Articles

Minerva Anestesiologica (2010) vol.76

Effects of hemoperfusion with an immobilized polymyxin-B fiber column on cytokine plasma levels in patients with abdominal sepsis

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1. Abstract

Aim. The beneficial role of hemoperfusion with immobilized polymyxin-B fiber (PMX) columns in sepsis, especially sepsis due to gram-negative bacteria, has previously been emphasized. Although the efficacy of PMX-B fiber-mediated hemoperfusion in reducing plasma levels of cytokines has been reported, other studies did not confirm this observation. Here we report the effects of PMX-B fiber-mediated hemoperfusion of outcome and cytokine plasma levels in patients with abdominal sepsis.

Methods. Twelve consecutive patients admitted to the Intensive Care Unit (October 2006 – December 2007) for severe sepsis/septic shock from abdominal infection were treated with standard therapy and 2 sessions of hemoperfusion with PMX cartridges. Clinical data and plasma levels of IL-6, IL-10, and TNF-alfa were measured 24 hours before and after PMX treatment.

Results. Plasma concentrations (pg/ml) of IL-6, IL-10 and TNF-alfa were significantly lower after hemoperfusion with a PMX fiber column (279.9±69.2 vs. 130.9±18.4, 166.4±36.7 vs. 45.5±12.2, 83.1±13.5 vs. 22.9±5.1, respectively; $P<0.05$). After treatment, patients required lower doses of norepinaphrine (0.8±0.1 vs. 0.3±0.1 μg/kg/min) and reduced lactate levels, recovery of respiratory function and improved Simplified Organ Failure Assessment (SOFA) scores. After 28 days, 6 patients (50%) had survived. Subgroup analysis demonstrated that survivors had higher IL-6 and lower IL-10 and TNF-alfa pre-treatment plasma levels (pg/mL) compared with deceased patients (324.4±41.1 vs. 235.3±38.4; 98.5±16.1 vs. 234.3 ±48.6; 44.5±9.0 vs. 121.6±52.3, respectively; $P<0.05$). No adverse events imputable to the treatment were recorded.

Conclusions. hemoperfusion with a PMX fiber column was able to reduce plasma levels of IL-6, IL-10 and TNF-alfa, especially in patients surviving at 28 days. Use of the technique was associated with lower norepinaephrine support and an increased PaO2/FIO2 ratio.

2. Points

The study showed 2 sessions of PMX treatment on severe sepsis /septic shock patients due to abdominal infection can enhance cardiovascular and respiratory functions as well as the reduction of the levels of inflammatory cytokines. The results of this paper describing 12 patients' data, in conjunction with the results of EUPHAS study published last year, strongly support the effectiveness of 2 sessions of PMX treatment for abdominal sepsis patients.

∗The original expression of 'hemofiltration' is changed to 'Hemoperfusion', whose expression is correct for Toraymyxin techniques.

(By N. Ida)

Articles

Indian Journal of Intensive Care Medicine (2010) vol.14 35-39

Effectiveness of early start of direct hemoperfusion with polymyxin B-immobilized fiber columns judging from stabilization in circulatory dynamics in surgical treatment patients

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1. Abstract

Background: Septic shock remains a major cause of multiple organ failure and is associated with a high mortality rate. In 1994, direct hemoperfusion using a polymyxin B-immobilized fiber column (PMX; Toray Industries Inc., Tokyo Japan) was developed in Japan and has since been used for the treatment of septic shock arising from endotoxemia.

Materials and Method: We treated 36 patients with septic shock using direct hemoperfusion with PMX. The patients were analyzed in two groups based on whether they had undergone surgery prior to DHP-PMX treatment (surgical group: surgical treatment before DHP-PMX, medical group: no surgical treatment). In surgical group, DHP-PMX was started within three hours after the surgical treatment. Various factors were measured before and after DHP-PMX.

Results: The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 27.4 ± 8.8, and the mean sepsis-related organ failure assessment (SOFA) score was 11.8 ± 4.9 before DHP-PMX. The SOFA score was significantly higher ($P = 0.0091$) and the PaO2/FiO2 ratio (P/F ratio) was significantly lower ($P = 0.0037$) in medical group than in surgical group prior to DHP-PMX. A chi-square test showed that the survival rate in surgical group was significantly better than in medical group ($P = 0.0027$). The survival rate of surgical group (84.2%) was judged to be very good because the predicated survival rate based on the APACHE II score (25.0) was only 46.5%. On the other hand, the survival rate of medical group (35.3%) was almost equal to that predicted by the APACHE II score (30.6; predicted survival rate, 27.4%).

Conclusion: The results of this study suggest the utility of early DHP-PMX in surgical group.

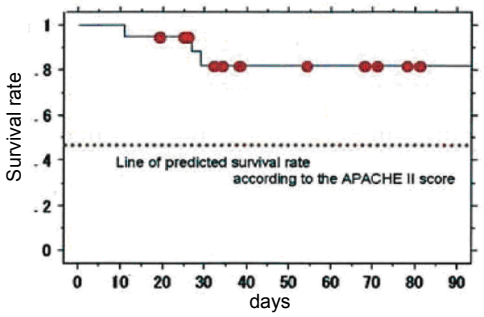

Figure: The survival rate of septic shock patients treated with Toraymyxin after within 3 hours from surgery. The survival rate (84.2%) was very high judging from the predicted survival rate (46.5 %) based on the APACHE II score before the treatment (mean value: 25.0) .

2. Points

This report from Japanese group shows the effectiveness of very early use of Toraymyxin (two sessions; the first session started within 3 hours after surgery) in septic shock patients mainly from peritonitis and pleuritis.
The authors suggest the important point is to start Toraymyxin treatment as early as possible together with the removal of infection source by surgery. These results are in good agreement with the results of EUPHAS study.

(By N. Ida)

Articles

Journal of Surgical Research (2010) in press (doi 10.1016/j.jss.2010.04.058)

Effect of Hemoperfusion using Polymyxin B-Immobilized Fibers on Non-Shock Rat Sepsis Model

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1. Abstract

Background

Direct hemoperfusion with a polymyxin B-immobilized column (PMX-DHP) is recognized to be effective for the treatment of septic shock and is widely applied in Japan. However, it is still unknown whether the efficacy is limited to cardiovascular dysfunction. Therefore, the purpose of this study was to examine the effects of PMX-DHP on a non-hypotensive sepsis model.

Methods

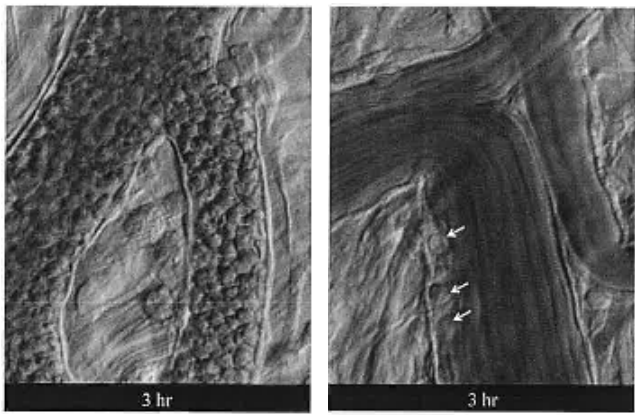
Wistar rats were assigned to either a PMX-DHP group, control group, or sham group (n = 7 in each group). A sepsis model was made by intravenous infusion of live *E. coli*. (LD50). The change in systemic blood pressure was less than 20% of the initial level in this model. In the PMX-DHP group, an arteriovenous extracorporeal circuit with a PMX column was applied until 3 h after *E. coli* injection. The same procedure with a dummy column was applied in the control group. Plasma levels of ALT, LDH, BUN, tumor necrosis factor alpha (TNF α), interleukin (IL)-1 β, IL-6, and IL-10 were measured. The mesenteric microcirculation was observed at 1 and 3 h after *E. coli* injection. In another series, survival was calculated up to 18 h (n = 14 in each group).

Results

Organ damage markers were lower in the PMX-DHP group. The levels of pro-inflammatory cytokines were significantly lower in the PMX-DHP group than in the control group. Microcirculation was better maintained in the PMX-DHP group. Survival was significantly better in the PMX-DHP group (93%) compared with that in the control group (57%, P = 0.03).

Conclusions

PMX-DHP was effective in a non-hypotensive sepsis model.



Mesenteric microvessel circulation of control rat **PMX-treated rat**

Figure. Intra-vital microscopic view of rat mesenteric microcirculation 3 hr after administration of E.coli.
In control rats, plugged leukocytes disturbed the blood circulation which made red blood cells visible (left). In PMX-treated rats, the blood circulation was maintained and the photograph was blurred due to red blood cell velocity (right).

2. Points

In this paper, the effects of Toraymyxin hemoperfusion on rat sepsis model was analyzed by using small experimental column circuits. The authors showed that the levels of pro-inflammatory cytokines were lower and survival rate were higher in Toraymyxin-treated group compared to sham column-treated group. Also, by microscopic visualization of microvessel circulation, Toraymyxin treatment was shown to improve the blood circulation by preventing leukocyte adhesion to vascular endothelial cells. Although the precise mechanism of this Toraymyxin's action on leukocytes are yet to be elucidated, this is an interesting observation which shows the possibility that Toraymyxin improves the organ functions by ameliorating peripheral microcirculations.

(By N. Ida)

Articles

Shock (2010) in press (PMID: 20386499)

APHERESIS OF ACTIVATED LEUKOCYTES WITH AN IMMOBILIZED POLYMYXIN B FILTER IN PATIENTS WITH SEPTIC SHOCK

Tuneyasu Kumagai[1], Naoshi Takeyama[1], Teru Yabuki[1], Makoto Harada[1], Yasuo Miki[1], Hideki Kanou[2], Sousuke Inoue[1], Takashi Nakagawa[1], and Hiroshi Noguchi[2]

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1. Abstract

In this study, we examined the effects of direct hemoperfusion through filters with immobilized polymyxin B PMX－DHP) on leukocyte function and plasma levels of cytokines in patients with septic shock. We found that PMX－DHP caused increased expression of C-X-C chemokine receptor 1（CXCR1）and CXCR2, along with decreased expression of CD64 and CD11b, by circulating neutrophils in patients with septic shock. Plasma levels of cytokines, including interleukin6（lL-6）, lL-8, lL-10, and high-mobility group box 1, were elevated in patients with septic shock compared with healthy controls, but cytokine levels were not altered by PMX-DHP. These results suggest that PMX-DHP infuences neutrophils via a mechanism that does not involve cytokine. Ex vivo perfusion of heparinized blood from patients with sepsis and septic shock through PMX filters in a laboratory circuit caused a significant decrease in neutrophil and monocyte counts. After 120min of perfusion, neutrophils, monocytes, and lymphocytes were decreased by 78%, 70%, and 10%, respectively, compared with baseline values. Flow cytometric analysis indicated that activated neutrophils with high levels of CD11b/CD64 expression and low levels of CXCR1/CXCR2 expression showed preferential adhesion to PMX filters. Neutrophils isolated from the blood after ex vivo PMX perfusion caused less damage to an endothelial cell monolayer than cells from sham-treated blood, whereas neutrophil phagocytosis of opsonized Escherichia coli was unaffected. These results indicate that PMX-DHP selectively removes activated neutrophils and reduces the ability of circulating cells to cause endothelial damage. Selective removal of activated neutrophils using PMX-DHP may improve the systemic inflammatory response in patients with septic shock.

