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Direct hemoperfusion with polymyxin B-immobilized cartridge in severe sepsis due to intestinal perforation: hemodynamic findings and clinical considerations in anticoagulation therapy

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ABSTRACT

Background. High levels of endotoxin have been reported as a risk factor for mortality in critical patients. Toraymyxin® is a column designed to remove circulating blood endotoxin by direct hemoperfusion widely used in Japan.

Objectives. To evaluate the effect of direct hemoperfusion with Toraymyxin® (DHP-PMX) as an adjuvant treatment in patients with severe sepsis due to intestinal perforation in terms of hemodynamic function and coagulation abnormalities.

Methods. Prospective cohort study with a historical control group. Cohort 1: prospective cohort undergoing two sessions of DHP-PMX (n=14). Cohort 2: retrospective historical cohort (n=7). The anticoagulation regime was used according to the protocol of each centre and to the special conditions of each patient.

Results. Mean norepinephrine dose was significantly reduced (0.9 ± 0.5 µg/kg/min pre-first DHP-PMX vs 0.3 ± 0.4 µg/kg/min post-second DHP-PMX treatment, p<0.05). Central venous pressure (CVP) and stroke volume variation (SVV) remained without significant changes during the study, as well as cardiac index (CI) in patients with initial CI≥2.5 L/min/m^2. CI significantly increased in patients with initial CI<2.5 L/min/m^2 (2.1±0.4 pre-first DHP-PMX vs 3.4 ± 0.4 pre-second DHP-PMX session, p=0.01). Mean platelet count pre-first and post-second DHP-PMX decreased significantly (213.9x10^3 ± 138.5x10^3 platelets/mm^3 vs 91.0x10^3 ± 53.5x10^3 platelets/mm^3, p=0.03), without significant changes during each DHP-PMX treatment. Patients did not experience bleeding nor complications derived from DHP-PMX treatments. Survival rates at 28 and 56 days did not differ significantly between cohort 1 and 2 (21.4% vs 42.9%; 42.9% vs 57.1%; respectively).

Conclusions. Performing two sessions of DHP-PMX treatment in a cohort of patients with abdominal sepsis is a feasible adjuvant therapeutic approach, safe in terms of coagulation abnormalities, can be done with different anticoagulation protocols, improves hemodynamic status and may impact on survival.

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Hemoperfusión directa con el cartucho de polimixina B fijada en la sepsis grave secundaria a perforación intestinal: hallazgos hemodinámicos y consideraciones clínicas con respecto a la anticoagulación

RESUMEN

Antecedentes. Los niveles altos de endotoxina se han identificado como un factor de riesgo para la mortalidad en pacientes críticos. Toraymyxin® es un cartucho diseñado para eliminar la endotoxina de la sangre circulante por medio de hemoperfusión directa ampliamente utilizado en Japón.

Objetivos. Evaluar el efecto de la hemoperfusión directa con Toraymyxin® (HPD-PMX) como tratamiento adyuvante en pacientes con sepsis grave secundaria a perforación intestinal en términos de función hemodinámica y anormalidades de la coagulación.

Métodos. Estudio de cohortes prospectivo con un grupo control histórico. Cohorte 1 (n=14): tratada de forma prospectiva con dos sesiones de DHP-PMX. Cohorte 2 (n=7): grupo histórico retrospectivo. El régimen de anticoagulación utilizado fue dejado a libertad de cada centro según práctica local y condiciones especiales de cada paciente.

Resultados. La dosis media de noradrenalina se redujo significativamente (0,9 ± 0,5 µg/kg/min antes de la primera hemoperfusión con DHP-PMX vs 0,3 ± 0,4 µg/kg/min tras la segunda, p<0,05). La presión venosa central (PVC) y la variación del volumen sistólico (VVS) permanecieron sin cambios significativos durante el tratamiento, así como el índice cardiaco (IC) en los pacientes con un IC inicial ≥ 2,5 L/min/m2. El IC aumentó significativamente en los pacientes con IC inicial ≤ 2,5 L/min/

m2 (2,1 ± 0,4 antes de la primera hemoperfusión vs 3,4 ± 0,4 tras la segunda sesión, p=0,01). El recuento plaquetario medio descendió significativamente entre antes de la primera sesión y después de la segunda (213,9x103 ± 138,5x103 plaquetas/mm3 vs 91,0x103 ± 53,5x103 plaquetas/mm3, p=0,03), sin cambios significativos durante cada tratamiento. Los pacientes no experimentaron hemorragias o complicaciones derivadas de los tratamientos con HPD-PMX. La supervivencia al día 28 y día 56 no difirió significativamente entre la cohorte 1 y 2 (21,4% vs. 42,9%; 42,9% vs. 57,1%; respectivamente).

