Hemapheresis

Clinical effects of direct hemoperfusion using a polymyxin-B immobilized column in solid organ transplanted patients with signs of severe sepsis and septic shock. A pilot study

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ABSTRACT: Background: Polymyxin B (PMX-B) is a polycationic antibiotic, known to bind the lipid A portion of endotoxin, a cell wall component found exclusively in gram negative bacteria (GNB). An extracorporeal hemoperfusion device (TORAYMYXIN) has been developed: PMX is covalently bound on the surface of an insoluble carrier material so that the endotoxin can be inactivated in the blood without exerting its toxicity on the brain and kidney. The aim of this study was to clarify the efficacy, safety and clinical effects of direct hemoperfusion with an immobilized polymyxin-B fiber column (DHP-PMX) in solid organ transplanted patients with severe sepsis or septic shock.
Methods: From June 2004 to May 2005, 15 patients (10 men and 5 women), mean age 55 years old (46-65 range), underwent kidney or liver transplantation and developed severe sepsis or septic shock, as defined by the Consensus Conference of American College Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria. GNB were detected in all the patients receiving conventional treatments including antibiotic therapy, vasopressive or inotropic agents, and ventilation support. The DHP-PMX treatment was performed three times in each patient. Hemodynamic and respiratory parameters, dosage of vasopressor/inotropic drugs were assessed at baseline and after each treatment.
Results: No adverse events occurred. From baseline to 3rd treatment, mean arterial pressure (MAP) was increased (from 63±5 to 83±4 mmHg), while the dosage of dobutamine (from 7.5±3 to 3±2 mcg/kg/min) and noradrenaline (from 1.3±0.45 to 0.05±0.02 mcg/kg/min) were reduced. The PaO_2/FiO_2 ratio increased (from 234±38.47 to 290±107.48 mmHg).
Conclusion: The use of DHP-PMX in association with conventional therapy may be an important aid in patients with sepsis. (Int J Artif Organs 2007; 30:)

KEY WORDS: Hemoperfusion, Polymyxin-B, Endotoxin, Sepsis, Septic shock, Solid organ transplantation, Liver transplantation, Kidney transplantation

INTRODUCTION

The increasing number of cases of sepsis and bacteremia observed in the last ten years is one of the most interesting aspects in emerging infective pathology. This rise is generally ascribed to a variety of causes: the widespread increase in invasive diagnostic and therapeutic procedures, the common use of intravascular devices and prosthetic materials as progress continues to be made [AUTHOR: please confirm the changes in red] in immunosuppressive regimens, and the changes in the pattern of pathogens and drug resistances, both in the hospital set-

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ting and the community.

Despite improvements in antibiotic therapies and resuscitation techniques, mortality attributable to sepsis is still about 30 to 50%. Mortality appears to be related to the severity of clinical status, progressively increasing from sepsis (estimated to be 17%), to severe sepsis (33%), and reaching 57% in patients with septic shock as a result of the progressive cellular damage leading to irreversible multiorgan dysfunction (1). Since transplant recipients undergo an immunosuppressive drug regimen to prevent graft rejection, the consequent immunosuppression-induced impairment of the inflammatory response can attenuate the signs and symptoms of invasive infection. Gram negative bacteria are a frequent cause of infection in the early post-transplantation period. Many works are published describing the extent and multiplicity of infective complications, above all during the early post-operative phase. Among these, bacteremia is a significant cause of morbidity and mortality after solid organ transplantation, while septic shock is a severe complication which worsens its prognosis. The incidence of bacteremia is estimated to be about 28% to 30% following liver transplantation, 5 to 10% following kidney transplantation, and 10% in heart transplantation (2). In 1992, Wagner et al (3) examined a population of 125 infected transplant patients, and observed a mortality rate of 33% in heart transplantation patients, 24% in liver transplantation patients and 11% in kidney transplantation patients. Higher mortality rates were observed in the case of isolated gram negative microorganisms and when the bacteremia originated from a pulmonary source.

