient's hemodynamics improve in proportion to the absorbed quantity.[6] On the other hand, in a Gram-positive bacterial infection, macrophages pass through a toll-like receptor 2 and are stimulated to produce ANA, which causes hypercytokinemia;[7] in other words, most of the mechanism is shared with that of the endotoxin shock caused by Gram-negative bacterial infection. When the SIRS state caused by infection is diagnosed, it is not necessary to identify the causative organism before initiat-

ing PMX-DHP. In the past, antiinflammatory drug therapies for septic shock failed to consistently improve the prognosis[8] PMX-DHP decreases the blood levels of cytokines and improves hemodynamics[9] so PMX-DHP not only removes endotoxin, but also other cytokines and thus improves the hemodynamics of patients with septic shock. There are many reports of improved clinical symptoms and outcome achieved by PMX-DHP therapy in the septicemic patient,[10] but without clear evidence of its efficacy. A recent pilot study showed that PMX-DHP improved the left ventricular stroke work index;[11] providing further evidence that PMX-DHP improves the hemodynamics of patients in septic shock. Hemocatharsis therapy plays 2 roles in the treatment of sepsis: supporting failing organs such as the kidneys, and treating the disease state itself. The 3 methods of mediator removal are PMX-DHP, high-volume hemofiltration, and plasma exchange. In the present cases, we chose PMX-DHP primarily because it improves the disease state by mediator removal, inducing an immediate effect with simple priming.

We diagnosed SIRS caused by postoperative infection in patients unresponsive to vasopressors and instituted PMX-DHP to improve their hemodynamics. Our findings showed clearly that PMX-DHP improved the systolic BP significantly in both the survivors and non-survivors, but reduced the catecholamine level only in the survivors. Ultimately, the results of PMX-DHP were either effective (survival) or ineffective (death), according to differences in the patients' general condition before the initiation of PMX-DHP. Moreover, significant differences were noted between survivors and non-survivors in the SOFA score, the number of failed organs, the P/F ratio, and the total bilirubin concentration. We believe that these differences affected the efficacy of PMX-DHP and the prognosis. There were no significant differences in the platelet count, BP or creatinine levels, so initiating PMX-DHP before lung and liver dysfunction occurs is important for optimizing its efficacy and improving the patient's prognosis. In the 12 patients whose cardiac output and systemic vascular resistance were measured, the cardiac output did not improve, but the systemic vascular resistance improved significantly 12 h after PMX-DHP was initiated. Therefore, we consider that PMX-DHP improves the hemodynamic status not by increasing the cardiac output, but by enhancing systemic vascular resistance. PMX-DHP is an effective radical treatment for septic shock. However, although it was reported that PMX-DHP improved lung function in acute lung injury and acute respiratory distress syndrome,[12] and renal function in combination with CHDF in acute renal failure,[13] those effects were not observed in the present study.

In conclusion, depressed cardiac function resulting from cardiac disturbance during cardiac surgery can easily evolve into multiple organ failure. Therefore, if SIRS related to postoperative infection results in shock that is refractory to vasopressor treatment, PMX-DHP must be initiated with drug treatment before lung and liver dysfunction progresses, in order to achieve optimum efficacy for improving the patient's hemodynamic status and reducing the catecholamine level.

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