Conclusiones. La realización de dos sesiones de HPD-PMX en una cohorte de pacientes con sepsis abdominal es una terapia adyuvante viable, segura en términos de alteraciones en la coagulación, factible con diferentes protocolos de anticoagulación, que mejora la situación hemodinámica y que puede tener un impacto en la supervivencia.

INTRODUCTION

It is well known that endotoxin, an essential outer membrane component of gram-negative bacteria, is an important pathogenic trigger for sepsis, as well as soluble peptidoglycans and lipoteichoic acid from gram-positive bacteria membranes. They all activate cytokines, complement, phospholipase A2, nitric oxide synthase, many other mediators and the coagulation cascade[1]. Endotoxin and cytokines play a key role during the inflammatory process, and may produce myocardial depression, decreased systemic vascular resistance, hypotension, metabolic acidosis and hyperglycemia, which may finally lead to multiorgan dysfunction syndrome and death. High levels of endotoxin have been reported as a risk factor for mortality in critical patients[2].

So that it is very plausible to reduce the plasmatic levels of endotoxin to prevent multiorgan failure and reduce mortality rate in septic patients[3].

Toraymyxin® (PMX) is a column designed to physically remove circulating endotoxin from the blood of patients with severe sepsis or septic shock by direct hemoperfusion (DHP). The PMX cartridge contains polymyxin B covalently bound to polystyrene fibers that can adsorb endotoxin and modulate cytokines during the hemoperfusion[4,5].

Several studies have shown hemodynamic status[6,7] or pulmonary oxygenation[8] improvement in septic shock patients treated with DHP-PMX, even more in a systematic review of 11 studies in which mortality was reported, DPH-PMX appeared to significantly reduce mortality compared with conventional medical therapy[9].

Although the efficacy and safety of DHP-PMX has been analyzed in several studies, most of them were performed in Japan and the information available in Europe is very limited[9]. The best experience with DHP-PMX comes from patients treated suffering gram-negative infections but DHP-PMX seems to be effective in patients infected with gram-positive bacteria as well[10,11]. Thus, DHP-PMX has been used to improve the hemodynamic status of patients, regardless of the causative microorganism involved[12] and this might be another reason why DPH-PMX is effective in mixed infections as abdominal ones are[13].

It is not very clear how many sessions of hemoperfusion the patients should receive. In a European study the use of one session of DHP-PMX in patients with abdominal sepsis showed to be safe and to improve renal dysfunction and both hemodynamic status and cardiac function[6]. However, significant changes either in IL-6 or plasma endotoxin levels were not detected raising the possibility that one session of DHP-PMX was not enough. Afterwards, two cycles of DHP-PMX in an Italian study showed to improve the efficacy of treatment, not only reducing significantly organ dysfunction and plasma levels of IL-6, IL-10 and TNF-α, but also improving both hemodynamic and respiratory function (PaO_2/FiO_2 ratio)[14]. A recent randomized controlled trial confirmed the beneficial effect of two sessions of DHP-PMX in patients with severe sepsis or septic shock due to abdominal infection. This therapy, added to conventional medical treatment in selected patients, improved hemodynamic status, organ dysfunction and PaO_2/FiO_2 ratio, as well as 28-day mortality[15].

This study aims to evaluate the effect of two cycles of direct hemoperfusion with Toraymyxin® (DHP-PMX) as adjuvant treatment in patients with severe sepsis due to intestinal perforation in terms of hemodynamic function and coagulation abnormalities.

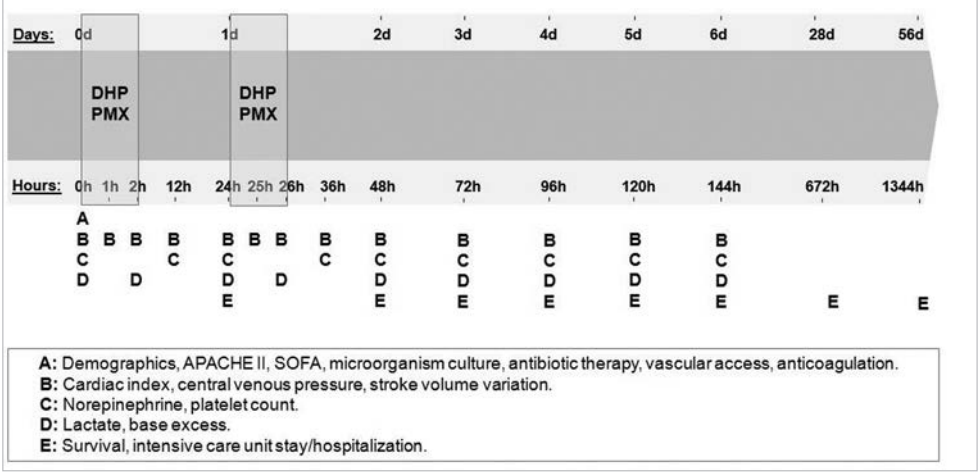
MATERIAL AND METHODS

A multicenter prospective cohort study with a historical control group conducted at four Spanish tertiary care intensive care units (ICUs) with wide experience in the management of abdominal sepsis and the use of extracorporeal blood purification treatments.

