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The Efficacy of Endotoxin Adsorption for Sepsis after Emergency Operations

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Circulating endotoxin in the blood is considered to be a serious pathogenic factor for septic shock and multiple systemic failure. We have been treating septic patients using blood purification cartridges which consist of polymyxin B immobilized (PMX-20R) to eliminate endotoxin from the blood circulation. We surveyed blood pressure, cardiac index (CI), systemic vascular resistance index (SVRI), oxygen delivery ($\dot{D}O_2$), oxygen consumption ($\dot{V}O_2$), oxygen extraction ratio (O_2ER) and concentration of endotoxin in the blood, before and after PMX-20R therapy for 25 septic surgical patients after emergency operation. The blood pressure, CI and SVRI showed statistically significant differences before and after PMX-20R, but $\dot{D}O_2$, $\dot{V}O_2$ and O_2ER and the concentration of endotoxin did not. Further, comparing survivors with non survivors, SVRI had increased in the former but not in the latter. For septic patients, the adsorption of endotoxin is very efficacious to improve the circulatory state after the elimination of this procedure, when the operation is performed immediately. The optimal time is at the hyperdynamic state, at the beginning of the fall in SVRI, because its increase plays a part in elevating the blood pressure.

Introduction

Sepsis is still, even now, a life-threatening complication and a major cause of death in the Intensive Care Unit. It is caused by endotoxin which is a cell-wall component of gram-negative bacteria. Circulating endotoxin in the blood is considered to be a serious pathogenic factor for septic shock and multiple organ dysfunction syndrome. In spite of the full uses of potent antibiotics and artificial supports which are continuous hemodiafiltration (CHDF) and plasma exchange (PEX)[1)2)] in critical care cases, the mortality remains high among patients with sepsis and gram-negative bacteremia. To eliminate endotoxin from the blood circulation, we currently have been treating sepsis with direct hemoperfusion (DHP) using a polymyxin B immobilized fiber column, called PMX-20R[3)].

Polymixin B has long been known to neutralize the various biologic activities of endotoxin, but it could hardly be used clinically because of its nephrotoxic side effect. PMX is bound by its amino group to alpha-chloracetamide-methyl polystyrene fibers. But biological and chemical examinations revealed no release of PMX-20R from its carrier.

In the present paper we report the efficacy, especially the improvement of the circulatory state, of PMX-20R on sepsis after emergency operations without side-effects.

Patients and Methods

Patients

There were 25 sepsis cases using PMX-20R after emergency operation in our intensive care unit of Tokyo Women's Medical University

Hospital, 15 males and 10 females whose mean age was 61.4 ± 6 years old, ranging from 21 to 89 years. Their were 6 patients with perforation of colon cancer, 5 with strangulated ileus, 3 with acute gangrenous cholecystitis, 3 with superior mesenteric artery obstruction, 3 with perforation of colonic diverticulitis and 1 each with acute pancreatitis, liver abscess, perforation of esophagus, perforation of small intestine, and rupture of duodenal varix. Ten surviving patients, of the total 25, were discharged from our hospital and 15 patients died. The mortality rate was 60% (Table 1).

Our indication for PMX-20R therapy is when endotoxemia, gram-negative bacteremia, systemic inflammatory response syndrome (SIRS), and septic shock needing a vasoactive agent but without severe liver dysfunction (Table 2).

Table 1 Patient characteristics

Sex:	male/female=15/10	cases
Diagnosis:	Perforation of colon cancer	6
	Strangulated ileus	5
	Acute gangrenous cholecystitis	3
	SMA thrombosis	3
	Perforation of colon diverticulitis	3
	Others	5
	acute pancreatitis, liver abscess, perforation of esophagus, perforation of small intestine, rupture of duodenal varix	

Table 2 Indication of PMX-20R

1. Endotoxemia or
   infection of gram-negative bacteremia
2. a) Body temperature: >38°C or <36°C
   b) Heart rate: >90 beats/min
   c) Respiratory rate: >20 times/min or
   $PaCO_2$: <32 mmHg
   d) WBC >12,000/μl or <4,000/μl
   or rods of neutrophils >10%
3. Septic shock patients needing vasoactive drugs except in severe liver dysfunction