Candel et al (4), in a prospective study carried out on 382 solid organ transplanted patients, described 66 cases of septic shock, obtaining similar results: gram negative bacteria was isolated in 53% of the septic population and gram positive bacteria in 24%, fungi were isolated in 7%, and polymicrobial flora in 12%. The most common sites of infection were the lungs (26%), abdomen (23%), urinary tract (13%) and external devices (9%).

These studies present interesting data on transplanted patients. During the early post-surgical phase, gram negative bacteria represent a common cause of sepsis and septic shock and the most common sites of infection are the lungs, abdomen and urinary tract. The kind and length of surgical procedure, and the immunosuppressive state strongly influence the organism's response to infection (5-8).

Gram negative bacteria (GNB) are a frequent cause of infection in the early post-transplantation period. Gram negative bacteria infections aroused particular interest for many years due to endotoxin. The endotoxin is a cell wall component exclusively found in GNB and is one of the most important toxins involved in the production of inflammatory mediators and in the development of septic shock and multiple organ failure. Polymyxin B (PMX) is a polycationic antibiotic, known to bind the lipid A portion of endotoxin and neutralize its toxicity, interrupting the cascade of cytokines that leads to septic shock. However, PMX-B cannot be used as an intravenous antibiotic because of its known nephro- and neurotoxicity.

The role of extracorporeal treatments for blood depuration in systemic inflammatory response syndrome (SIRS) and septic shock are still under debate (9). Plasmapheresis and high volume hemofiltration were studied on humans during phase I/II studies, providing interesting results (10-12). In 1994, an extracorporeal hemoperfusion device was developed by the Japanese Toray Industries which carries immobilyzed PMX on the surface of polypropylene and alpha-cloroacetammide-metal polystyrene fibers. These behave as an insoluble carrier material so that endotoxin can be inactivated in the blood without exerting its toxicity on the brain and kidney (13).

The aim of our study is to clarify the efficacy, safety and clinical effects of direct hemoperfusion with an immobilized polymyxin-B fiber column (DHP-PMX) in kidney or liver transplanted patients with severe sepsis or septic shock. Other end-points of the study are the evaluation of the clinical effects of the PMX-F treatment, focusing on changes which may occur in patients' vital signs.

MATERIALS AND METHODS

This study was carried out in the Organ Transplant Post-Surgical Intensive Care Unit of the Umberto I Polyclinic, Sapienza University of Rome, from June 2004 to May 2005. Fifteen patients were prospectively enrolled. All of them had undergone a solid organ transplant (liver or kidney) in the 30 days prior to the study and had experienced a severe sepsis state (with or without shock) due to a suspected gram negative infection documented by clinical diagnosis.

Patients were enrolled in the study after the clinical diagnosis of suspected gram negative severe sepsis or septic shock, according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (14). Organ dysfunction was evaluated using the SOFA score (15).