The patients observed prospectively (cohort 1) were recruited between September and December 2006. The control group consisted of a historical cohort of patients treated at these ICUs between June and August 2006 (cohort 2).

The study was conducted in accordance with the Declaration of Helsinki and applicable legislation. The study was approved by the ethics committees and the patients' relatives gave their written informed consent to participate in the study.

Patient selection. The main inclusion criterion was persistence of severe sepsis due to intestinal perforation for more than 6 hours and less than 24 hours after administering wide spectrum antibiotics and effective surgical source control. Severe sepsis was defined according to the consensus definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee[16]. Patients were also required to have a Sepsis-related Organ Failure Assessment (SOFA) score > 5 and sepsis must have been managed according to the recommendations of the Surviving Sep-



APACHE: Acute Physiology and Chronic Health Evaluation; DHP-PMX: Direct hemoperfusion with Toraymyxin®; SOFA: Sepsis-related Organ Failure Assessment.

Figure 1 Study schedule

sis Campaign[17]. Patients younger than 18 years old, pregnant women and those with confirmed hypersensitivity to polymyxin B were excluded.

Hemoperfusion. DHP was performed in the ICU using an extracorporeal hemoperfusion cartridge with polymyxin B immobilized on polystyrene fibers (Toraymyxin®, Toray Industries Inc, Tokyo, Japan).

The study therapy consisted of 2 sessions of DHP-PMX of 2 hours each, with an interval of 24 hours between them. The anticoagulation drug and its dose to maintain the patency of the system was used according to the protocol of each centre and to the special conditions of each patient.

Patient evaluations. The information of the patients belonging to cohort 1 was collected prospectively for a maximum period of 56 days from the first DHP-PMX. The information of cohort 2 was collected retrospectively from the patients' medical charts.

The variables assessed at patient entry in the study included demographic data, severity of disease state using the Acute Physiology and Chronic Health Evaluation (APACHE II) score[15], and severity of organ dysfunction using the SOFA score[16,17]. Results of blood culture and antimicrobial treatment adequacy were analyzed. Information on vascular access and type of catheter, anticoagulant therapy, vasopressor treatment, cardiac index (CI), central venous pressure (CVP), stroke volume variation (SVV), blood lactate, base excess levels and platelet count was assessed pre and post each period of hemoperfusion and survival at 28 and 56 days of treatment (figure 1).

Statistical considerations. Continuous variables were expressed as mean and standard deviation (SD) and categorical ones as frequencies. Comparison of the two cohorts was performed using Mann-Whitney U test, the Chi-square test and Fisher's exact test, as appropriate. P-values < 0.05 were considered statistically significant. All analyses were performed with the SPSS 11.0 for Windows computer program (SPSS® Inc., Chicago, IL, USA).

RESULTS

Patient population. Between September and December 2006, a total of 14 patients were enrolled in the study and treated with two cycles of DHP-PMX therapy in the first two days of the septic episode (cohort 1). Likewise, historical data were collected from 7 matched patients treated between June and August 2006 without hemoperfusion, who constituted the control cohort (cohort 2). Baseline characteristics of patient cohorts are described in table 1.

Gram-negative microorganisms were isolated in 10 patients (71.4%) in cohort 1 and in 5 patients (71.4%) in cohort 2 (table 1). Antimicrobial therapy was inappropriate just in one patient in cohort 1, in whom gram-positive, gram-negative and fungal microorganisms were isolated.

Hemoperfusion. The mean time from the surgical procedure performed to control the intestinal perforation and the first DHP-PMX was 14.0 ± 2.0 hours. In each patient, two sessions of DHP-PMX of 2 hours each were performed on the first 2 days, within a 24-hour interval and a flow rate of 120 mL/minute. The characteristics of the vascular access used in each patient are shown in table 2.

Table 1 Baseline patient characteristics

Characteristics	Cohort 1 (n=14)	Cohort 2 (n=7)
Age, mean ± SD, years*	70.8 ± 7.5	77.9 ± 7.3
Gender, n (%):		
Male	7 (50.0)	2 (28.6)
Female	7 (50.0)	5 (71.4)
APACHE II score, mean ± SD	23.4 ± 5.6	28.0 ± 2.8
SOFA score at admission, mean ± SD	9.4 ± 2.1	10.1 ± 1.5
Maximum SOFA score, mean ± SD	10.9 ± 3.7	11.4 ± 3.3
Microbiological culture and antibiotic therapy, n (%):		
No microorganisms	4 (28.6)	2 (28.6)
Gram-negative	6 (42.8)	5 (71.4)
Satisfactory antibiotic therapy	6 (100.0)	5 (100.0)
Gram-negative + gram-positive	4 (28.6)	0 (0.0)
Satisfactory antibiotic therapy	3 (75.0)	0 (0.0)

*p=0.044. APACHE: Acute Physiology and Chronic Health Evaluation; SD: Standard deviation; SOFA: Sepsis-related Organ Failure Assessment.