Table 3 Methods

DHP (direct hemoperfusion) : 2 hrs, flow rate 100 ml/min
Blood access: via femoral vein double-lumen catheter
Anti coagulant: Nafamostat mesilate (30~40 mg/hr)
Laboratory items:
1) Hemodynamic state
   MAP, CI, SVRI
2) Tissue metabolism
   VO_2, DO_2, O_2ER,
3) Bacteriological examination
   Endotoxin concentration
   Pathogenic microorganism in the blood

Methods

Direct hemoperfusion (DHP) using PMX-20R was performed with a double-lumen catheter inserted into the femoral vein by the Seldinger method. DHP was carried out for 2 hours at a flow rate of 100 ml/min with 30~40 mg/hr nafamostat mesilate as an anti-coagulants (Table 3).

Laboratory items

We surveyed the hemodynamic state and tissue oxygen metabolism, and performed bacteriological examination to estimate the value of PMX-20R therapy.

Hemodynamic state: We measured as circulatory parameters; the mean arterial blood pressure (MAP), cardiac index (CI), and systemic vascular resistance index (SVRI) using the Swan-Ganz catheter method both before and after therapy.

Tissue-oxygen metabolism: We evaluated metabolism of tissue-oxygen both before and after PMX-20R therapy using the Swan-Ganz catheter method meaning at the oxygen consumption ($\dot{V}O_2$), oxygen delivery ($\dot{D}O_2$) and oxygen extraction ratio (O_2ER).

Bacteriological examination: We also surveyed the blood concentration of endotoxin by the endospecy with the perchloric acid (PCA) and Toxicolor methods[4].

Statistical analysis

Values were expressed as the mean ± standard deviation. Significant differences were analyzed by the Student's t-test and differences were considered significant when $p<0.05$.

Results

Hemodynamic state

In 10 surviving patients, the mean arterial pressure increased significantly from 86 ± 8 mmHg at pretreatment to 100 ± 8 mmHg at

the end of PMX treatment. In 15 patients who died, the pressure decreased from 92 ± 8 to 83 ± 7 mmHg after the treatment, but there was no statistically significant change (Fig. 1).

The pretreatment CI formed the basis for dividing the patients into the hypodynamic shock group (<3.0 l/min/m²), the normodynamic shock group (3.0 to 5.0 l/min/m²), and the hyperdynamic shock group (>5.0 l/min/m²). In 7 patients in a hypodynamic state, the mean value increased significantly from the pretreatment level of 2.6 ± 0.05 to 3.2 ± 0.2 l/min/m². In 5 patients with a normal CI, the mean value changed from 4.4 ± 0.1 to 4.2 ± 0.1 l/min/m² but not significantly. In 5 patients in a hyperdynamic state, the mean value decreased significantly from 7.6 ± 0.5 to 6.6± 0.3 l/min/m² (Fig. 2).

SVRI in 10 surviving patients, increased significantly from the pretreatment value of 1546.2 ± 202.0 to 2268.2 ± 329.0 dyn • sec/m² cm⁵ after the treatment. But in 15 patients who died it changed from 1760.3 ± 120.0 vs 1796 ± 982.2 dyn•sec/m²cm⁵, but not significantly (Fig. 3).

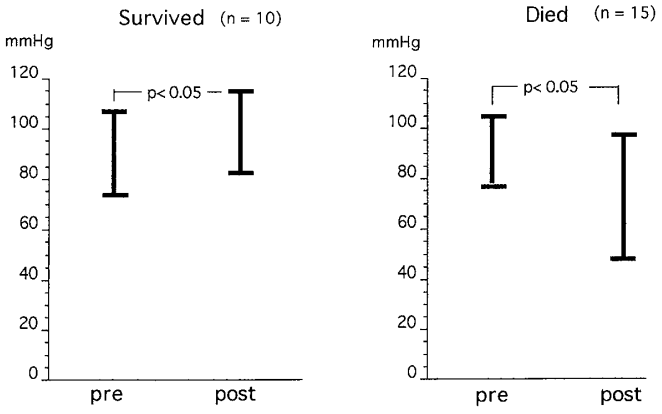

Fig. 1 Changes in mean arterial pressure (MAP, mmHg) in survivors (left) and non-survivors (right)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