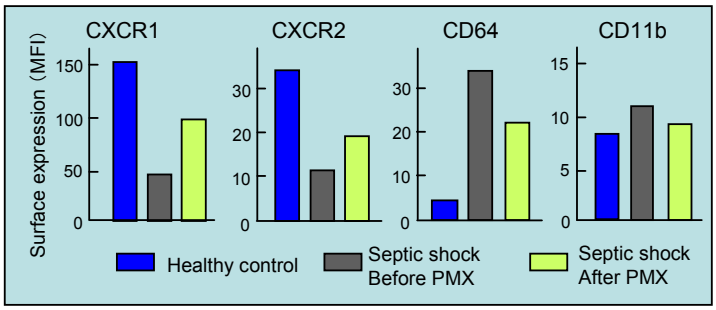

Figure Expression of leukocyte surface markers
CXCR1 and CXCR2 expressions, which were decreased in septic shock patients, were significantly increased by PMX treatment. CD64 and CD11b expressions, which were decreased in septic shock patients, were significantly increased by PMX treatment. (modified from original table)

2. Points

In this paper from Japan, the effects of Toraymyxin hemoperfusion on various cytokines and leukocyte surface markers were studied in septic shock patients. The authors found that expression of neutrophil surface markers in septic shock patients were normalized by PMX treatment. They also showed that monocytes and neutrophil numbers were decreased by ex vivo whole blood perfusion. There are also several other papers reporting the absorption of leukocytes to PMX fibers or alteration of cell surface markers or cellular functions, which would be interesting to investigate further to elucidate the precise mechanisms of the effects of PMX treatments.

(by N. Ida)

Articles

Nitric Oxide (2010) in press (doi: 10.1016/J.niox.2010.09.001)

Intrinsic nitric oxide-stimulatory activity of lipoteichoic acids from different Gram-positive bacteria

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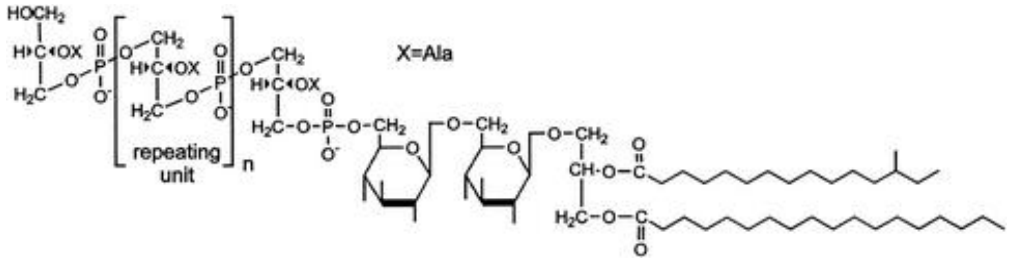
3 Institute of Pharmacology and Toxicology, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic

1. Abstract

Lipoteichoic acid (LTA) is a structural component of the cell walls of Gram positive bacteria. Similar to lipopolysaccharide (LPS) which is expressed in Gram-negative bacteria, LTA exhibits immunostimulatory properties. Frequently observed positive response of LTA in the Limulus amebocyte lysate (LAL) assay has been interpreted as a sign of LPS contamination, raising doubts about the intrinsic immune activities of LTA. Regarding many similarities in immunobiological and physicochemical properties of LTA and LPS, we hypothesized that similar to LPS, the LAL reactivity of LTA might be due to its ability to bind to LAL. Our data confirm the positivity of Bacillus subtilis, Staphylococcus aureus, Streptococcus faecalis and Streptococcus pyogenes LTAs in the LAL test. The estimates of suspected LPS content were 605, 10.3, 6.2 and 127 pg/mg LTA, respectively. The effectiveness of LTAs to induce the NO production in rat peritoneal cells was remarkably higher than that of equivalent concentrations of reference LPS (Escherichia coli). The LPS-induced NO was inhibited by polymyxin B (PMX), the IC50 of PMX:LPS concentration ratio (pg:pg) being 1050:1. Many fold higher concentrations of PMX were needed to partially suppress the NO-augmenting effects of LTAs, applied at concentrations representing the equivalents of LPS. Transposed to the concentrations of LTAs per we, the IC50s of the PMX:LTA ratios (mg :mg) ranged from 0.3:1 (S. aureus) to 7.5:1 (B. subtilis). It is concluded that LTA is not necessarily contaminated with LPS, The results prove the intrinsic immunostimulatory properties of LTAs of Gram-positive bacteria. The positive response of LTA in the LAL assay results from its capacity to bind to LAL. In addition, LTA binds with high affinity to PMX.



Structure of lipoteichoic acid (LTA) from *S.aureus* (Ref: Clin Microbiol Rev. 2003, 16: 379–414)

2. Points

The purpose of this paper is to examine various biological activity of Gram-positive bacterial component, lipoteichoic acid (LTA), is derived from intrinsic activity of LTA, or caused by contaminated LPS in LTA preparations. In the study, the authors found that polymyxin B binds to LTA as well as LPS. This result suggests a possibility that Toraymyxin cartridge binds and removes LTA in the blood stream, which may explain the effectiveness of Toraymyxin to patients of Gram-positive infection.

There exists another report published in 1998, which showed the binding of LTA to Toraymyxin (Jaber BL et al. ASAIO J (1998) vol.44, No.1, 48-53).

Articles

Intensive Care Med (2010) vol.36 906-907

Hypercytokinemia with 2009 pandemic H1N1 (pH1N1) influenza successfully treated with polymyxin B-immobilized fiber column hemoperfusion

Shinhiro Takeda 1 , Ryo Munakata 1, Shinji Abe 2, Seiji Mii 1, Manabu Suzuki 1, Takeru Kashiwada 2, Arata Azuma 2, Takeshi Yamamoto 1, Akihiko Gemma 2 Keiji Tanaka 1

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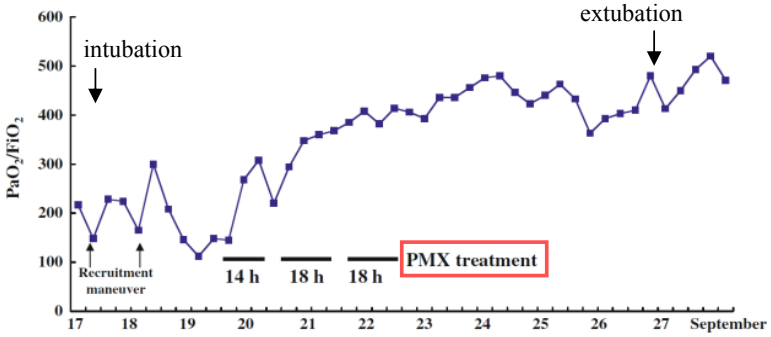

IL-6 (pg/ml)	1843	2674	5388	393	208	93	64	82	30	29
IL-8 (pg/ml)	1220	1912	424	92	54	0	0	0	54	150
IFN-gamma(pg/ml)	462	330	356	<15	<15	<15	<15	<15	<15	<15
HMGB-1 (ng/ml)	23	40	48	35	328	269	110	57	58	30

Fig. Clinical course of the patient. PaO_2/FiO_2 (P/F) ratio and serum inflammatory cytokine levels improved after PMX hemoperfusion on three consecutive days.

J Clin Apheresis (2010) in press PMID: 20623785

A case of severe ARDS caused by novel swine-origin influenza (A/H1N1pdm) virus: A successful treatment with direct hemoperfusion with polymyxin B-immobilized fiber

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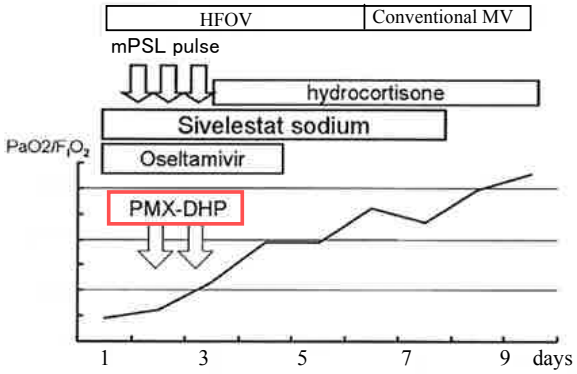

Fig. Clinical course of the treatment. HFOV: high-frequency oscillatory ventilation, MV:mechanical ventilation, mPSL: Methylpredonisolone, PMX-DHP:direct hemoperfusion with polymyxin B-immobilized fiber, PaO_2/FIO_2:arterial oxygen concentration/inspiratory oxygen fraction ratio.

Points

There have been two case reports of Toraymyxin treatment for severe ARDS caused by 2009 pandemic H1N1 influenza virus infection in Japan. In both reports, Toraymyxin treatment improved the patients hemodynamic status and successfully increased PaO_2/FIO_2 ratio, leading to full recovery of the patients.

Although the precise mechanism of the improvement of respiratory function is to be explored in the future, Toraymyxin hemoperfusion may offer a treatment method for severe cases of respiratory distress including influenza virus infection. (by N. Ida)

Articles

Pediatr Surg Int (2010) 26:187-193

Effect of polymyxin B-immobilized fiber hemoperfusion on respiratory impairment, hepatocellular dysfunction, and leucopenia in neonatal sepsis model.

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2 Department of Obstetrics and Gynecology, Nagoya City University Graduate School of Medical Sciences, Nagoya , Japan
3 Maternal and Child Health Department, VACSRA, Giza, Egypt
4 Neonatal Intensive Care Unit, Pediatric Hospital, Cairo University, Cairo, Egypt
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6 Department of Pediatrics Surgery, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

1. Abstract

Purpose Sepsis and septic shock remain a major source of morbidity and mortality in neonates despite advances in antimicrobials and aggressive supportive care. Our aim was to study the effects of polymyxin-B direct hemoperfusion (PMX-DHP) therapy on sepsis-induce respiratory impairment, liver dysfunction and leucopenia in a neonatal cecal ligation and perforation (CLP) model.

Methods Fourteen anesthetized and mechanically ventilated 3-day-old piglets underwent CLP and an arteriovenous extracorporeal circuit from 3 hr until 6 hr post-CLP, with a PMX column in the PMX-DHP treated group (7 piglets). Changes in oxygen saturation, PCO_2, base excess, white blood cell (WBC) count, platelet count, hematocrit (Hct%), serum glutamate pyruvate transaminase (SGPT), and serum glutamic oxaloacetic transaminase were measured before CLP and at 1, 3 and 6 hr after.

Results At 6 hr, the PMX-DHP group showed lower Hct%, and SGPT in comparison to the control group, but higher oxygen saturation and WBC count. No effects on the platelet count were found. The survival times of the PMX-DHP group were longer than in control.

Conclusion PMX-DHP therapy limited the respiratory impairment, liver dysfunction and leucopenia in a neonatal septic model, which resulted in an improvement of survival time.

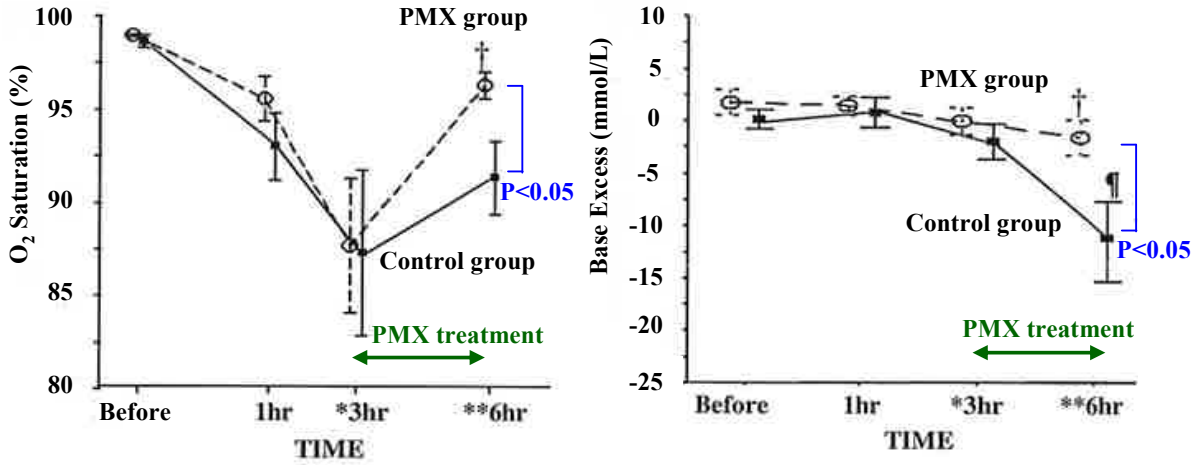

Figure Changes in oxygen saturation and base excess in neonatal piglet CLP model. Open circle and interrupted line: PMX-treated group (n=7). Closed square and continuous line: control group (n=7).