No anticoagulant therapy was used during DHP-PMX therapy in 2 patients (14.3%), a combination of unfractionated heparin (UFH) and prostacyclin (PGI2) was used in 1 patient (7.1%), and only UFH in 11 patients (78.6%) (table 2). UHF doses varied considerably as shown in table 2. There was just an early coagulation of one of the PMX cartridges in the 28 sessions of HPD-PMX performed.

Vasopressor therapy. The only vasopressor agent used was norepinephrine. The mean norepinephrine dose was gradually reduced in both cohorts 1 and 2 (table 3). It should be noted that in cohort 1 between the times pre-first DHP-PMX and post-second DHP-PMX a significant decrease in norepinephrine (0.9 ± 0.5 µg/kg/min vs 0.3 ± 0.4 µg/kg/min) was observed (p<0.039).

From then on, mean epinephrine doses in cohort 1 remained below those of cohort 2 until the end of the study, with significantly lower values at 72 hours (0.06 ± 0.08 vs 0.32 ± 0.1, p=0.016) and 96 hours (0.03 ± 0.05 vs 0.22 ± 0.08, p=0.003) from the start of the first DHP-PMX.

Preload: central venous pressure and stroke volume variation. CVP values remained stable in cohort 1 during the study, ranging from a mean value of 10.2 ± 3.5mmHg to 12.4 ± 3.2mmHg (figure 2). Although SVV showed a tendency to decrease during the first DHP-PMX from 18.8 ± 5.9% to

Table 2 Vascular access characteristics and anticoagulant regimens used in cohort 1

Pt	Vascular access			Anticoagulant treatment		
	Vein	Catheter		Drug	Dose	
		Gauge (Fr)	Length (cm)		1st DHP-PMX	2nd DHP-PMX
1	Left femoral	12	20	-	-	-
2	Left femoral	12	20	-	-	-
3	Left femoral	12	20	UFH	4 U/kg/h	4 U/kg/h
4	Right femoral	13.5	20	UFH	5 U/kg/h	10 U/kg/h
5	Right jugular	13.5	15	UFH	5 U/kg/h	-
6	Right femoral	13.5	20	UFH	5 U/kg/h	-
7	Right femoral	13.5	20	UFH	5 U/kg/h	-
8	Left femoral	12	15	UFH	7 U/kg/h	5 U/kg/h
9	Left femoral	12	20	UFH	15 U/kg/h	7.5 U/kg/h
10	Left jugular	13.5	15	UFH	15 U/kg/h	10 U/kg/h
11	Left femoral	12	20	UFH	18 U/kg/h	18 U/kg/h
12	Left femoral	12	16	UFH	20 U/kg/h	10 U/kg/h
13	Left femoral	12	16	UFH	20 U/kg/h	20 U/kg/h
14	Right femoral	13.5	24	UFH+PGI2	6 U/kg/h+5 µg/kg/h	6 U/kg/h+5 µg/kg/h

DHP-PMX: Direct hemoperfusion with Toraymyxin®; PGI2: Prostacyclin; Pt: Patient; UFH: Unfractionated heparin.

11.6 ± 6.5%, without a positive fluid balance and with sustained CVP, the difference did not reach statistical significance due to the small number of patients monitored (n=5) (figure 2).

CVP and SVV values of cohorts 1 and 2 could not be compared due to the lack of information available on these parameters in the medical history of cohort 2 patients.

Cardiac index. CI remained stable during the study in those patients of cohort 1 with an initial CI ≥ 2.5 L/min/m2 (figure 2). However, a significant increase in CI was observed in 3 patients with an initial CI below 2.5 L/min/m2 between the start of the first and the second DHP-PMX (2.1 ± 0.4 vs 3.4 ± 0.4, p=0.01), reaching levels comparable to those patients with an initial CI ≥ 2.5 L/min/m^2. These values could not be compared with those of cohort 2 because of lack of information available in the medical history of cohort 2 patients.

Acid-base balance. Lactic acid levels in cohort 1 gradually decreased during the study, reaching a mean value of 1.4 ± 0.3mmol/L at 144 hours from the start of the first DHP-PMX. In addition, mean base excess levels significantly rose over the day of the first DHP-PMX from -9.0 ± 4.8mEq/L to -2.5 ± 4.2mEq/L (p=0.011). Subsequently, these levels continued rising until 4.4 ± 4.2mEq/L at 144 hours from the start of the first DHP-PMX. Comparisons with cohort 2 could not be made due to the lack of data in the medical history of these patients.