Tissue metabolism

The oxygen consumption ($\dot{V}O_2$) and delivery ($\dot{D}O_2$) did not change in the surviving patients, neither before nor after the treatment (Fig. 4).

Neither did the oxygen consumption or oxygen delivery change significantly in the patients who died (Fig. 5).

$\dot{V}O_2$ in those who survived changed from 232.9 ± 245.6 to 205 ±218.6 ml/min/m and that in those who died changed from 105.34 ± 25.38 to 134.30 ± 24.69 ml/min/m. On the other hand, $\dot{D}O_2$ in the survivors changed from 387.1 ± 246.9 to 351.5 ± 222.3 ml/min/m, while the change in those who died from 474.35 ± 168.7 to 500.3 ± 167.5 ml/min/m.

The oxygen extraction ratio, in 10 surviving patients increased from 0.17 ± 0.01 to 0.24 ± 0.01 to normal range after the treatment, but it was not statistically significant. Nor did the ratio change significantly in 15 patients who died from 0.42 ± 0.01 vs 0.43 ± 0.01 (Fig. 6).

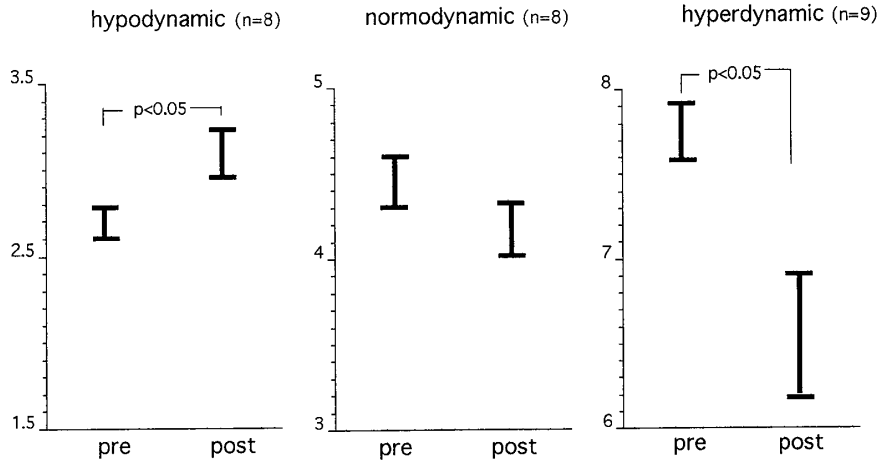

Fig. 2 Changes in cardiac index (CI, l/min/m²)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

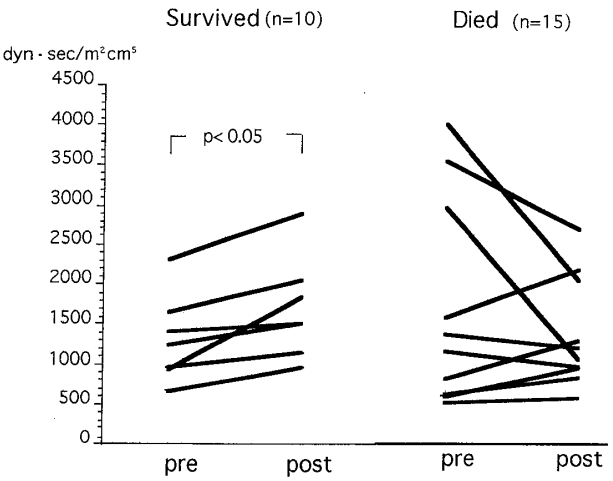

Fig. 3 Changes in systemic vascular resistance index (SVRI, dyn • sec/m²cm⁵)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