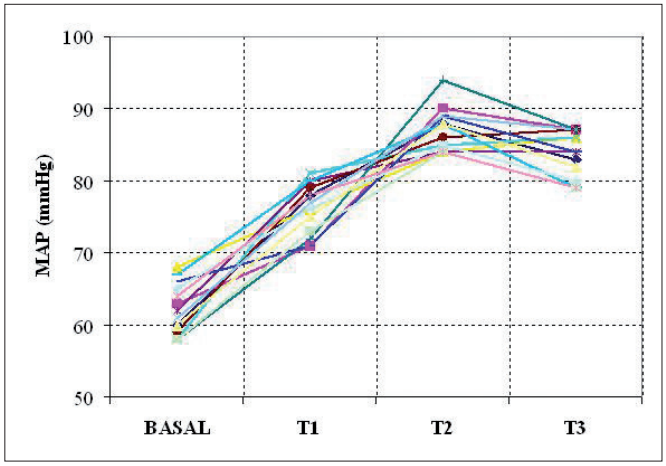

Fig. 1

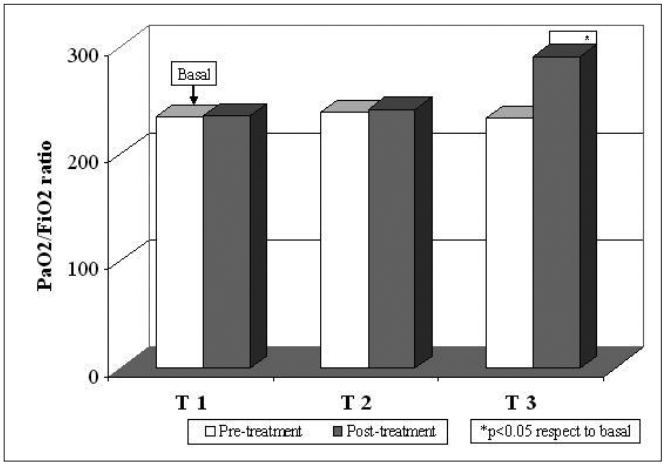

Fig. 2

The following hemodynamic parameters were continuously monitored:
– heart rate (HR)
– systemic mean arterial pressure (MAP)
– Central Venous Pressure (CVP)
– pulsed peripheral saturation (SpO_2)
– body temperature

Cardiac performance was monitored by transthoracic echocardiography performed once daily during the treatment. The following were also recorded during the study: respiratory rate, blood gas analysis, general blood chemistry/hematology for safety assessment and hourly urine output.

All patients received aggressive resuscitation therapy, including fluid challenge, appropriate antibiotic therapy, vasopressors and/or inotropes to achieve a MAP ≥65 mmHg, mechanical ventilation and, if needed, surgical debridement of infected sites.

Clinical targets

The following targets were pursued in the clinical management of patients.

Cardiovascular support was optimized to maintain the following hemodynamic parameters: a central venous pressure (CVP) of 8 to 12 mmHg, a systemic mean arterial pressure (MAP) ≥65 mmHg, a left ventricular ejection fraction >40% and an hourly diuresis ≥0.5 mL/Kg/h^{-1}. When CVP was lower than 8 mmHg, crystalloids and colloids were administered to achieve a CVP of 10 to 15 mmHg. Concentrated erythrocytes were administered for hemoglobin values lower than 10mg/dL. Fresh Frozen Plasma was administered for INR values >2 in presence of active bleeding or before invasive procedures. Human albumin 20% was infused for values lower than 2g/dL; platelets were administered if lower than 30000/mm and in the case of active bleeding. Norepinephrine was infused to obtain MAP values ≥65 mmHg after fluid challenge. Dobutamine (5-10 mcg/kg/min) was administered in the case of ejection fraction (EF) values <40% despite adequate fluid replacement, in order to reach a EF value >40% (Toshiba Power Vision 8000 ultrasound machine, Toshiba Medical Systems, Tochigi-Ken, Japan).

Ventilatory support was used in the following cases: a PaO_2/FiO_2 ratio lower than 150, a Glasgow Coma Score (GCS) ≤8, a respiratory rate above 30 breaths/min or under 10 breaths/min, hemodynamic instability, acidosis. All patients were orotracheally intubated and mechanically ventilated in controlled volume mode or controlled pressure to achieve an oxygen saturation value >95% in normocapnia. Tidal volume was set in order to obtain a minute ventilation equal or higher to 6 ml/kg, positive end expiratory pressure (PEEP) value was equal or higher than 5 cmH_2O. Non-invasive ventilation (NIV) techniques were used only in one patient with GCS values between 9 and 12 when under stable hemodynamic conditions.

Antibiotic therapy was administered in the case of bacterial isolation in accordance with the antibiogram; in the case of no bacterial isolation, wide-spectrum empiric antibiotic therapy was started according to clinical suspicions (de-escalation therapy). Antibiotic therapy was adjusted for creatinine clearance values.

Careful surgical debridement was performed in the case of surgically treatable infection sites. Medication of surgical wounds was performed daily; when needed, surgical drains were positioned and infected necrotic tissue and potentially infected devices were removed.

Immunosuppressive therapy included micofenolic acid (1-2 g/day), methilprednisolone (20 mg/day) and cyclosporine or tacrolimus. Plasmatic dosage of the latter two was performed daily, maintaining therapeutic ranges between 200 and 250 ng/mL and 10 to 13 ng/mL, respectively. On the onset of sepsis, the daily dosage of immunosuppressive drugs was halved in accordance with literature-based recommendations (16).