Coagulation. Mean platelet counts of cohort 1 pre-first DHP-PMX and post-second DHP-PMX significantly decreased form 213.9x10^3±138.5x10^3 platelets/mm^3 to 91.0x10^3 ± 53.5x10^3 platelets/mm^3 (p=0.03) (figure 3). However, no statistically significant differences were observed when platelet counts before and after each session of DHP-PMX were analyzed separately (213.9x10^3 ± 138.5x10^3 plalets/mm^3 vs 136.6 ± 71.1x10^3 platelets/mm^3, 110.3x10^3 ± 64.8x10^3 platelets/mm^3 vs 91.0x10^3 ± 53.5x10^3 platelets/mm^3).

When platelet counts were compared between cohorts 1 and 2, the latter cohort did not show such a marked decrease in the first 36 hours (164.8x10^3 ± 36.6x10^3 platelets/mm^3 vs 134.2x10^3 ± 131.8x10^3 platelets/mm^3) (figure 3). However, the decreasing tendency was maintained for more days, without significant differences and reaching a mean value of 88.6x10^3 ± 91.6 x10^3 platelets/mm^3 at 120 hours from the start of the first DHP-PMX.

No bleeding was detected during the study period. Only one patient received a platelet transfusion, which was due to low platelet count at the start of the study.

Intensive care unit stay/hospitalization and survival. Neither were there significant differences observed between cohorts 1 and 2 in mean days of ICU stay (16.5 ± 11.8 days vs 11.0 ± 8.5 days), nor in the number of patients requiring surgical reoperation (3 patients [21.4%] vs. 1 patient [14.3%]). Twenty-eight-day mortality rates were 21.4% (3 patients) and 42.9% (3 patients) in cohorts 1 and 2, respectively (relative risk=0.5; 95% confidence interval: 0.13-1.87; p=0.354). These mortality rates rose on day 56 to 42.9% (6 patients) and 57.1% (4 patients) in cohorts 1 and 2, respectively (relative risk=0.75; 95% confidence interval: 0.31-1.81; p=0.659).

When patients' characteristics in cohort 1 were analyzed, a higher maximum SOFA score was noted in patients who died compared to those who did not (13.7 ± 3.1 vs. 8.8 ± 2.5, p=0.03). However, no statistically significant differences were observed in the SOFA score at patient admission, APACHE II score, requirement of surgical reoperation, or use of adequate antibiotic therapy. Regarding this last point, it should be noted that in the cultures of one of the patients who died grew gram-positive, gram-negative and fungal microorganisms not adequately treated with the empirical antimicrobial treatment.

Adverse reactions. The only adverse reaction observed was early coagulation of one of the PMX cartridges. No other procedure-related complication was detected during the study.