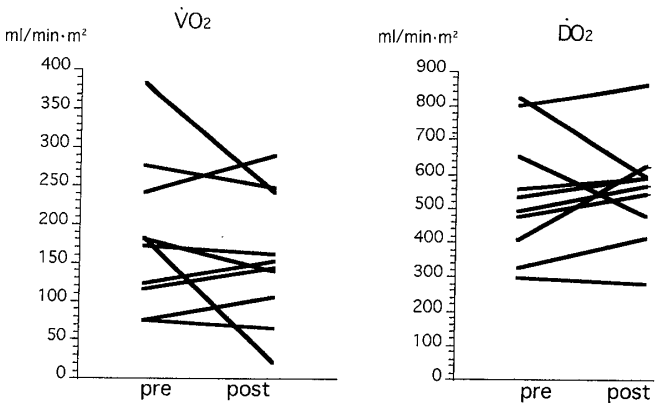

Fig. 5 O_2 consumption ($\dot{V}O_2$) and delivery ($\dot{D}O_2$) and delivery ($\dot{D}O_2$) in died 15 patients (ml/min • m²)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

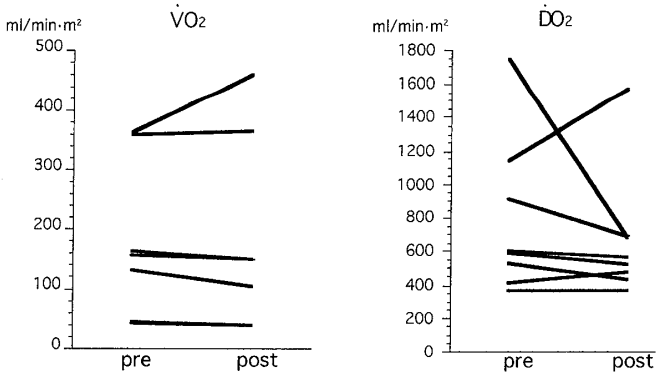

Fig. 4 O_2 consumption ($\dot{V}O_2$) and delivery ($\dot{D}O_2$) in survived 10 patients (ml/min • m²)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

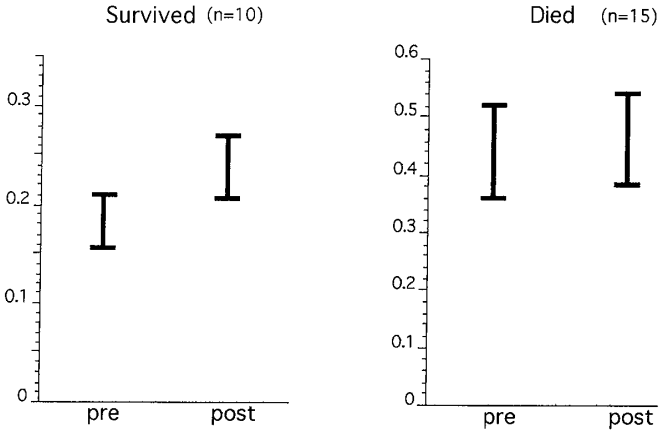

Fig. 6 Changes of O_2 extraction ratio (O_2ER) in survivors (left) and non-survivors (right)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

Bacteriological examination

The endotoxin levels in patients' blood were determined by the endospecy method with PCA (perchloric acid) and by the toxicolor method before and after the treatment. In neither the surviving patients nor those who died, did the toxicolor method reveal a significant change in the mean concentration.

In the surviving patients, the concentration of endotoxin decreased from 31.72 ± 24.25 to 23.96 ± 17.28 pg/ml, but not statistically significant. Also in those who died, endotoxin concentration decreased from 15.74 ± 6.58 to 11.42 ± 7.37 pg/ml, but it was not statistically significant (Fig.7). The endospecy method did not reveal any change. There were changes from 1.41 ± 0.70 to 1.45 ± 0.62 pg/ml in the survivors and in those who died from 1.51 ± 0.55 to 1.64 ± 1.10 pg/ml by endospecy methods (Fig.8).