The PMX-F treatment began within 24 hours from diagnosis of sepsis. Hemoperfusion using a polymyxin-B immobilized column was carried out using a double lumen catheter 12 Fr, 16 cm (Arrow International, Inc., Reading, PA, USA) positioned in the subclavian or jugular vein using Seldinger's technique. Three consecutive 2-hour treatments were administered over three days. Blood flow velocity was set from 80 to 120 ml/min (Estorflow, Estor SPA, Pero, Milano, Italia). No anticoagulant was administered during treatments. Clinical parameters were registered at the following times: before (pre-T1 or basal) and after the first treatment (post-T1), before (pre-T2) and after the second hemoperfusion (post-T2) and before (pre-T3) and after the last procedure (post-T3). Laboratory parameters such as hemocoagulative profile, serum electrolytes, blood cell count and hemoglobin were obtained twice daily.

Statistical analysis

The statistical analysis was performed using the software Spss for Windows, version 8 (Spss Inc., Chicago, Illinois, USA). Data are presented as mean ± standard deviation (SD) for variables which are normally distributed, or median (range) for non-normally distributed variables. All data underwent the analysis of variance for repeated measures; statistical significance was obtained for $p < 0.05$.

RESULTS

The study was carried out at the Post Surgical Intensive Care Unit of the Organ Transplantation Department of the Umberto I Polyclinic at the Sapienza University of Rome. Fifteen patients were enrolled in the study between June 2004 and May 2005. All patients had undergone a solid organ transplantation during the previous 30 days: 10 orthotopic liver transplantations and 5 kidney transplantations, respectively (Tab. I). The mean plasmatic dosages of tacrolimus and cyclosporine at T1 were, respectively, 4.5 ng/mL (range 3.6-6) and 103 ng/mL (range 87-122).

Surgical toilette was carried out in 6 patients; a biliary prosthesis was endoscopically removed from one patient and a percutaneous nephrostomy was performed in one patient by an interventional radiologist. Before the hemoperfusion treatment, removal and substitution of the central line and bladder catheters were performed in all patients.

TABLE I - DESCRIPTION OF PATIENTS INCLUDED IN THE STUDY BY ANTHROPOMETRIC CHARACTERISTICS, SOFA SCORE, TYPE OF TRANSPLANTATION, SITES AND TYPES OF INFECTION

	Age	Sex	Weight	SOFA	Type of transplant	Site of infection	Infecting organism	Surgical debridement performed
Patient n 1	59	M	75	16	Liver	Abdominal abscesses	*Klebsiella Pneumoniae*	Yes
Patient n 2	55	F	80	15	Liver	Abdominal abscesses	*Peseudomonas Aeruginosa*	Yes
Patient n 3	60	M	73	13	Kidney	Urinary tract	*Escherichia Coli*	No
Patient n 4	61	M	82	13	Liver	Biliary infections	*Pseudomonas aeruginosa*	Yes
Patient n 5	46	F	75	16	Kidney	Urinary tract	*Pseudomonas aeruginosa*	No
Patient n 6	65	M	88	15	Liver	Biliary infections	*Escherichia Coli*	Yes
Patient n 7	58	F	93	16	Liver	Abdominal abscesses	*Proteus mirabilis*	Yes
Patient n 8	59	M	90	16	Liver	Others	*Candida Albicans + Proteus mirabilis*	No
Patient n 9	63	M	85	15	Liver	Abdominal abscesses	*Serratia merscens*	No
Patient n 10	56	M	74	15	Kidney	Urinary tract	*Escherichia Coli*	No
Patient n 11	48	M	78	15	Liver	Biliary infections	*Klebsiella Pnumoniae*	Yes
Patient n 12	50	F	74	16	Kidney	Others	*Candida Kruzei + Klebsiella Pneumoniae*	No
Patient n 13	53	F	75	13	Liver	Biliary infections	*Candida Kruzei + Klebsiella Pneumoniae*	No
Patient n 14	53	M	84	15	Liver	Others	*Serratia Marcescens*	Yes
Patient n 15	62	M	86	15	Kidney	Urinary tract	*Paeudomonas Aeruginosa*	No

SOFA = Sequential Organ Failure Assesment.