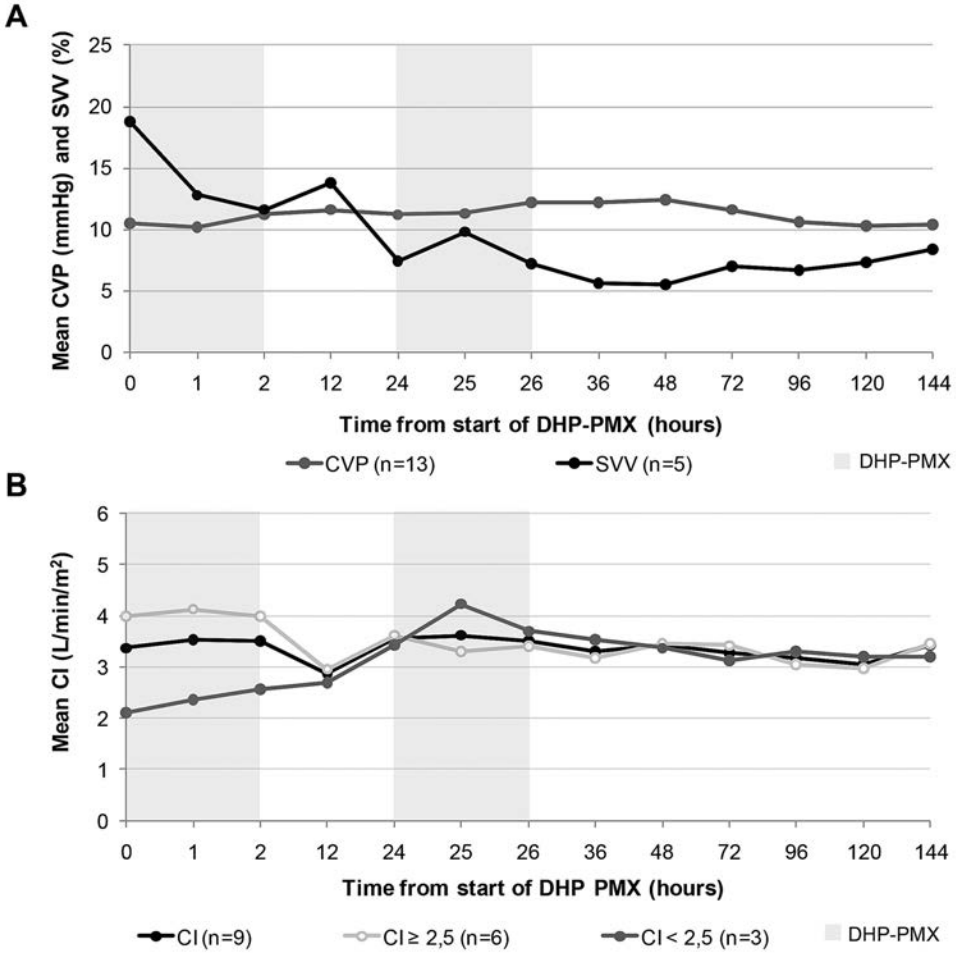
DISCUSSION

Adequate management of patients in the first hours after diagnosis of sepsis is a key aspect that determines the outcome of the episode[18]. Thus, many efforts have been made to develop treatment protocols and clinical management guidelines. This study has shown the feasibility, in a day-to-day basis, of adding two sessions of PMX-DHP to the international medical guidelines in patients with severe sepsis due to intestinal perforation. It has also been proved that the use of different anticoagulation regimens depending on the clinical status of the patient, as opposed to the use of fixed regimens,

Table 3 Mean norepinephrine doses administered during the study

Norepinephrine dose from start of DHP-PMX (µg/kg/min)	Cohort 1 (n=14)	Cohort 2 (n=6)
0 hours,	0.87 ± 0.52	0.56 ± 0.27
12 hours,	0.65 ± 0.54	0.71 ± 0.31
24 hours,	0.63 ± 0.67	0.78 ± 0.30
36 hours,	0.32 ± 0.42	0.58 ± 0.26
48 hours,	0.26 ± 0.44	0.46 ± 0.23
72 hours,	0.07 ± 0.09	0.33 ± 0.13
96 hours,	0.04 ± 0.05	0.23 ± 0.10
120 hours,	0.02 ± 0.04	0.10 ± 0.14
144 hours,	0.01 ± 0.02	0.15 ± 0.24

SD: Standard deviation; DHP-PMX: Direct hemoperfusion with Toraymyxin®.



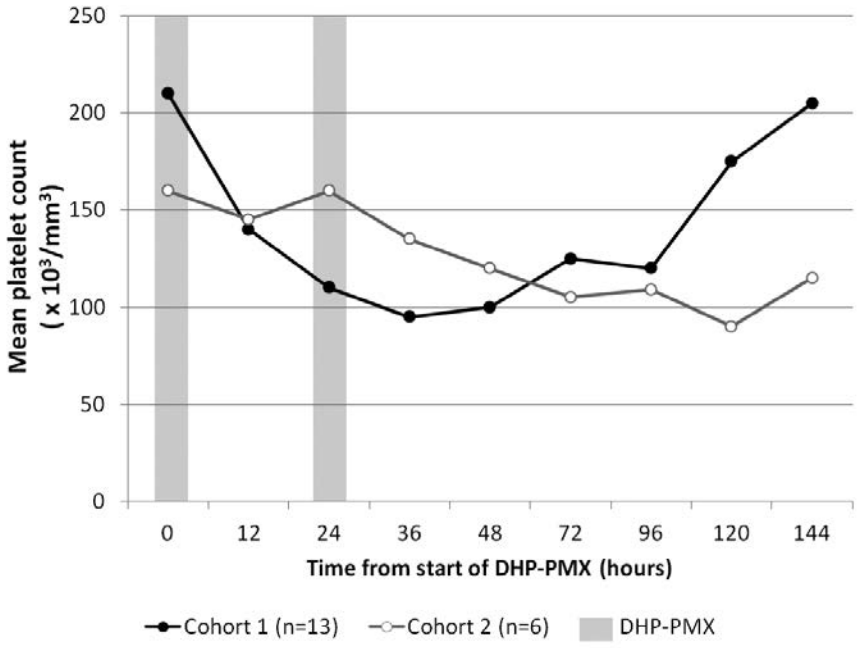
CI: Cardiac index; CVP: Central venous pressure; DHP-PMX: Direct hemoperfusion with Toraymyxin®; SVV: Stroke volume variation.

Figure 2 | **Mean central venous pressure, stroke volume variation (A) and cardiac index (B) in patients of cohort 1 during the study**

might be an additional factor to improve the patency of the cartridges, in addition to the use of large catheters. Although a reduction in platelet count was seen in the first 2 days of hemoperfusion, no platelet transfusion was needed. The minimum platelets count level attained was similar to those of the control group, and did not produce any complications. The information available in this patient population is limited, but no concerns regarding the platelet count were reported in the clinical trial conducted in patients with severe sepsis secondary to abdominal infection with one PMX-DHP session and the control group[6]. In addition, no bleeding-related adverse events have been reported during or after one[6] or two[15] PMX-DHP sessions in patients with abdominal sepsis.