The detected microorganisms in the blood were gram-negative bacilli in 41% of the patients, mixed infection which were gram-negative and methicillin-resistant *Staphylococcus aureus* or candida, in 29% and gram-positive cocci in 18%. No growth was observed in 12% (Fig. 9).

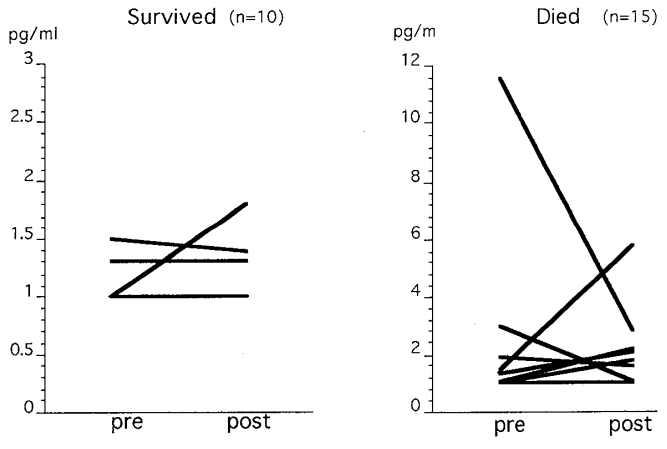

Fig. 7 Endodtoxin concentration in blood (endospecy methods, pg/ml)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

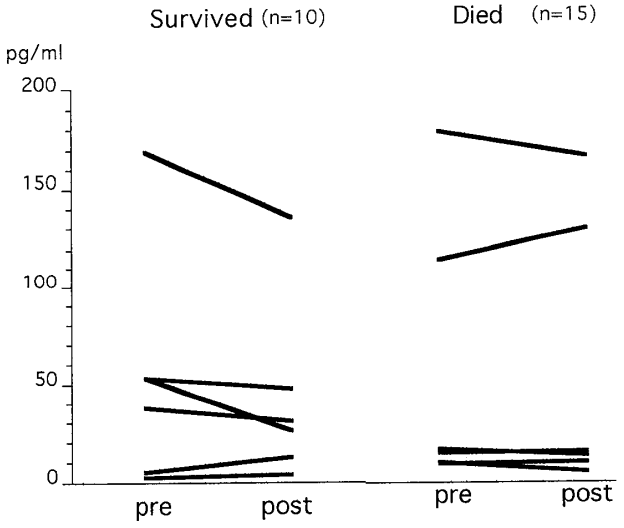

Fig. 8 Endotoxin concentration in blood (Toxicolor methods, pg/ml)
Results are expressed as mean ± SD, pre and post treatment of PMX-20R.

Discussion

We have been treating septic patients using PMX-20R to eliminate endotoxin from the blood circulation. We surveyed following both before and after the therapy;

1. MAP, CI and SVRI,
2. $\dot{V}O_2$, $\dot{D}O_2$ and O_2ER and
3. The concentration of endotoxin and pathogenic bacteria in the blood in 25 septic surgical patients, after emergency operations. Both MAP, CI and SVRI showed statistically significant improvement after the treatment; but $\dot{V}O_2$, $\dot{D}O_2$, O_2ER and concentration of endotoxin did not. A method of measuring endotoxin concentration has not yet been established[4], therefore, it could increase after treatment in some patients depending on the clinical course[5]. But PMX-20R treatment markedly alleviated symptoms of septic shock. The efficacy rate afforded by PMX-20R treatment was 40%, it was still effective at a much later stage when patients did not respond to other therapeutic methods; moreover, the survival rate was much higher than that reported in other conventional treatments[6].