The diagnosis of a gram negative infection was confirmed by blood cultures in all cases. Infection sites and bacteria are reported in Table I.

The mean SOFA score at the beginning of the study was 15 (range 13-17). During the hemoperfusion procedures, no complications causing suspension of the protocol were reported for any of the enrolled patients, allowing the study to be successfully completed.

Mortality was evaluated after 4 weeks from the end of the study and proved to be 26% (4 patients out of 15).

At the beginning of the study (Basal) all the patients were administered vasopressors and inotropes to maintain stable hemodynamics; the dobutamine mean dosage was 7.5 ± 3 mcg/kg/min and the noradrenaline mean dosage was 1.3 ± 0.45 mcg/kg/min. The hemodynamic data are reported in Table II. The dosage of vasoactive drugs and inotrope was adjusted to obtain a MAP of 63 (SD±5) mmHg.

During the study, a progressive improvement of the hemodynamic parameters was observed. The MAP value was 63 ± 5 mmHg at pre-T1 and 76 mmHg (SD±5) at post-T1, 68 ± 5 mmHg at pre-T2 and 89 mmHg (SD±5) at post-T2, 80 ± 5 mmHg at pre-T3 and 83 mmHg (SD±4) at post-T3. A statistically significant increase in the MAP ($p<0.05$) was observed during the study. Moreover, the increase in pressure values corresponded to a downregulation of the administration of vasoactive drugs; in particular, the dosage of dobutamine was reduced from a mean of 7.5 ± 3 mcg/kg/min to a mean of 3 ± 2 mcg/kg/min, while mean norepinephrine doses were reduced from 1.3 ± 0.45 mcg/kg/min to 0.05 ± 0.02 mcg/kg/min. Although a heart rate reduction was observed, it did not reach statistical significance.

Non-invasive ventilation was performed in only one patient; all the other patients underwent orotracheal intubation and mechanical ventilaton.

Before the first treatment (Basal), mean PaO_2/FiO_2 ratio was 234 ± 38.47 mmHg, at post-T1 237 ± 35.38 mmHg, 242 ± 18.38 mmHg at post-T2 and 290 ± 107.48 mmHg at post-T3. These data reached statistical significance ($p<0.05$).

No statistically significant differences were observed in diuresis values during the study.

DISCUSSION

The use of PMX-F hemoperfusion began in Japan in 1994 and over 30 thousand treatments have been performed since then without any related adverse events. Despite the fact that our study was carried out on a small number of cases, the use of the PMX-F hemoperfusion technique was demonstrated to be safe and easily performed; no adverse events occurred during the treatments. No coagulopathy ascribable to the extracorporeal circuit or enhanced by its use was reported. The recorded hemodynamic data show that the extracorporeal treatment has no negative impact on hemodynamics; con-

TABLE II - DATA ON HEMODYNAMICS, VASOPRESSOR DOSAGES AND PAO_2/FIO_2 RATIO REPORTED BEFORE AND AFTER EACH PMX TREATMENT AS MEAN ± SD

	Basal (pre- T1)	post- T1	pre- T2	post -T2	pre - T3	post- T3
Hemodynamics						
SAP (mmHg)	96 ± 26	106 ± 29	104 ± 18	127 ± 18*	124.5 ± 21*	135 ± 21*
DAP (mmHg)	48 ± 5	51 ± 7	50 ± 8	59 ± 6+	63 ± 6+	66 ± 5+
MAP (mmHg)	63 ± 5	76 ± 5	68 ± 5	89 ± 5	80 ± 5	83 ± 4§
CVP (mmHg)	15 ± 3.6	12 ± 5	13 ± 3	11 ± 4	9 ± 3	11 ± 3
HR (beats/min)	100 ± 7	91 ± 9	89 ± 8	90 ± 9	88 ± 7	85 ± 7‖
Vasopressors						
Noradrenaline (mcg/Kg/min)	1.3 ± 0.45	1 ± 0.7	0.5 ± 0.3	0.1 ± 0.06	0.08 ± 0.04	0.05 ± 0.02
Dobutamine (mcg/Kg/min)	7.5 ± 3	5 ± 1.9	5 ± 1.56	4 ± 2.13	4 ± 1.8	3 ± 2
Ratio PaO_2/FiO_2	234 ± 38.47	237 ± 35.38	239 ± 12.02	242 ± 18.38	233 ± 35.35	290 ± 107.48[4]