2. Points

This paper studied the effectiveness of Toraymyxin in a neonatal piglet sepsis model. Toraymyxin treatment improved respiratory impairment, liver dysfunction and leukopenia in a neonatal septic model, resulted in longer survival time. (By N. Ida)

Articles

Therapeutic Apheresis and Dialysis (2010) 14:589-595

Adverse Events in Therapeutic Apheresis: A Single Center Survey of Various Therapies

Takeshi Ishihara1, **Satoko Inoue**1, **Yukiko Takagi**1, **Taro Shimomura**1, **Yoshiaki Sagami**1, **Sayomi Katayama**2, **Yoko Eguchi**2, **Kenji Watase**3, **Masahiko Miyamoto**3, **and Tamotsu Minakata**3

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2 Department of Nursing, Osaka Red Cross Hospital, Osaka, Japan
3 Division of Nephrology, Osaka Red Cross Hospital, Osaka, Japan

1. Abstract

The aim of the study was to review the adverse events associated with various treatment modalities performed in a single apheresis facility. A total of 854 sessions with 10 types of apheresis therapies were performed and 154 (18.0 %) adverse events were observed over a four-year period. Of the adverse events, 77 were related to operational problems and another 77 sere complications associated with treatment. A transmembranous pressure abnormality constituted more than 80% of the operational problems. Nausea was the most frequent complication, accounting for 19 of the 77 treatment-related events. A total of 26 (16.9%) adverse events occurred in the early stage of the sessions, 40 (26.0%) in the middle stage, and 88 (57.1%) in the late stage. The information in this study can be used to improve the safety and efficacy of apheresis therapy.

Table Frequency of adverse events by treatment modality

	No. of treatments	No. of adverse events	Frequency of adverse events
LCAP	243	74	30.5%
LDL-A	207	6	2.9%
SPE	140	17	12.1%
GMA	84	6	7.1%
DFPP	75	34	45.3%
A-ECUM	41	4	9.8%
IA	33	8	24.1%
BA	14	5	35.7%
EA	14	0	0 %
ACA	3	0	0 %
Total	854	154	18.0%

Toraymyxin treatment

ACA, activated charcoal adsorption; A-ECUM, ascitic extracorporeal ultrafiltration method; BA, bilirubin adsorption, DFPP, double-filtration plasmapheresis; EA, endotoxin adsorption; GMA, granulocyte and monocyte adsorptive apheresis; IA, immunoadsorption; LCAP, leukocytapheresis; LDL-A, low-density lipoprotein adsorption; SPE, simple plasma exchange

2. Points

In this paper, authors examined the adverse events associated with various aphresis therapies in Japan. Among ten therapies performed in the authors' hospital, Toraymyxin therapy showed the lowest frequency of adverse events (frequency:0%, 0/14), while other apheresis therapies showed 3% to 45 % adverse events except for one therapy (0%, 0/3).
This results confirmed that Toraymyxin treatment is safe and low risk therapy. (By. N. Ida)

Articles

Journal of Critical Care (2010) doi:10.1016/j.jcrc.2010.11.010

Suppression of high-mobility group box-1 and receptor for advanced glycation end-product axis by polymyxin B-immobilized fiber hemoperfusion in septic shock patients

Tsukasa Nakamura1, **Eiichi Sato**1, **Nobuharu Fujiwara**1, **Yasuhiro Kawagoe**1, **Sayaka Maeda**2, **Sho-ichi Yamagishi**2

1 Division of Nephrology, Department of Internal Medicine, Shinmatsudo Central General Hospital, Chiba, Japan
2 Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume, Japan

1. Abstract

Purpose: Endotoxin plays a role in organ failure in septic shock patients. High-mobility group box 1 (HMGB1) and receptor for advanced glycation end-products (RAGE) axis is also involved in septic shock. We investigated here the effects of endotoxin removal by polymyxin B-immobilized polystyrene fiber (PMX-F) treatment on circulating levels of HMGB1, soluble RAGE (sRAGE), and interleukin-6 (IL-6) in septic shock patients.

Materials and Methods: Fifteen septic shock patients (70.1 ± 8.5 years) and 15 age- and sex-matched healthy volunteers were included in this study. Polymyxin B-immobilized polystyrene fiber treatment was repeated twice, separated by an interval of 24 hours. Blood samples were collected before and immediately after the second PMX-F treatment for determinations of biochemical variables.

Results: Systolic and diastolic blood pressures were significantly lower, and endotoxin, IL-6, HMGB1, and sRAGE levels were higher in septic shock patients compared with healthy volunteers. These parameters were significantly improved by PMX-F treatment. The changes in endotoxin obtained by PMX-F treatment were correlated with those in HMGB1, sRAGE, and IL-6. Multiple stepwise regression analysis revealed that IL-6 was a sole independent correlate of endotoxin.

Conclusions: Our present study suggests that PMX-F treatment could block the HMGB1-RAGE axis in patients with septic shock via removal of endotoxin-induced inflammatory reactions.

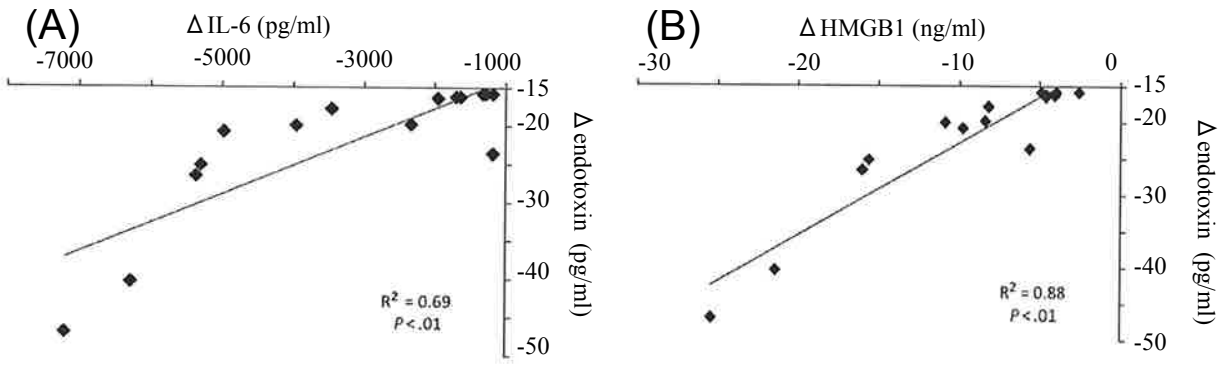

Figure Correlation of the changes in endotoxin (Δ endotoxin) obtained by PMX-F therapy with those in (A) IL-6 (Δ IL-6) and (B) HMGB1 (Δ HMGB1).

2. Points

HMGB1 is known as a late mediator of endotoxin shock. HMGB1 binds to cell surface receptor of AGE, RAGE, and the inhibition of HMGB1-RAGE axis is suggested to be a possible therapeutic strategy of sepsis.

In this paper, two sessions of PMX hemoperfusion decreased serum levels of endotoxin, as well as those of IL-6, HMGB1, and sRAGE, and the changes in endotoxin levels significantly correlated with those of IL-6(A), HMGB1(B), and sRAGE.

The results of this paper suggest that Toraymyxin treatment could block inflammatory reactions through IL-6 and HMGB1-RAGE axis in septic shock patients via endotoxin removal from the patients blood. (By N. Ida)

Articles

Gen Thorac Cardiovasc Surg (2011) 59: 98-104

Intraoperative direct hemoperfusion with a polymyxin-B immobilized fiber column for treatment of infective endocarditis

Toshinori Totsugawa, MD · Masahiko Kuinose, MD
Hidenori Yoshitaka, MD · Yoshimasa Tsushima, MD
Atsuhisa Ishida, MD · Genta Chikazawa, MD
Keijiro Katayama, MD · Arudo Hiraoka, MD

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1. Abstract

Purpose. Endotoxin adsorption treatment (direct hemoperfusion using a polymyxin-B immobilized fiber column, or PMX-DHP) is now considered a useful option for treating severe sepsis. However, the efficacy of PMX-DHP for infective endocarditis (IE), in which the causative microorganisms are usually Gram-positive cocci, remains unclear. In the present study, we investigated the impact of intraoperative PMX-DHP on clinical parameters during the treatment of IE.

Methods. From November 2006 to December 2009, a total of 11 patients with active IE underwent emergent surgery using intraoperative PMX-DHP. The perioperative courses of these patients were compared with those of seven patients who underwent emergent surgery for active IE with the conventional method from January 2003 to October 2006.

Results. PMX-DHP was associated with a significant decrease in the postoperative catecholamine dose and duration. Intubation time and intensive care unit length of stay for the PMX-DHP group was significantly shorter than that for the conventional therapy group. There was also a significant difference in the number of failed organs postoperatively between the two groups.

Conclusion. Intraoperative PMX-DHP demonstrated several positive effects, such as a drastic decrease in the doses of inotropic agents and shortening of the duration

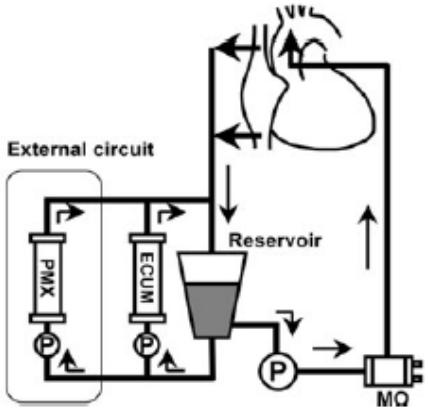

Figure Cardiopulmonary bypass circuit combined with PMX direct hemoperfusion

Table 4 Clinical parameters

Parameter	Conventional ($n = 7$)	PMX-DHP ($n = 11$)	P
Postoperative MAP (mmHg)	62 ± 6.9	68 ± 7.2	0.085
Postoperative CaI	7.1 ± 3.8	1.3 ± 0.6	0.0001
Duration of catecholamine administration (h)	82 ± 56	19 ± 10	0.0019
Postoperative P/F ratio	187 ± 59	237 ± 153	0.42
Intubation time (h)	31 ± 18	12 ± 11[a]	0.014
Postoperative SOFA score	8.0 ± 1.5	6.8 ± 2.2	0.24
No. of postoperative failed organs	1.29 ± 0.48	0.64 ± 0.67	0.043

[a]One patient who was intentionally managed under 7 days of intraaortic balloon pumping support and deep sedation with mechanical ventilation for prevention of recurrent left ventricular rupture was excluded from the comparison of intubation time

2. Points

In this report from Japan, PMX column was used combined with cardiopulmonary bypass circuit during the surgery of infective endocarditis (IE) patients. PMX showed positive effects on clinical parameters such as postoperative catecholamine administration, intubation time and the number of failed organs. Although common causative microorganism of IE is gram positive cocci, several studies have demonstrated that cardiac surgery using cardio-pulmonary bypass could induce endotoxemia. The use of PMX during or after cardiac surgery may benefit patients through the reduction of blood endotoxin. (By N. Ida)

Articles

Lancet Infectious Disease (2011) 11: 65–71

Endotoxin removal devices for the treatment of sepsis and septic shock

Davies B and Cohen J

Department of Clinical Microbiology and Infectious Diseases, Brighton and Sussex Medical School, and Brighton and Sussex University Hospitals Trust, Brighton, UK

1. Abstract

A substantial body of experimental and clinical evidence suggests that neutralizing or removing lipopolysaccharide endotoxin would be an effective adjunctive approach to the management of Gram-negative sepsis. Polymyxins are a group of cyclic cationic polypeptide antibiotics. Although they have useful antimicrobial activity against Gram-negative bacteria, their clinical use has been limited because of toxicity. However, in addition to their antimicrobial property, polymyxins can bind to and neutralise endotoxin. Thus, investigators have explored the possibility of using polymyxin bound to a solid-phase carrier for specific haem-adsorption in patients with sepsis, thereby retaining the lipopolysaccharide-binding properties but minimising systemic toxic effects. This system has been widely used in Japan for many years, but convincing clinical evidence of efficacy is lacking. A recent Italian study has some promising data. Although polymyxin has been the principal agent used to explore this approach, other molecules have the ability to bind endotoxin, and some of these have very recently been proposed as the basis for other endotoxin-removal devices. The available evidence is reviewed to assess the potential use of such devices in clinical practice.