Recently, antilipopolysaccharide antibody treatments have been developed, and the effects of the administration of various types of anti bodies in large-scale clinical studies were reported. However, in these reports, the improvement in the clinical findings that were clearly due to endotoxin have not been demonstrated. For sepsis, the adsorption of endotoxin (PMX-20R)

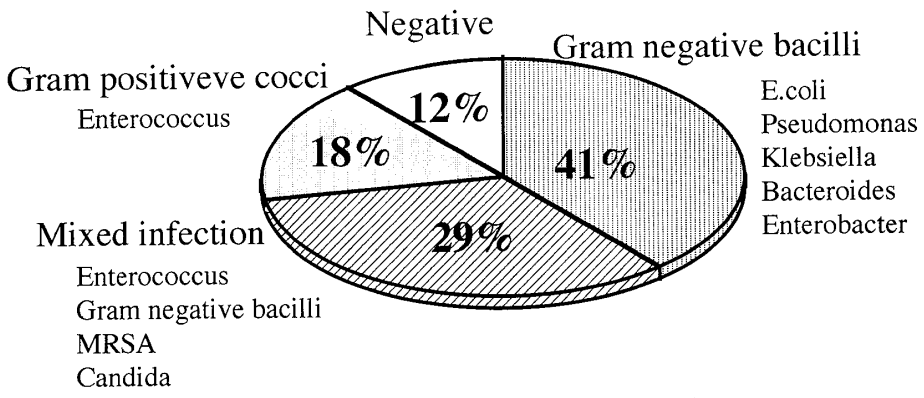

Fig. 9 Pathogenic bacteria in the blood

is very efficacious to improve the circulatory state after the elimination of the original focus, when the operation is performed immediately. PMX-20R can not be used to treat sepsis until of this procedure septic focus is eliminated by surgical drainage or antibiotics. The optimal time is at the hyperdynamic state, the beginning of the fall in SVRI, because its increase directly affects that in the blood pressure[7].

Conclusion

1. We treated 25 septic patients with PMX-20R after emergency operations.
2. MAP and SVRI showed significant differences before and after therapy.
3. For sepsis, the adsorption of endotoxin is very efficacious to improve the circulatory state.
4. The best time is especially at the beginning of the fall in SVRI, because its increase affects that of the blood pressure.

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敗血症症例における緊急手術後のエンドトキシン吸着療法の有用性について

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敗血症症例における緊急手術後のエンドトキシン吸着除去療法の有用性について検討した．対象は，当科ICUに入院し，SIRS（systemic inflammatory response syndrome)の診断基準で敗血症と診断され，緊急手術後にエンドトキシン吸着除去療法を施行した全25症例である．対象症例に対し，エンドトキシン吸着除去療法前後におけるスワンガンツカテーテルによる循環動態（平均血圧MBP，全末梢血管抵抗係数SVRI，心係数CI），酸素消費量（$\dot{V}O_2$），酸素供給量（$\dot{D}O_2$），酸素摂取率（O_2ER）および血中エンドトキシン濃度（エンドスペシー法，トキシカラー法）を測定し，その有用性について検討した．25症例の平均年齢は61.4歳，男性15例，女性10例であった．25例中15例が死亡し死亡率は60％であった．

1) 循環動態では，吸着前後の平均血圧は，生存例では上昇したが，死亡例では低下した．心係数は，hypodynamic stateの症例では有意に上昇したが，hyperdynamic stateの症例では減少した．全末梢血管抵抗は，生存例で有意に上昇したが，死亡例では変化が認められなかった．

2) 組織酸素代謝では，生存例，死亡例のいずれも有意な変化は認められなかった．

3) 血中エンドトキシン濃度は，エンドスペシー法およびトキシカラー法のいずれの測定でも統計学上，有意な変化はなかった．エンドトキシン吸着除去療法の前後において，血中のエンドトキシン濃度の変化は認められなかったが，測定法の問題と考えられる．一方，平均血圧，全末梢血管抵抗係数の有意な増加が認められ，循環動態の改善にエンドトキシン吸着除去療法は有用と思われた．血圧の改善に末梢血管抵抗の上昇が関与しており，エンドトキシン吸着除去療法は，敗血症患者に対し，原疾患に対する手術後で末梢血管抵抗が低下し始める早期に施行するのが最も望ましいと考えられる．