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure; CVP = central venous pressure; HR = heart rate; T1 = 1st treatment; T2 = 2nd treatment; T3 = 3rd treatment

* $P < 0.05$ post-T2, pre-T3 and post-T3 vs basal

+ $P < 0.05$ post T2, pre-T3 and post-T3 vs basal

§ $P < 0.05$ post-T3 vs basal

‖ $P < 0.05$ post-T3 vs basal

[4] $P < 0.05$ post-T3 vs basal.

versely, it allowed the dosage of inotropes and vasoactive drugs administered in all the patients to be significantly reduced, raising MAP values after each treatment in a statistically significant way. This suggests that the treatment could "purify" the circulating blood from toxins, primarily endotoxin, but also sepsis cascade mediators able to decrease vascular peripheral resistance, contributing to maintain hypotension and myocardial depressants. There are currently many studies which present the use of the polymixin-B-based cartridge, mainly carried out in Japan, but none of them has been carried out on the use of PMX-F in transplanted patients.

The most interesting European work is that presented by Vincent et al (17), a multicenter study performed in 6 university centers. In this study, 36 patients with severe sepsis and septic shock were enrolled and randomized into two groups. The first group received the appropriate standard medical therapy. The second group received the standard therapy and one PMX-F treatment. The conclusion of the study showed a statistically significant improvement of the hemodynamic parameters but no change in outcome was observed. The PMX-F group showed an increase in cardiac index (CI), left ventricolar stroke work indicized (LVSWI) and oxygen delivery (DO2). These data are in partial agreement with those we observed during our study, above all for hemodynamic data. Even though the study by Vincent et al was a multicentric one, considering the small number of cases, the conclusions seem hasty.

A very interesting study is the one carried out by Nakamura (18), a single-center study on 324 patients with severe sepsis. The patients were randomized into 2 groups: the first, consisting of 206 patients, was treated using PMX-F, while the other group of 108 patients was treated using standard medical therapy without hemoperfusion. In the PMX-F group the survival rate at 4 weeks was 68% compared to 28% of the untreated group. The PMX-F group showed a statistically significant improvement in systolic arterial pressure with concomitant reduction of heart rate, and an improved PaO_2/FiO_2 ratio. It is noteworthy that in this study the plasmatic dosage of endotoxin was used. In the PMX-F group, the value of endotoxins and other mediators of sepsis were reduced in all cases, and the greatest reduction was observed in the patients who survived.

In a recent case report (19), the PMX-F treatment was performed in a septic patient in parallel with continuous hemodiafiltration, obtaining good results in terms of the increase in arterial pressure and reduction in the administration of inotropic drugs. All the published works agree in their observation of an improvement in the hemodynamic parameters.

The effect on the respiratory system was recently assessed in a study carried out by Hidehico et al (20), evaluating the PaO_2/FiO_2 ratio in 36 patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) induced by sepsis. Each patient was treated once with PMX-F for 3 hours. All the patients were mechanically ventilated following a strict protocol in the setting of the ventilation parameters. The PaO_2/FiO_2 value was recorded at 24, 36, 72 and 96 hours from the beginning of the treatment. The results show a statistically significant improvement of the mean PaO_2/FiO_2 ratio at 96 hours from the treatment. Moreover, a negative correlation with IL-8 levels was found.

An interesting work by Tojimbara (21) shows the effects of the use of PMX-F in patients with chronic renal failure. The 24 patients under investigation were affected by severe sepsis or septic shock caused by abdominal infections; 19 of the patients were on a dialysis regimen. All the patients underwent 2 PMX-F treatment cycles. The results showed a significant increase in MAP and a reduction in inotropes administered; the 28-day mortality was 10%.