A randomized controlled clinical trial showed that DHP-PMX improved organ dysfunction, particularly the cardiovascular component, in patients with abdominal severe sepsis or septic shock[15]. The results obtained in our study also support the improvement in cardiovascular function in a day-to-day basis as in another recent Spanish cohort study[19]. Blood pressure control required lower doses of norepinephrine over the course of the study, with a significant decrease during the two PMX-DHP cycles. Although increases in mean arterial pressure have been reported after only one DHP-PMX session in patients with sepsis due to abdominal infection[6,20] the reduction in vasopressor dose did not reach statistical significance in one of the studies[6] in contrast to the other that did reach it[21]. However, performance of two PMX-DHP cycles significantly reduced vasopressor requirements, decreasing mean norepinephrine doses to levels similar to those of our study, of about 0.3 µg/kg/min[14]. Two clinical trials also showed a reduction in vasopressors requirements after two PMX-DHP sessions, resulting in an increase in mean arterial pressure and a decrease in vasopressor dependency index[13,15].

The mean CI of patients remained within the normal range throughout the study, as well as in the subgroup of patients with initial CI ≥ 2.5. However, patients with CI < 2.5 at



DHP-PMX: Direct hemoperfusion with Toraymyxin®.

Figure 3 Mean platelet count measured during the study

the start of the study achieved a significant increase during the first PMX-DHP session that enabled them to achieve and maintain CI values within the normal range during the rest of the study. Another study had previously reported significantly higher CI in patients with sepsis caused by abdominal infection undergoing a single session of DHP-PMX compared with the control group6. However, our results should be taken with caution because only 3 patients had CI < 2.5 at baseline. These findings could be explained due to the direct removal of a cardio-depressor molecule as endotoxin is[22].

Analysis of CVP as an indicator of preload showed that mean values above 8 mmHg were maintained throughout the study, as recommended in the Surviving Sepsis Campaign guidelines[18]. Moreover, another indicator of preload used in this study, SVV, showed a significant reduction in mean values during the first DHP-PMX without a positive fluid balance, and its subsequent maintenance below 10%. The absence of this positive fluid balance could also help to reduce potential capillary leak syndrome resulting from the effect of endotoxin on vascular permeability. In addition to the effect of DHP-PMX on endotoxin adsorption, its effect on regulation of humoral mediators could be related to the improvement in hemodynamic function. Actually, the elimination of certain myocardial depressant mediators such as anandamide[23] could contribute to the improvement in cardiac function. Although the exact mechanism of action is still not known, the beneficial effect of DHP-PXM on cardiac function has been reported in patients with abdominal sepsis, with a significant increase in left ventricular stroke work index during hemoperfusion[6].

The presence of inadequate tissue perfusion could also cause a de-compensation of the acid-base balance, increasing lactate levels that could lead to the development of metabolic acidosis[21]. Our results show a reduction in lactate levels and an increase in base excess. These results agree with those obtained in another study where a decrease in lactate levels was detected in patients with abdominal sepsis treated with two DHP-PMX sessions[14]. Since measurements of base excess and lactate might be considered as prognostic factors in patients admitted to ICU[20], the improvement in acid-base balance detected in our study may have contributed to improve patients' outcomes. Actually, a recently conducted study in patients with abdominal sepsis showed that patient survival was related to the reduction in plasma lactate levels, decrease in plasma cytokines, reduction in norepinephrine infusion and improvement in PaO_2/FiO_2 ratio[14].

In our study, patients undergoing two sessions of DHP-PMX had lower 28-day and 56-day mortality rates than cohort 2, although significant differences were not detected. Lack of significant reduction in mortality rate was also reported in patients who received one DHP-PMX session[6]. Conversely, another study has shown a reduction in 28-day mortality rate in patients who received two DHP-PMX sessions[15]. Despite showing significant differences or not, the studies performed in patients with abdominal sepsis undergoing one or two DHP-PMX reported similar 28-day mortality rates, which ranged from 21.4% to 32.3% and were comparable to the one observed in our study[6,13,15,20].

Because of the observational nature of our study with a small number of patients and the limitations related to data collection from patients' medical charts in cohort 2, the results obtained should be considered with caution. However, although our results should be confirmed in subsequent studies with larger sample size, they are in agreement with previously published ones[6,15].

In conclusion, this study shows that performing two sessions of DHP-PMX in a day-to-day basis is feasible in centers with experience in the use of extracorporeal blood purification systems, and could result especially beneficial in the management of patients with severe sepsis due to intestinal perforation after controlling the source of infection. In these patients, DHP-PMX was safe in terms of coagulation abnormalities, which should be flexible adapting the anticoagulant regimen to the clinical status of the patient. The use of large diameter catheters could improve patency as well. In addition, the improvement of the hemodynamic status of patients could be seen from the first DHP-PMX, particularly in those with a CI below 2.5 L/min/m^2. Based on these results, the use of DHP-PMX could be added, to

the best clinical practice, as an adjuvant extracorporeal blood purification treatment in selected septic patients, representing another component of the necessary dynamic approach to the blood clearance in the critically ill septic patient.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Elena Escudero and Toray for her proactive assistance and support in the preparation of this article.