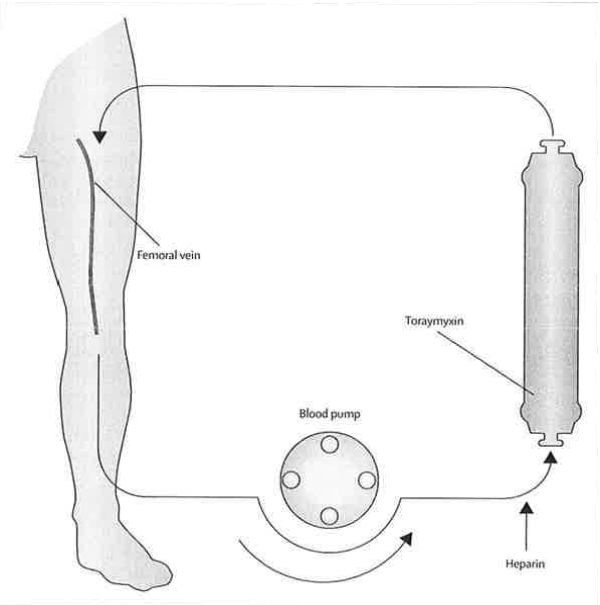

Figure. Clinical application of Toraymyxin

2. Points

In this newly published article, various endotoxin removal treatments were reviewed with main focus on Toraymyxin. The authors pointed out the high potential of this treatment, mentioning that “Despite a strong scientific rationale, endotoxin-removal devices have been seen as inconvenient, time consuming to set up, non-specific in their action, and potentially too expensive. But with the failure of other new drugs (which are potentially just as expensive), and the ease and frequency with which haemofiltration and haemodialysis are now carried out in ICUs, there is renewed interest in this approach.” Also, the authors showed the high expectation toward the ongoing clinical trials (EUPHRATES and EUPHAS2) for the wider use of Toraymyxin treatment outside of Japan. You can see the full article in the following website.

http://www.mdconsult.com/das/article/body/239937810-3/jorg=journal&source=&sp=23846769&sid=0/N/779490/s1473309910702206.pdf?issn=1473-3099

Articles

J Anesthesia (2010) 24: 705–715

Early recovery in hemodynamics after direct hemoperfusion with polymyxin B-immobilized fibers may predict mortality rate in patients with septic shock

Atsuko Kobayashi, Yasushi Iwasaki, Yuichi Kimura, Yoshiaki Kawagoe, Yoshihito Ujike

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1. Abstract

Purpose This retrospective and observational study attempted to determine whether the rapid improvement in hemodynamic parameters and the subsequent discontinuation or decrease of catecholamine infusion shortly after direct hemoperfusion with polymyxin B-immobilized fibers (PMX) may be strong predictors of mortality in patients with septic shock.

Methods Retrospectively, 46 patients were divided into two groups; those who survived more than 30 days after PMX (survival group, S group) and those who died within 30 days (nonsurvival group, NS group). Sequential Organ Failure Assessment (SOFA) scores, mean arterial pressure, catecholamine index (CAI), and vasopressor dependency index (VDI) were examined before and after PMX. The same parameters were examined on days 3, 4, 5, 6, 8, and 16 after PMX.

Results CAI in the S group significantly decreased from 14.7 (95% CI, 10.3–19.1) at baseline to 6.4 (95% CI, 3.7–9.2; P<0.001) at post-PMX, whereas a significant decrease in CAI was not observed in the NS group (23.1; 95% CI, 15.4–30.7 to 18.1; 95% CI, 11.6–24.7; P = 0.114). The significant decrease in VDI at post-PMX was observed both in the S group and in the NS group. If the cutoff point of VDI at post-PMX is 0.2, there is a significant difference in numbers of the S group (VDI≧0.2, n = 24; VDI<0.2, n = 2) and NS group (VDI ≧ 0.2, n = 8; VDI<0.2, n = 20) using Fisher's exact test.

Conclusions We concluded that the early improvement in CAI and VDI shortly after PMX might be prognostic indicators for survival.

Table 3 Physiological endpoints by treatment group at baseline and at post-polymyxin B-immobilized fiber (PMX) hemoperfusion

Physiological endpoints	Mean (95% confidence interval)					
	S group (n = 26)			NS group (n = 20)		
	Baseline (n = 26)	Post-PMX (n = 26)	P value	Baseline (n = 20)	Post-PMX (n = 20)	P value
Mean arterial pressure, mmHg	57 (54–61)	92 (85–98)	<0.0001	53 (48–58)	71 (62–80)	<0.0001
Catecholamine index (CAI)	14.7 (10.3–19.1)	6.4 (3.7–9.1)	<0.0001	23.1 (15.4–30.7)	18.1 (11.6–24.7)	0.114
Vasopressor dependency index	0.27 (0.18–0.37)	0.08 (0.04–0.11)	<0.0001	0.48 (0.31–0.65)	0.32 (0.18–0.46)	0.026
PaO_2/F_IO_2	281 (236–326)	305 (257–353)	0.378	251 (180–323)	224 (176–271)	0.701
Creatinine, mg/dl	1.8 (1.2–2.4)	1.9 (1.3–2.6)	0.557	2.8 (1.9–3.7)	2.8 (1.9–3.7)	0.797
Renal replacement therapy	5 (19.2%)	4 (15.4%)	>0.99	8 (40%)	9 (45%)	0.9999

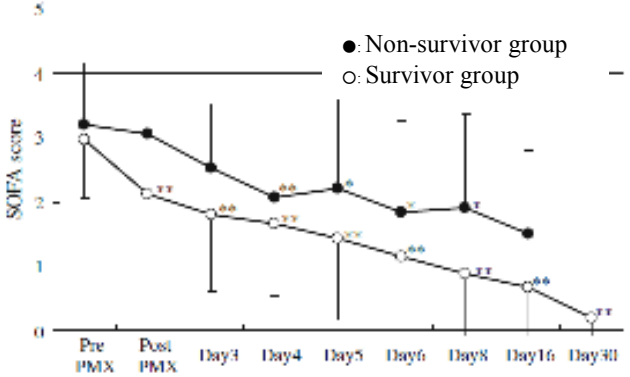

Fig Change in cardiovascular SOFA score

CAI = (dopamine dose X 1) + (dobutamine dose X 1) + (adrenaline dose X 10) + (noradrenaline dose X100) + (phenylephrine dose X 100)

VDI = CAI/mean arterial pressure

2. Points

In this study from Japan, the efficacy of Toraymyxin on 46 septic shock patients was analyzed retrospectively. Cardiovascular SOFA score improved most rapidly in response to Toraymyxin treatment in each item of other five SOFA scores (central nervous system, pulmonary, blood coagulation system, hepatic and renal SOFA). This means the high potential of the column for the rapid recovery from patients' shock state. (By N. Ida)

Articles

Transplantation Proceedings 2011; **43**:1085-1093

Management of sepsis during Mars treatment in acute on chronic liver failure.

Novelli G, Morabito V, Pugliese F, Ferretti G, Novelli S, Ianni S, Lai Q, Rossi M, Berloco PB.
SourceDipartimento "P. Stefanini," Chirurgia Generale e Trapianti d'Organo, Sapienza Università di Roma, Rome, Italy.

1. Abstract

INTRODUCTION: The aim of our study was a 30-day follow-up of the use of early detection of endotoxin by the endotoxin activity assay (EAA) for patients with acute liver failure superimposed on chronic liver disease (AoCLF) and treated with polymyxin-B hemoperfusion-based (PMX-DHP) treatment and albumin dialysis in the molecular adsorbent recirculating system (MARS*).
MATERIALS AND METHODS: From February 2008 to July 2010, we evaluated 10 AoCLF patients experiencing systemic inflammatory response syndrome (SIRS) in association with suspected infection and an EAA-positive test (>0.60). These patients awaiting liver transplantation (OLT) showed similar Model End-Stage Liver Disease (MELD) scores (range, 19-25) and encephalopathy grade ≤ 2. Five patients received therapy to remove endotoxins with PMX-DHP with MARS treatment for liver failure (group A); the other 5 patients received MARS treatment only (group B).
RESULTS: Two PMX-DHP treatments were performed in 4 group A patients (average EA = 0.66 [range, 0.61-0.70]) and 3 treatments for 1 patient (EA = 0.92). All 5 subjects underwent an average of 4 MARS treatments (range, 3-5). At the end of therapy, the median EA level was 0.42 (range, 0.37-0.48). As reported in the literature, we achieved a significant improvement in liver and kidney functions using MARS. Measurements of lactate, interleukin (IL)-6, and tumor necrosis factor (TNF)-α were significantly improved among patients treated with the extracorporeal therapies. At 30 days of observation, all 5 patients treated with MARS plus PMX-DHP are alive. In group B, a mean of 7.5 MRAS treatments were performed. We observed an improvement in hemodynamic and liver functions with reduced levels of proinflammatory cytokines and lactates in 4 patients. One patient showed no improvement in clinical status with the development of sepsis and subsequent multiorgan failure after 24 days.
CONCLUSION: The possibility of an early diagnosis using the EAA in AoCLF patients could prevent the progression of the sepsis cascade. The use of PMX-DHP and MARS in these patients, could lead to resolution of clinical status in a short time.

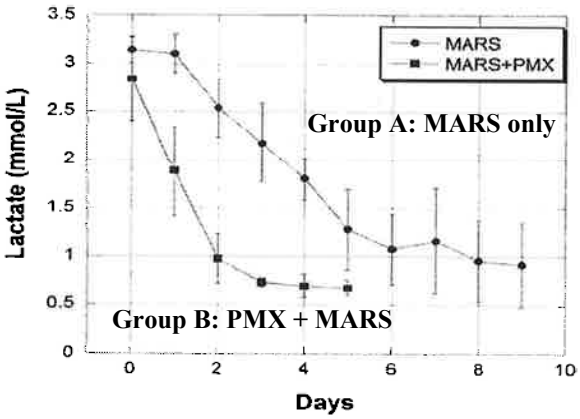

Fig. Modulation of lactate level in two groups.
The association between MARS and PMX can determine a more rapid decrease of lactate levels <2 mmol/L within 48 hours.