Two relevant and unequivocal data arise from the analysis of all the studies analyzed in the literature: the improvement of hemodynamics and gas exchange. These are the same conclusions that we obtained in our study. Interpretation of these improvements is not unequivocal, however: the most reliable hypothesis is that polymixin-B binds a substance belonging to the endogenous cannabinoids, the so-called anandamide. This substance, produced by platelets and macrophages during gram negative induced sepsis, seems to be able to bind to peripheral vase receptors, inducing vasodilation and hypotension (22, 23). Studies on animals confirm the role of anandamide in sepsis. The role of anandamide was recently studied in a work carried out on patients with septic shock (24). Anandamide was dosed in these patients before and after the PMX-F treatment. The plasmatic values of anandamide were significantly lower after a treatment cycle in surviving patients, corresponding to an improvement in the SOFA score and hemodynamic and oxyphoretic parameters.

PMX-F treatment could be considered a therapeutic adjuvant in the treatment of sepsis. Considering the data from our center, the treatment with PMX-F seems to induce an improvement in hemodynamics. Further studies

should be carried out to investigate whether this behavior can result in improved outcomes. It is certain that the transplanted patient represents an interesting model to study due to the great infective risk during the first months after transplantation and the reduced efficiency of the immune system. The literature reports the incidence of septic shock in solid organ transplanted patients to be 14%, with a 54% mortality rate of septic patients (4). In transplanted patients transferred to ICUs, the incidence of septic shock is estimated to be between 9% and 10.6 % (25-26) with an associated mortality of 50%.

All the studies present clear limits. No multicentric randomized study exists that takes into consideration a high number of patients and which is thereby able to verify the effectiveness of this treatment. Moreover, a great deal of the studies do not present the plasmatic endotoxin dosage, due to the low sensitivity of the currently-used laboratory tests. A reliable instrument is now available: the Smart Line TL (Spectral Diagnostic Inc., Toronto, Canada) is sensitive, easy-to-use and able to provide a guideline both for the time to begin the treatment and for evaluating its efficacy.

The absence of a control group and the small number of patients constitute a limit to our study, but the results are, in any case, interesting and encouraging. They suggest further investigations involving more centers and a bigger number of patients should be conducted, including both a control group and a systematic dosage of the plasmatic endotoxin level.

No single treatment exists for sepsis that is able to change patient outcomes; this is due to the complexity and multiplicity of the mechanisms involved. For this reason, a multidisciplinary approach including prevention, accurate knowledge of the biology of the phenomenon, and new drugs constitute the best approach for obtaining results. Transplantology currently considers immunomodulation to be of more interest than immunosuppression; from this point of view, PMX-F treatment could play an important role.

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REFERENCES

1. Alberti C, Brun-Buissoh C, Burchardi H, Martin C et al. Epidemiology of sepsis and infections in ICU patients from an international multicentre cohort study. Intensive Care Med 2002; 28: 108-21.
2. Moreno A, Mensa J, Almeda M et al. 138 episodes of bacteremia or fungemia in patients with solid organ (renal or hepatic) transplantation. Med Clin (Barc) 1994; 103: 161-4.
3. Wagener MM, Yu VL. Bacteremia in transplant recipients: a prospective study of demographics, etiologic agents, risk factors and outcomes. Am J Infect Control 1992; 20: 239-47.
4. Candel FJ, Grima E, Matesanz M, Cervera C, Soto G, Almela M, Martinez JA, Navasa M, Cofan F, Ricart MJ, Perez-Villa F, Moreno A. Bacteremia and septic shock after solid-organ transplantation. Transplant P 2005; 37: 4097-9.
5. Lichtenstern C, Schmidt J, Knaebel HP, Martin E, Buchler M.W., Weigand MA. Postoperative Bacterial/Fungal Infections: A Challenging Problem in Critically Ill Patients after Abdominal Surgery. Digest Surg 2007; 24: 1-11.
6. Wallace WC, Cinat ME, Nastanski F, Gornick WB, Wilson SE. New epidemiology for postoperative nosocomial infections. Am Surg 2000; 66: 874-8.
7. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Regnier B. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. A multicenter prospective study in intensive care units. JAMA 1995; 27; 274: 968-74.
8. Singh N, Wagener MM, Obman A, Cacciarelli TV, de Vera ME, Gayowski T. Bacteremias in liver transplant recipients: shift toward gram-negative bacteria as predominant pathogens. Liver Transpl 2004; 10: 844-9.
9. Bellomo R, Honore PM, Matson J, Ronco C, Winchester J. Extracorporeal blood treatment methods in SIRS/sepsis. Int J Artif Organs 2005; 28: 450-8.
10. Busund R, Koukline V, Utrobin U, Nedashkovsky E. Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002; 28: 1434-9.
11. Bellomo R, Baldwin I, Ronco C. Extracorporeal blood purifi-