DISCLAIMERS

The authors declare no conflict of financial interest.

SOURCES OF FINANCIAL SUPPORT

This work was supported by Toray.

REFERENCES

1. Rangel-Frausto MS. Sepsis: still going strong. Arch Med Res 2005; 36:672-81.
2. Marshall JC, Foster D, Vincent JL, Cook DJ, Cohen J, Dellinger RP, et al. Diagnostic and prognostic implications of endotoxemia in critical illness: results of the MEDIC study. J Infect Dis 2004; 190:527-34.
3. Candel FJ, Martinez-Sagasti F, Borges M, Maseda E, Herrera-Gutierrez M, Garnacho-Montero J, et al. Endotoxin adsortion as adjuvant therapy in gram negative severe sepsis. Rev Esp Quimioter 2010; 23:115-21.
4. Shimizu T, Hanasawa K, Sato K, Umeki M, Koga N, Naganuma T, et al. Direct hemoperfusion with polymyxin-B-immobilized fiber columns improves septic hypotension and reduces inflammatory mediators in septic patients with colorectal perforation. Langenbecks Arch Surg 2009; 394:303-11.
5. Tani T, Hanasawa K, Kodama M, Imaizumi H, Yonekawa M, Saito M, et al. Correlation between plasma endotoxin, plasma cytokines, and plasminogen activator inhibitor-1 activities in septic patients. World J Surg 2001; 25:660-8.
6. Vincent JL, Laterre PF, Cohen J, Burchardi H, Bruining H, Lerma FA, et al. 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.
7. Uriu K, Osajima A, Hiroshige K, Watanabe H, Aibara K, Inada Y, et al. Endotoxin removal by direct hemoperfusion with an adsorbent column using polymyxin B-immobilized fiber ameliorates systemic circulatory disturbance in patients with septic shock. Am J Kidney Dis 2002; 39:937-47.
8. 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:R653-61.
9. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, et al. Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review. Crit Care 2007; 11:R47.
10. Nakamura T, Ushiyama C, Suzuki Y, Inoue T, Shoji H, Shimada N, et al. Combination therapy with polymyxin B-immobilized fibre haemoperfusion and teicoplanin for sepsis due to methicillin-resistant Staphylococcus aureus. J Hosp Infect 2003; 53:58-63.
11. Kawamata T, Imaizumi H, Yoshida M, Kaneko M. Polymyxin B-immobilized fiber improves hyperdynamic state in MRSA septic patients. Intensive Care Med 1997; 23:130-1.
12. Murakami M, Miyauchi Y, Nishida M, Okada H, Hamano K. Direct hemoperfusion using polymyxin-B immobilized fiber for septic shock after cardiac surgery. Circ J 2009; 73:658-61.
13. Antonelli M, Fumagalli R, Cruz DN, Brienza N, Giunta F. PMX endotoxin removal in the clinical practice: results from the EUPHAS trial. Contrib Nephrol 2010; 167:83-90.
14. Zagli G, Bonizzoli M, Spina R, Cianchi G, Pasquini A, Anichini V, et al. Effects of hemoperfusion with an immobilized polymyxin-B fiber column on cytokine plasma levels in patients with abdominal sepsis. Minerva Anestesiol 2010; 76:405-12.
15. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. JAMA 2009; 301:2445-52.
16. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:1250-6.
17. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 2004; 30:536-55.
18. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36:296-327.
19. Navarro R, Guerrero M, Gonzalez M, Quecedo L, Garcia A, Ramasco F. Description of the hemodynamic and respiratory effects of hemoperfusion treatment with polymyxin B in patients with abdominal septic shock. Rev Esp Anestesiol Reanim 2012 Dec 28.
20. Kojika M, Sato N, Yaegashi Y, Suzuki Y, Suzuki K, Nakae H, et al. Endotoxin adsorption therapy for septic shock using polymyxin B-immobilized fibers (PMX): evaluation by high-sensitivity endotoxin assay and measurement of the cytokine production capacity. Ther Apher Dial 2006; 10:12-8.
21. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001; 27:74-83.
22. Stamm C, Cowan DB, Friehs I, Noria S, del Nido PJ, McGowan FX, Jr. Rapid endotoxin-induced alterations in myocardial calcium handling: obligatory role of cardiac TNF-alpha. Anesthesiology 200; 95:1396-405.
23. Wang Y, Liu Y, Sarker KP, Nakashima M, Serizawa T, Kishida A, et al. Polymyxin B binds to anandamide and inhibits its cytotoxic effect. FEBS Lett 2000 Mar 24; 470:151-5.