2. Points

In this study from Italy, the efficacy of Toraymyxin for patients with acute liver failure superimposed on chronic liver disease (AoCLF) with high EAA level was evaluated. Toraymyxin treatment in combination with MARS (albumin dialysis) was more effective than the treatment with MARS alone, resulted in the improvement of clinical status in all 5 patients. Toramyxin could also reduce the hospital stay days as well as achieve more rapid decrease of lactate and inflammatory cytokine levels. (By N. Ida)

* MARS system web site;
http://www.gambro.com/en/global/Products/Acute-Care/Acute-Monitors/MARS/

Articles

Shock (2011) doi:10.1097/SHK.0b013e318225f839, PMID:21654557

Polymyxin B-Immobilized Fiber Column Hemoperfusion Therapy for Septic Shock.

Mitaka C and Tomita M

Department of Critical Care Medicine, Tokyo Medical and Dental University Graduate School
Clinical Research Center, Tokyo Medical and Dental University Hospital Faculty of Medicine.

1. Abstract

Endotoxin, an outer membrane component of Gram-negative bacteria, plays an important role in the pathogenesis of septic shock. Endotoxin adsorption therapy by polymyxin B-immobilized fiber column hemoperfusion (PMX) has been used for the treatment of septic shock patients in Japan since 1994. The covalent binding of polymyxin B onto the surface of the polystyrene-based carrier fiber in PMX inactivates the endotoxin in the blood without exerting toxicity. This study was performed as a systematic review to evaluate the efficacy and mechanism of PMX treatment in patients with septic shock. The PubMed database and references from identified articles were used to search and review the literature relating to the efficacy and mechanism of PMX treatment in patients with septic shock. PMX adsorbed monocytes, activated neutrophils, and anandamide as well as endotoxin through direct covalent bond, hydrophobic and ionic interactions, and hydrodynamics, and reduced the blood concentrations of inflammatory cytokines, plasminogen activator inhibitor (PAI)-1 and adhesion molecules. PMX increased blood pressure and reduced the dosage requirements for vasopressive/inotropic agents. The meta-analysis showed that PMX treatment had beneficial effects on the hemodynamics, pulmonary oxygenation, and mortality. These beneficial effects may be attributable to the direct adsorption of endotoxin, monocytes, activated neutrophils, and anandamide, as well as indirect decrease in inflammatory cytokines and other mediators. PMX treatment has additional effects on reducing endothelial damage, proapoptotic activity and immunosupression. Further studies will be needed to confirm the efficacy and mechanism of PMX treatment in septic shock.

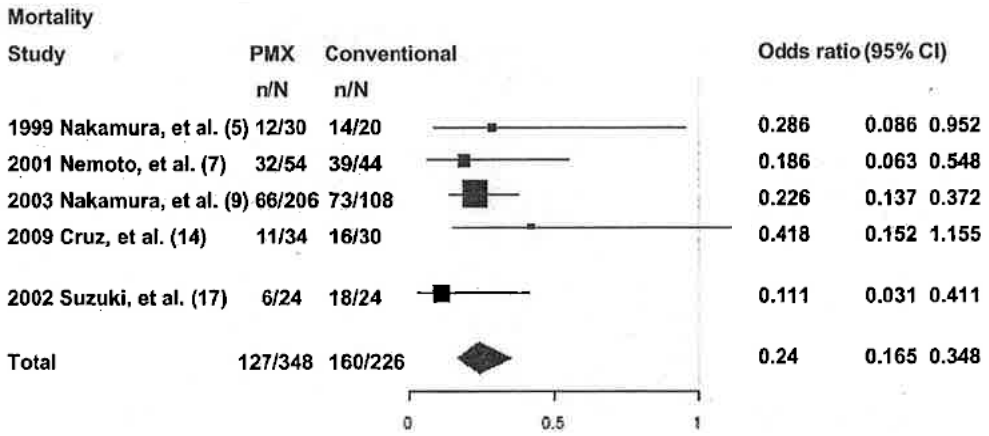

Fig. Effect of PMX treatment on mortality. Size of data markers is proportional to the weight of each study in the forest plot. n; number of non-survivor, N; number of patients, Horizontal bars = 95% confidence interval (CI).

2. Points

This systematic review from Japan evaluated 17 papers from 1999 to 2009 on Toraymyxin treatment for septic shock patients including EUPHAS study. Results of this meta-analysis clearly showed the beneficial effects of the treatment on hemodynamics, pulmonary oxygenation and mortality in patients with septic shock. The changes of blood levels of endotoxin and various mediators by Toraymyxin hemoperfusion were also reviewed. We think the article is helpful to comprehend the clinical efficacy of Toraymyxin treatment. (By N. Ida)

Articles

Blood Purification 2011; **32**:139-142

Hemoperfusion Treatment in a Septic Shock Patient with Autosomal Dominant Polycystic Kidney Disease and Increased HMGB1 Protein Levels

Nakamura T[a]. , Kagawa Y[a]. , Ueda Y[b], Yamada S[c]. and Koide H[d]

[a] Department of Medicine, Shinmatsudo Central General Hospital, Chiba , [b] Department of Pathology, Koshigaya Hospital, Dokkyo University School of Medicine, Saitama , [c] Central Institute, Shino-Test Corporation, Kanagawa , and [d] Department of Medicine, Koto Hospital, Tokyo , Japan

1. Abstract

This case report describes polymyxin B-immobilized fiber (PMX-F) treatment of septic shock caused by pyelonephritis in a 68-year-old woman with autosomal dominant polycystic kidney disease. She was admitted for severe lower left abdominal pain, high fever (40℃) and gross hematuria. Her endotoxin and high-mobility group box-1 protein (HMGB1) levels were extremely elevated. Her blood pressure was 68/36 mm Hg. Urinalysis revealed innumerable white blood cells (WBCs).

Blood and urine cultures were positive for Klebsiella pneumoniae and Pseudomonas aeruginosa . Plain abdominal radiography showed large kidney shadows and calcium deposition. Septic shock with endotoxemia was diagnosed. Her symptoms of septic shock persisted for 3 days with antibiotics, γ-globulin and dopamine. Direct hemoperfusion was performed twice with a PMX-F column. The patient's body temperature, WBC count and C-reactive protein level decreased. Her blood endotoxin level and blood HMGB1 level also decreased to an almost normal level. She was discharged on day 23 after admission.

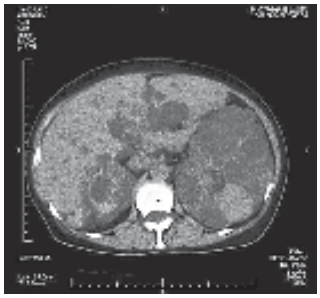

Fig. 1. Abdominal CT image. Multiple cysts are seen in the liver and kidneys. High density areas are seen in both kidneys.

Table 1. Clinical variables before and after PMX-F hemoperfusion

	Admission	Before PMX-F	After 1st PMX-F	After 2nd PMX-F	Next day
SBP, mm Hg	68	78	96	116	122
DBP, mm Hg	36	46	68	74	80
Body temperature, °C	40.0	39.6	38.0	37.2	36.6
WBC, /μl	30,000	28,600	11,000	8,000	6,800
CRP, mg/dl	32.0	34.0	8.6	4.2	2.0
Endotoxin, pg/ml	2,200	2,280	220.0	86.4	22.2
HMGB1, ng/ml	230.8	240.6	48.5	18.2	3.7

SBP = Systolic blood pressure; DBP = diastolic blood pressure.

2. Points

The paper is a case report from Japan about PMX treatment for a septic shock patient with autosomal dominant polycystic kidney disease. Before the treatment, she was in a severe inflammation state with extremely high levels of blood endotoxin and HMGB1, a late mediator of lethal endotoxemia. After two sessions of PMX treatment, blood pressure and body temperature were normalized concomitant with normalization of WBC, CRP levels. Endotoxin and HMGB1 levels were also decreased significantly after PMX treatment. This report provides a case of successful PMX treatment for severe septic shock due to pyelonephritis. (By N. Ida)

Articles

Therapeutic Apheresis and Dialysis 2011; **15**:349-354

Angiopoietin Balance in Septic Shock Patients with Acute Lung Injury: Effect of Direct Hemoperfusion with Polymyxin B-Immobilized Fiber

Itaru Ebihara,[1] Kouichi Hirayama,[2] Miho Nagai,[2] Tomoko Kakita,[3] Kentaro Sakai,[1] Reiko Tajima,1 Chihiro Sato,[1] Hiromi Kurosawa,[1] Amane Togashi,[1] Akiko Okada,[1] Joichi Usui,[4] Kunihiro Yamagata,[4] and Masaki Kobayashi[2]

[1]Department of Nephrology, Mito Saiseikai General Hospital, Mito, [2]Department of Nephrology, Tokyo Medical University Ibaraki Medical Center, Ami, [3]Department of Nephrology, Osaka Medical College Hospital, Takatsuki, Osaka, and [4]Department of Nephrology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

1. Abstract

Acute lung injury (ALI) in sepsis is characterized by an increase in microvascular permeability, resulting in pulmonary edema. Several studies have suggested that angiopoietin-1 and -2 play a contributory role in the pathogenesis of ALI. Polymyxin B-immobilized fiber column hemoperfusion is effective for sepsis-induced ALI. We investigated the angiopoietin levels before and after direct hemoperfusion with polymyxin B-immobilized fiber column (PMX) therapy. Enzyme-linked immunoassay was used to measure the serum angiopoietin-1 and -2 levels in 25 patients with septic shock treated with PMX. Eleven of the 25 patients were diagnosed with ALI. There was a significant positive correlation between the angiopoietin-1 level and the PaO2/FiO2 ratio, but there was a significant inverse correlation between the angiopoietin-2 level and the PaO2/FiO2 ratio. The mean angiopoietin-1 level before PMX therapy in the ALI group was significantly lower and the mean angiopoietin-2 level was significantly higher than in the non-ALI group.The mean angiopoietin-1 level of the ALI patients in response to PMX therapy was increased during PMX therapy, but that of the non-ALI patients with newly occurring ALI showed a decreased angiopoietin-1 level. On the other hand, the mean angiopoietin-2 level of the responders was decreased during PMX therapy, but that of patients with newly occurring ALI showed an increased angiopoietin-2 level. This result suggested that each angiopoietin-1 and -2 level may play a role in the pathogenesis of ALI and that PMX therapy ameliorates the angiopoietin balance in patients with ALI in sepsis.

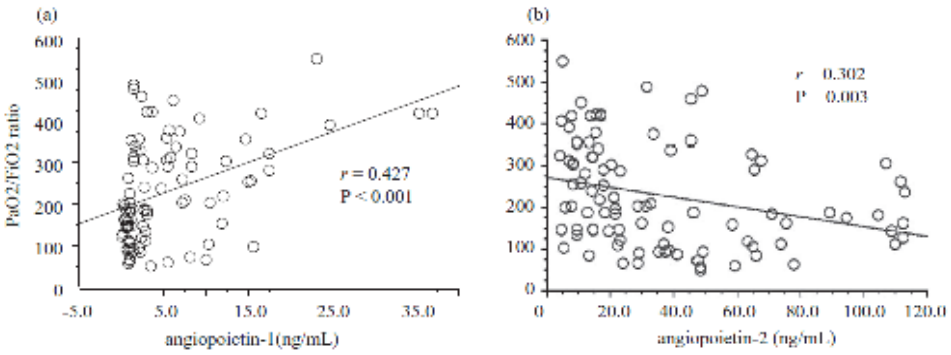

Fig.1 Correlation between plasma angiopoietin levels and PaO2/FIO2 ratio.