cation therapy for sepsis and systemic inflammation: its biological rationale. Contrib Nephrol 2001; 132: 367-74.
12. Bellomo R, Baldwin I, Ronco C. High-volume hemofiltration. Contrib Nephrol 2001; 132: 375-82.
13. Shoji H. Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). Ther Apher Dial 2003; 7: 108-14.
14. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101: 1644-55.
15. Bernard GR. Quantification of organ dysfunction: seeking standardization. Crit Care Med 1998; 26: 1767-8.
16. Angele MK, Loehe F, Faist E. Immunomodulation during sepsis in organ transplanted children. Minerva Pediatr 2005; 57: 259-68.
17. Vincent JL, Laterre PF, Cohen J, Burchardi H, Bruining H, Lerma FA, Wittebole X, De Backer D, Brett S, Marzo D, Nakamura H, John S. A pilot-controlled study of a Polymyxin B-immobilized hemoperfusion cartridge in patients with severe sepsis secondary to intra-abdominal infection. Shock 2005; 23: 400-5.
18. Nakamura T, Matsuda T, Suzuki Y, Shoji H, Koide H. Polymyxin B-Immobilized Fiber Hemoperfusion in Patients with Sepsis. Dial Transplant 2003, 32: 602-07
19. Yonekawa C, Nakae H, Tajimi K, Asanuma Y. Combining continuous endotoxin aphaeresis and continuous hemodiafiltration in the treatment of patients with septic multiple organ dysfunction syndrome. Ther Apher Dial 2006; 10: 19-24.
20. Kushi H, Miki T, Okamaoto K, Nakahara J, Saito T, Tanjoh K. Early hemoperfusion with an immobilized Polymyxin B fiber column eliminates humoral mediators and improves pulmonary oxygenation. Crit Care 2005; 9: R653-R661.
21. Tojimbara T, Sato S, Nakajima I, Fuchinoue S, Akiba T, Teraoka S. Polymyxin B-immobilized fiber hemoperfusion after emergency surgery in patients with chronic renal failure. Ther Apher Dial 2004; 8: 286-92.
22. Wang Y, Liu Y, Sarker KP, Nakashima M, Serizawa T, Kishida A, Akashi M, Nakata M, Kitajima I, Maruyama I. Polymyxin B binds anandamide and inhibits its cytotoxic effect. FEBS Lett 2000; 470: 151-5.
23. Varga K, Wagner JA, Bridgen DT, Kunos G. Platelet and macrophage derived endogenous cannabinoids are involved in endotoxin-induced hypotension. FASEB J 1998; 12: 1035-44.
24. Kohro S, Imaizumi H, Yamakage M, Masuda Y, Namiki A, Asai Y, Maruyama I. Anandamide absorption by direct hemoperfusion with Polymyxin B-immobilized fiber improves the prognosis and organ failure assessment score in patients with sepsis. J Anesth 2006; 20: 11-6.
25. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome and associated costs of care. Crit Care Med 2001; 29: 1303-10.
26. Sands KE, Bates DW. Epidemiology of sepsis syndrome in 8 academic medical centers. JAMA 1997; 278: 234-40.