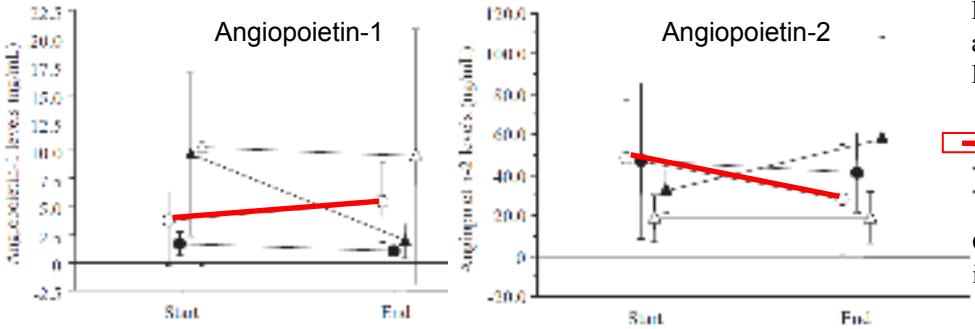

Fig.2 Changes of plasma angiopoietin levels during PMX treatment.

Group B: ALI patients who improved during PMX therapy

2. Points

Angiopoietins are proteins associated with blood vessel integrity and capillary permeability. Recent publications showed that blood levels of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) are clinically relevant biomarkers for severe sepsis and acute lung injury. In this paper from Japan, the authors investigated the changes of angiopoietin levels of septic ALI patients during PMX treatment and found out that Ang-1/ Ang-2 balance were improved in parallel with the improvement of lung function of the patients. It would be worth studying further about the usefulness of angiopoietins as an indicator of clinical effectiveness of PMX treatment.

Articles

Eur Surg Res 2011; **47**:135-140

Changes in Serum S100A12 and sRAGE Associated with Improvement of the PaO(2)/FiO(2) Ratio following PMX-DHP Therapy for Postoperative Septic Shock.

Takahashi G, Hoshikawa K, Matsumoto N, Shozushima T, Onodera C, Kan S, Akitomi S, Kikkawa T, Tomisawa Y, Kojika M, Sato N, Inoue Y, Suzuki K, Wakabayashi G, Endo S.

Department of Critical Care Medicine, Iwate Medical University, School of Medicine, Morioka, Japan.

1. Abstract

Background: Endotoxin (Et) adsorption therapy with a column of polymyxin B-immobilized fibers (PMX) is effective in improving the partial pressure of arterial oxygen/fraction of inspired oxygen ratio (PaO(2)/FiO(2) ratio) and increasing mean arterial blood pressure (MAP) in sepsis. S100A12 and soluble receptor for advanced glycation end product (sRAGE) are useful as early markers of acute lung injury. Purpose: To investigate the effect of improving the PaO(2)/FiO(2) ratio by PMX-direct hemoperfusion (PMX-DHP) on production of S100A12 and sRAGE. Subjects and Methods: Sepsis patients after surgery for perforation of the lower gastrointestinal tract were adopted as the subjects. We retrospectively reviewed the cases of 20 patients on mechanical ventilation and continuous administration of norepinephrine. We recorded PaO(2)/FiO(2) ratio, MAP, and norepinephrine doses. S100A12, sRAGE, and Et levels were measured before and after PMX-DHP. Results: The PaO(2)/FiO(2) ratio and MAP improved significantly after PMX-DHP ($p < 0.05$). S100A12 and Et decreased significantly after PMX-DHP ($p < 0.05$). No differences were observed in sRAGE. Conclusion: S100A12 is useful as a marker that reflected improvement in the PaO(2)/FiO(2) ratio after PMX-DHP. We consider PMX-DHP to be useful as adjunctive therapy for sepsis that reduces the Et and corrects the pathology in the early stage.

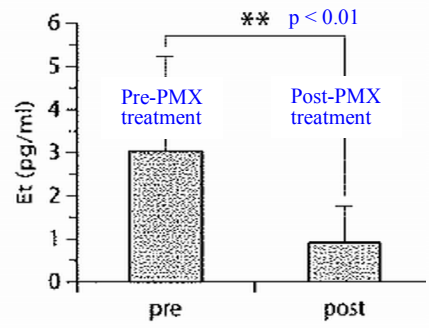

Fig.1 Changes in Et level

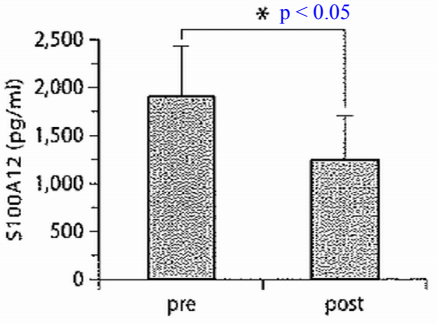

Fig.2 Changes in S100A12 level

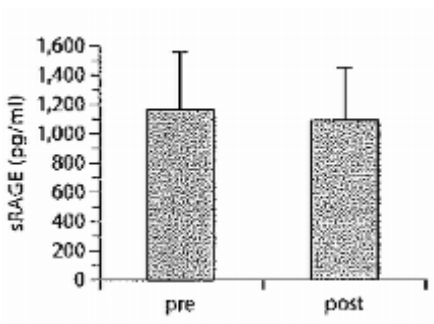

Fig.3 Changes in sRAGE level

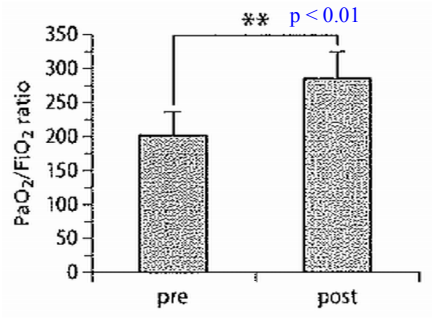

Fig.4 Changes in P/F ratio

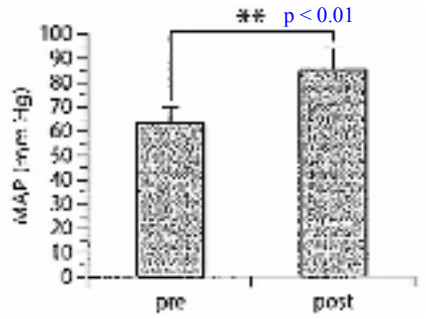

Fig.5 Changes in MAP

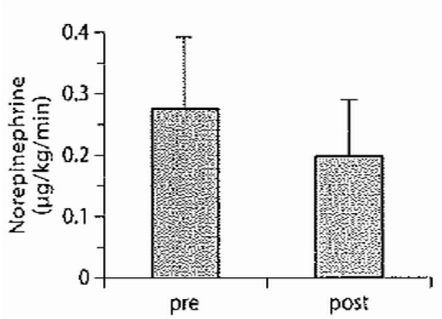

Fig.6 Changes in Norepinephrine dose

2. Points

In recent years, S100A12 and its soluble receptor, sRAGE, have drawn attention as specific markers of ALI. S100A12 expression in neutrophils increases in response to LPS stimulation and causes inflammatory response via the signaling through its cell surface receptor, RAGE (receptor for advanced glycation endoptoduct). In this paper from Japan, Toraymyxin treatment was shown to reduce plasma endotoxin and S100A12 level, as well as to improve P/F ratio and mean arterial pressure, raising the possibility that S100A12 is one of the key mediators which reflect the therapeutic effects of Toraymyxin.

Articles

Blood Purification 2011; **32**:331-340

Cost-Effectiveness Analysis of Polymyxin-B Immobilized Fiber Column and Conventional Medical Therapy in the Management of Abdominal Septic Shock in Italy.

Berto P[a], Ronco C[b], Cruz D[b], Melotti RM[c], Antonelli M[d].

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1. Abstract

Introduction: Severe abdominal sepsis and septic shock are common problems in intensive care units (ICUs), and carry high mortality. The purpose of this economic analysis was to determine the cost-effectiveness of polymyxin B immobilized fiber column (PMX-F) plus conventional therapy (CT) (PMX-F-CT) versus CT alone for patients with severe sepsis/septic shock of abdominal origin, in the perspective of the Italian hospital. Methods: This was a retrospective cost-effectiveness analysis (CEA) based on data of clinical efficacy and consumption of resources collected alongside an Italian randomized clinical trial. 64 patients were enrolled following emergency surgery for intra-abdominal infection in 10 tertiary care ICUs from December 2004 to December 2007. Direct medical costs analyzed in the study included the consumption of hospital days, ICU days, catecholamine treatment days, renal replacement therapy days, mechanical ventilation treatment days, and the use of the PMX-F device. Resources were valued using published 2010 tariffs and market values. All-cause hospital mortality was extrapolated to survival as expected life years (LY) per patient/arm: for each survivor, average age-gender-related years of life expectancy were retrieved from national life tables; for deceased patients, only the number of CRF reported survival days was retained. Baseline expected years of survival were weighed by the severity of sepsis, according to individual Acute Physiology and Chronic Health Evaluation (Apache) II scores, showing that age/disease severity were comparable in the two groups before treatment initiation. Life expectancy per patient in each treatment group was thus calculated as the combination of life expectancy from Italian National Statistics Institute life tables and intra-hospital mortality detected in the Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock (EUPHAS) study. After all costs and 3% discounted survival years were calculated per patient per treatment arm, the incremental CEA was run to obtain the incremental cost-effectiveness ratio (ICER). Univariate sensitivity analyses and 2,000 bootstrap replications were run to test the robustness of the study results. Results: Based on the expected survival years (mean discounted PMX-F-CT 9.37 LY/patient, CT 4.92 LY/patient; difference for PMX-F-CT 4.45 LY/patient; mean undiscounted PMX-F-CT 13.92 LY/patient, CT 7.19 LY/patient; difference +6.73 LY/patient), and the expected mean cost (PMX-F-CT mean 59,922 EUR/patient, CT mean 42,712 EUR/patient; difference for PMX-F-CT 17,211 EUR/patient), the mean ICER for PMX- F-CT resulted in 3,864 EUR/life year gained (LYG; ICER 2,558/undiscounted LYG). Results of the base-case CEA were confirmed by all sensitivity analyses, with ICER values always well below commonly accepted value thresholds. Conclusion: PMX-F-CT versus CT is a cost-effective intervention for treatment of severe sepsis/septic shock of abdominal origin and could be considered for use in the Italian National Health System hospital setting.

Table 4. Cost effectiveness analysis

	Effect, years			Cost, EUR			
	CT (n = 30)	PMX-F-CT (n = 34)	difference	CT (n = 30)	PMX-F-CT (n = 34)	difference	ICER
Undiscounted survival years							
Mean	7.19	13.92	6.73	42,712	59,922	17,211	2,558
SD	12.51	14.55		57,659	31,338		
SE	2.67	3.10		12,293	6,681		
Median	0.08	11.23		25,081	49,857		
p value*	0.0112				0.0005		
Discounted survival years							
Mean	4.92	9.37	4.45	42,712	59,922	17,211	3,864
SD	7.69	8.95		57,659	31,338		
SE	1.64	1.91		12,293	6,681		
Median	0.08	9.41		25,081	49,857		
p value*	0.0112				0.0005		

$$\frac{\text{Costs (EUR)}_{\text{PMX-F}} - \text{Costs (EUR)}_{\text{CT}}}{\text{Outcome (years)}_{\text{PMX-F}} - \text{Outcome (years)}_{\text{CT}}} = \text{ICER}$$

2. Points

This study, conducted in Italy by an unrestricted grant from ESTOR SpA, demonstrates the effectiveness of Toraymyxin from health economics' point of view. Cost-effectiveness analysis of medical treatments is getting more attractions in recent years. (By N. Ida)

Articles

J Intensive Care Med (2011); doi:10.1177/0885066611425759

Extracorporeal Therapies in Sepsis.

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1. Abstract

The treatment of sepsis is an ongoing challenge for clinicians; despite the wide choice of effective antibiotics to treat infection, sepsis remains the leading cause of morbidity and mortality for patients admitted to an intensive care unit. Dysregulation of the immune response is now recognized to be a key factor in multiple organ dysfunction, yet our therapy for inflammation remains ineffective. It has been advocated for more than a decade that cytokine reduction in blood compartment could lead to a reduction in mortality in sepsis. Over the years, multiple extracorporeal techniques have evolved, with the intent of influencing the circulating levels of inflammatory mediators like cytokines and chemokines, the complement system, as well as factors of the coagulation system. These include high-volume hemofiltration, use of high cutoff membranes, and systems based on adsorption, such as coupled plasma filtration adsorption and the polymyxin-B column. In addition, new experimental systems that utilize human phagocytic cells and immobilized antibodies for targeted immunomodulation have emerged. In the context of limited resources and growing expansion in the availability of technologies, a better understanding of these therapies is required before they can be properly integrated into standard clinical practice in the hope of influencing major clinical outcomes. In this article, we will provide a concise overview of selected extracorporeal modalities currently in clinical use and briefly introduce some new promising techniques for sepsis.

Table. Extracorporeal Blood Purification Techniques in Sepsis

Technique	Aim	Principle	Reported Results
High-volume hemofiltration (HVHF)	Nonselective removal of inflammatory mediators	Convection	Reduces vasopressor requirements, reduces concentrations of inflammatory mediators in blood, and observed mortality lower than predicted mortality
High cutoff membranes (HCOM)	Nonselective removal of inflammatory mediators	Convection	Reduces vasopressor requirements, high clearance of inflammatory mediators moderates leukocyte proliferation, normalizes PMN phagocytosis
Polymyxin-B column (PMX-F)	Selective removal of endotoxin	Adsorption	Reduces vasopressor requirement, increases blood pressure, ameliorates organ dysfunction, reduces short-term mortality
Coupled plasma filtration adsorption (CPFA)	Nonselective removal of inflammatory mediators	Plasma adsorption	Reduces concentrations of inflammatory mediators in blood, restores leukocyte responsiveness
Cytokine adsorbing columns	Nonselective removal of inflammatory mediators	Plasma adsorption	Reduces cytokine levels, improvement in respiratory parameters
Renal assist device (RAD)	Substitute the filtration, transport, metabolic, endocrine and immunologic functions of the kidney	Cell-based therapy	Ameliorates the cytokine profile, improves calcium, phosphate, urea, and creatinine levels
Extracorporeal immune support system (EISS)	Attenuation of excessive antiinflammatory response	Cell-based therapy	Reduces vasopressor requirement, reduces concentrations of endotoxin and inflammatory markers (eg CRP, procalcitonin) in blood
Leukocyte inhibition module (LIM)	Attenuation of excessive proinflammatory response	Antibody-based therapy	No studies in sepsis

Abbreviations: CRP, C-reactive protein; PMN, polymorphonuclear

2. Points

This article reviews various extracorporeal blood purification techniques for sepsis treatment including Toraymyxin. The authors comment that extracorporeal therapies in sepsis is now being increasingly used not only for renal support for acute renal failure but also for multiple organ support and even for immunomodulation. Among them, Toraymyxin is one of few techniques which have evidence from randomized trials to lend support to their use in specific clinical settings

Articles

Critical Care 2011, 15 (Suppl 3):P42 (doi: 10.1186/cc10411)

POSTER PRESENTATIONS

Sepsis 2011

P42 "Efficacy of endotoxin absorption therapy on sepsis by polymyxin B-attached fibers"

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1. Abstract

Introduction Endotoxin plays a role in the development of Gramnegative bacterial sepsis. In Japan, polymyxin B-attached fibers (PMX-B) are used clinically as an endotoxin absorption therapy to neutralize the biological activity of lipid A, the immunomodulatory center of lipopolysaccharide (LPS) endotoxin. Because hemodynamic improvement is not seen in all cases, it cannot be assumed that this therapy will be effective against all cases of sepsis.

Hypothesis Endotoxin absorption therapy is effective against abdominal infection. Moreover, the mortality rate significantly improved in endotoxin-positive cases of abdominal infection.

Methods Between 1997 and April 2008, endotoxin absorption therapy was performed on 105 septic patients in the ICU of Hyogo College of Medicine and the Osaka City General Hospital. The 105 cases were divided into an abdominal infection group (n = 45) and a nonabdominal infection group (n = 60). Before and after therapy, the endotoxin level was measured in patients using the limulus amoebocytelysate (LAL) and endotoxin activity assay (EAA) methods. Moreover, we measured blood pressure, cardiac index, and the administered dose of catecholamine. Using a retrospective analysis, we compared Sequential Organ Failure Assessment (SOFA) scores; the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria; and the 28-day survival rate between the two groups.

Results After the endotoxin absorption therapy, mean blood pressure increased significantly from 67.9 ± 11.4 to 86.4 ± 6.3 mmHg in the abdominal infection group, whereas there was no change in the nonabdominal infection group. After the therapy, the SOFA scores and RIFLE criteria improved in both groups, but they improved significantly in the abdominal infection group. Patients in the abdominal infection group, especially the endotoxin-positive cases, recovered earlier from shock and had a significantly higher rate of survival than the abdominal infection group.

Conclusion In endotoxin-positive patients with an abdominal infection, absorption therapy improved survival rate and cardiac and renal dysfunction due to sepsis or septic shock. However, further studies are required to verify the effectiveness of endotoxin absorption therapy.

2. Points

Sepsis 2011 Beijing, an International symposium hosted by ISF (International Sepsis Forum), was held in Beijing from October 27 through 28 2011. (please refer to December 2011 issue of "Toraymyxin World ") The abstract above is from this meeting's poster session, presented by a Japanese doctor. Effectiveness of Toraymyxin, especially for patients with abdominal infection was shown by the analysis of 105 cases of Toraymyxin treatments for eleven years in two hospitals.

The program book of Sepsis 2011 with all abstracts of lectures and poster presentation is available from ISF web site below.

http://www.sepsisforum.org/pastconferences/Sepsis2011/ISF%20Prog-Abs%20Book%20Beijing.pdf

(By N. Ida)

Articles

Blood Purification 2011, 32 310-316

Reduction in Serum High Mobility Group Box-1 Level by Polymyxin B-Immobilized Fiber Column in Patients with Idiopathic Pulmonary Fibrosis with Acute Exacerbation

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1. Abstract

Background/Aim: Recent reports suggest that polymyxin B (PMX)-immobilized fiber may have beneficial effects in idiopathic pulmonary fibrosis (IPF) with acute exacerbation (AE). High mobility group box-1 (HMGB-1) is an important pro-inflammatory mediator that contributes to acute lung inflammation. This study was aimed to investigate whether PMX treatment affects serum HMGB-1 levels and oxygenation in IPF patients with AE.

Materials and Methods: Twenty IPF patients with AE were treated by PMX. PMX treatment was carried out once daily for 2 successive days. Serum HMGB-1 levels were measured before and after PMX treatment. We also monitored arterial oxygen tension (PaO2)/inspiratory oxygen fraction (FiO2) (P/F) ratio. PMX fiber columns were analyzed to examine whether HMGB-1 was absorbed by PMX.

Results: PMX treatment significantly improved both the serum HMGB-1 level and P/F ratio. HMGB-1 was detected in washing medium from the PMX column.

Conclusion: PMX treatment may reduce serum HMGB-1 and improve oxygenation in patients with IPF with AE.

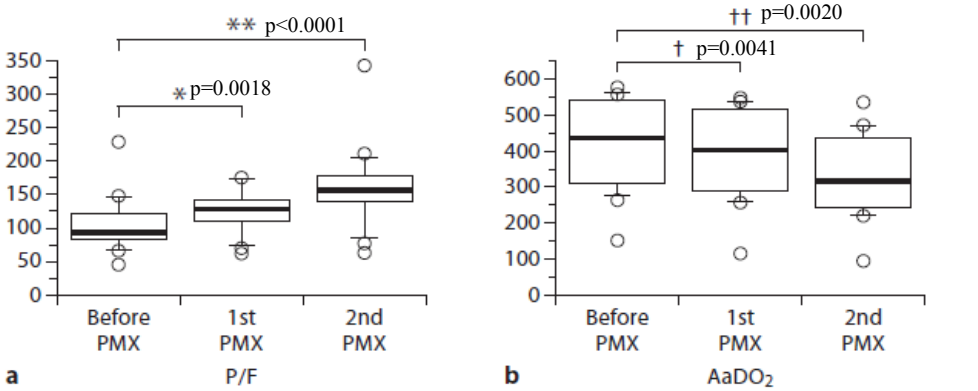

Fig 1. Changes in P/F ratio (a) and $AaDO_2$ (b) by PMX treatment.

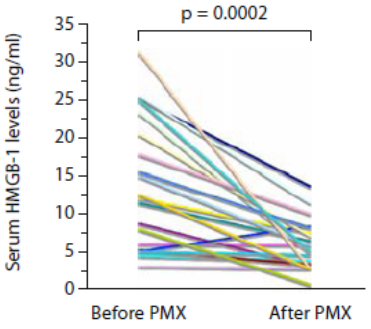

Fig 2. Changes in serum HMGB-1 levels by PMX treatment.

2. Points

In this paper from Japan reports the effectiveness of Toraymyxin on the patients with idiopathic pulmonary fibrosis with acute exacerbation. Two sessions of Toraymyxin treatment improved severely impaired lung function of the patients, shown by the changes in P/F ratio and $AaDO_2$. Significant increases of P/F ratio of sepsis patients by Toraymyxin treatment have been reported in various studies including EUPHAS trial. This paper further supports the effectiveness of Toraymyxin on respiratory functions in critically ill patients.

Articles

Blood Purification 2012, 33 252-256

Time to Initiation of Treatment with Polymyxin B Cartridge Hemoperfusion in Septic Shock Patients

Naoshi Takeyama[a], Hiroshi Noguchi, Akihiko Hirakawa, Hideki Kano, Kazuma Morino, Toru Obata, Tetsuya Sakamoto, Fumihiro Tamai, Hiroyasu Ishikura, Youichi Kase, Makoto Kobayashi, Toshio Naka, Yoshiki Takahashi, the Japan Sepsis Study Group

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1. Abstract

Background: We investigated whether early initiation of hemoperfusion with a polymyxin B cartridge (PMX) after the diagnosis of septic shock could improve the clinical outcome.
Methods: A prospective, open-labeled, multicenter cohort study was performed at intensive care units in Japan. 41 patients received PMX within 6 h after the diagnosis of septic shock (early group) and 51 patients were treated after 6 h (late group).

Results: The early group had a significantly shorter duration of ventilator support and also had a lower catecholamine requirement. PMX was effective for improvement of hypotension, hypoperfusion, the sequential organ failure assessment score, and pulmonary oxygenation regardless of the timing of its initiation. The 28-day mortality rate did not differ between the two groups.
Conclusions: Early initiation of PMX shortened the duration of ventilator support and also reduced the catecholamine requirement, so early treatment of septic shock should achieve a better outcome.

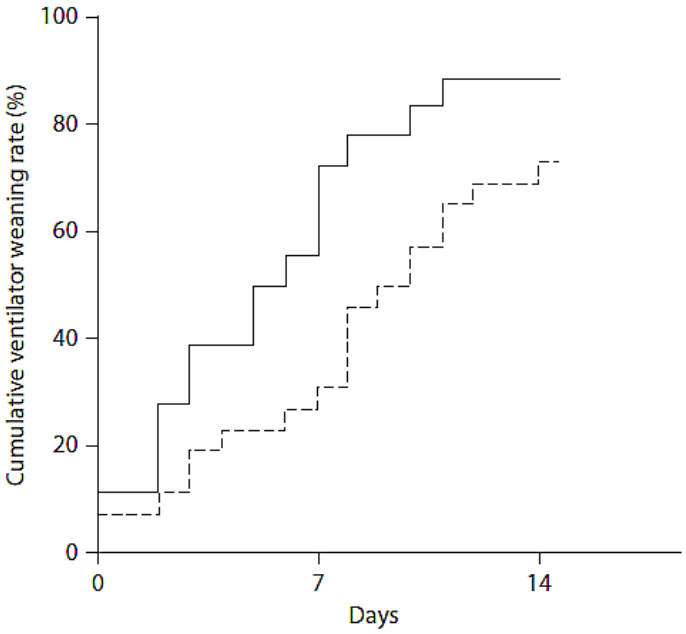

Fig 1. Ventilator-free rate: the duration of ventilator support was significantly shorter in the early group (black line) than in the late group (dotted line).

2. Points

This paper from Japan reports the results of multi-center study about the timing of PMX treatment after the diagnosis of septic shock. Thirty-five hospitals in Japan took part in the study and the results showed beneficial effects of early use of PMX in the duration of ventilator support.
In accordance with other reports, early start of PMX treatment is an important point to obtain better results against septic shock patients. (By N. Ida)

Article

Internal Med (2012) 51 1487-1491

Polymyxin B-immobilized Fiber Column (PMX) Treatment for Idiopathic Pulmonary Fibrosis with Acute Exacerbation: A Multicenter Retrospective Analysis

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1. Abstract

Objective The prognosis of idiopathic pulmonary fibrosis (IPF) patients with acute exacerbation (AE) is reported to be extremely poor. Several clinical studies suggest that direct hemoperfusion with polymyxin Bimmobilized fiber (PMX) may have beneficial effects on AE in patients with interstitial pneumonia (IP). The aim of this multicenter retrospective analysis was to investigate whether PMX treatment could provide improvement of oxygenation and survival benefits in IPF patients with AE.

Methods We conducted a retrospective study of 160 IP patients (including 73 IPF) with AE treated by PMX at 18 institutions in Japan. PMX treatment was carried out twice. The total hemoperfusion time of PMX treatment was, on average, 12 hours. Data concerning oxygenation on PMX treatment and survival after AE were collected and analyzed.

Results In IPF patients with AE, arterial oxygen tension (PaO2)/inspiratory oxygen fraction (FiO2), (P/F) ratio was significantly improved at the end of the 2nd treatment with PMX (173.9±105.4 to 195.2±106.8 Torr, p=0.003). White blood cell count was significantly reduced at the end of the 2nd treatment (13,330±7,002 to 9,426±5,188/mm3, p<0.001). These clinical changes were also observed on analysis of all 160 IP patients with AE. The one- and three-month survival rates of IPF patients after AE were 70.1% and 34.4%, respectively.

Conclusion PMX treatment may improve oxygenation and survival in IPF patients with AE. Prospective, controlled trials of PMX treatment for IPF with AE are warranted to verify this potential benefit.

Table Effect of PMX on P/F in Interstitial Pneumonia (all and IPF) Patients with Acute Exacerbation

	pre-PMX	end of 1st PMX	end of 2nd PMX
all patients	148.9±87.2	177.7±108.7*	175.1±92.5*
IPF	173.9±105.4	205.4±122.1#	195.2±106.8#§

Data are given as mean ± SD (Torr)
*p<0.0001 compared to pre-PMX
#p<0.001 compared to pre-PMX, #§p=0.003 compared to pre-PMX

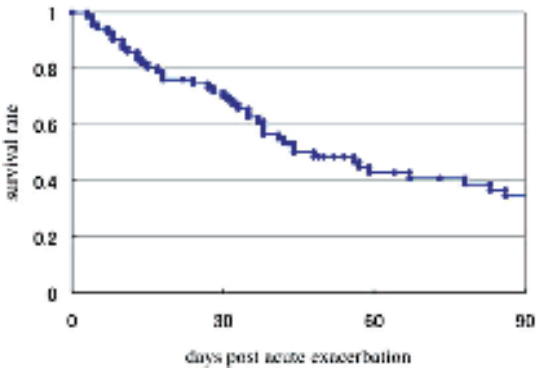

Figure Kaplan-Meier plot of the survival rate from the diagnosis of acute exacerbation for idiopathic pulmonary fibrosis (IPF) patients treated with polymyxin B-immobilized fiber column (PMX) (n=73, censored at 90 days).

2. Points

This paper from Japan shows the results of retrospective multi-centered study of Toraymyxin applied for the patients of acute exacerbation of interstitial pneumonia including idiopathic pulmonary fibrosis (AE-IPF). Three months survival rate for Toraymyxin-treated AE-IPF patients in this study was 34.5%, which is much higher than the reported survival rate of less than 10%. Although the precise mechanism of the improvement of pulmonary function by Toraymyxin treatment is not clear, they speculate that the adsorption of activated neutrophils and inflammatory mediators, in addition to endotoxin-removal, contributes to this beneficial effects.

Articles

JAMA (2013) 309: 1154-1162

Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial.

Opal SM, Laterre PF, Francois B, LaRosa SP, Angus DC, Mira JP, Wittebole X, Dugernier T, Perrotin D, Tidswell M, Jauregui L, Krell K, Pachl J, Takahashi T, Peckelsen C, Cordasco E, Chang CS, Oeyen S, Aikawa N, Maruyama T, Schein R, Kalil AC, Van Nuffelen M, Lynn M, Rossignol DP, Gogate J, Roberts MB, Wheeler JL, Vincent JL; ACCESS Study Group.

1. Abstract

IMPORTANCE: Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor. LPS is a major component of the outer membrane of gram-negative bacteria and is a potent activator of the acute inflammatory response.
OBJECTIVE: To determine if eritoran, a TLR4 antagonist, would significantly reduce sepsis-induced mortality.
DESIGN, SETTING, AND PARTICIPANTS: We performed a randomized, double-blind, placebo-controlled, multinational phase 3 trial in 197 intensive care units. Patients were enrolled from June 2006 to September 2010 and final follow-up was completed in September 2011.
INTERVENTIONS: Patients with severe sepsis (n = 1961) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1 ratio with a 6-day course of either eritoran tetrasodium (105 mg total) or placebo, with n = 1304 and n = 657 patients, respectively.
MAIN OUTCOME MEASURES: The primary end point was 28-day all-cause mortality. The secondary end points were all-cause mortality at 3, 6, and 12 months after beginning treatment.
RESULTS: Baseline characteristics of the 2 study groups were similar. In the modified intent-to-treat analysis (randomized patients who received at least 1 dose) there was no significant difference in the primary end point of 28-day all-cause mortality with 28.1% (366/1304) in the eritoran group vs 26.9% (177/657) in the placebo group (P = .59; hazard ratio, 1.05; 95% CI, 0.88-1.26; difference in mortality rate, -1.1; 95% CI, -5.3 to 3.1) or in the key secondary end point of 1-year all-cause mortality with 44.1% (290/657) in the eritoran group vs 43.3% (565/1304) in the placebo group, Kaplan-Meier analysis of time to death by 1 year, P = .79 (hazard ratio, 0.98; 0.85-1.13). No significant differences were observed in any of the prespecified subgroups. Adverse events, including secondary infection rates, did not differ between study groups.
CONCLUSIONS AND RELEVANCE: Among patients with severe sepsis, the use of eritoran, compared with placebo, did not result in reduced 28-day mortality.
TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00334828.

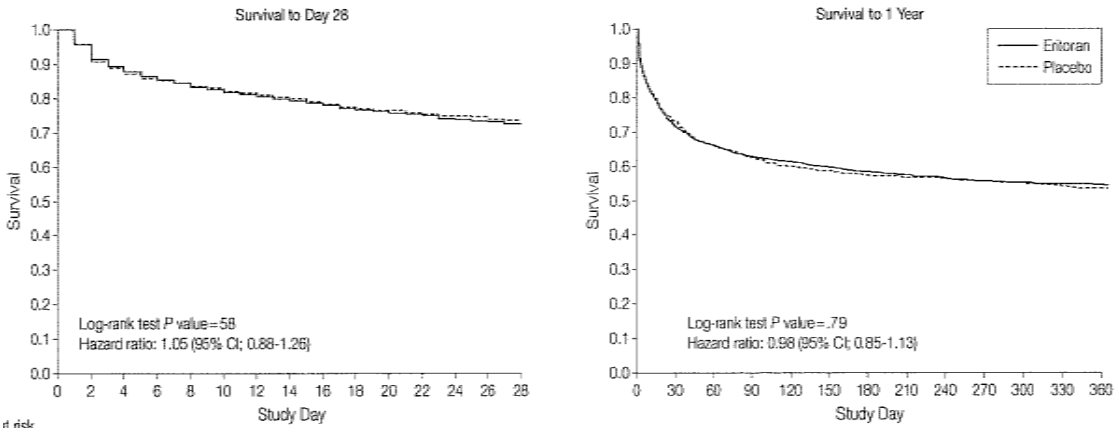

Figure. Kaplan-Meier analysis of time to death by (A) day 28 and (B) 1 year.

2. Points

The results of the "ACCESS trial", a phase3 study of endotoxin antagonist "eritoran" was published in the latest issue of JAMA. Although the efficacy of the drug was evaluated in various subgroups such as different severity of the disease, infection sites and bacterial types, there were no significant difference of the mortality in any of these prespecified subgroups. One interesting point for us is that the baseline endotoxin level was measured by EAA in 209 patients among 1961, and 28-day mortality was lower in eritoran group (12%, n=83) than in placebo group (31.7%, n=41) in the patient group whose EA level was less than 0.6. Interpretation of this result is not written in the article, but we speculate the possibility that the drug was effective when the endotoxin level was medium range, which could be effectively antagonized by the drug. (By N. Ida)

Articles

Anaesth, Pain & Inetensive Care (2013) 17: 88-90

Successful treatment of severe *Legionella* pneumonia and acute kidney injury with polymyxin B-immobilized fiber column direct hemoperfusion

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1. Abstract

Legionella pneumonia is often complicated by multiple organ failure. Although acute kidney injury is relatively rare in the context of *Legionella* pneumonia, it is associated with an increase in mortality rate. This report describes a case of a patient with *Legionella* pneumonia and acute kidney injury who was successfully treated with polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP). We conclude that PMX-DHP may be a useful therapeutic modality in patients with *Legionella* infection and acute kidney injury.

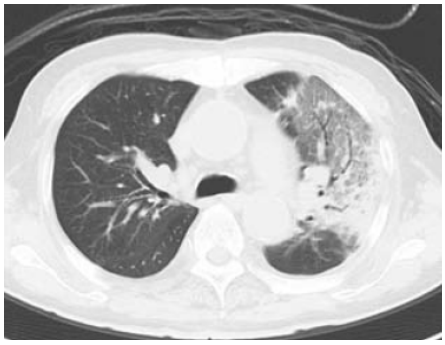

Fig 1. Chest computed tomography on admission showing consolidation with ground-glass opacities in the left lung field

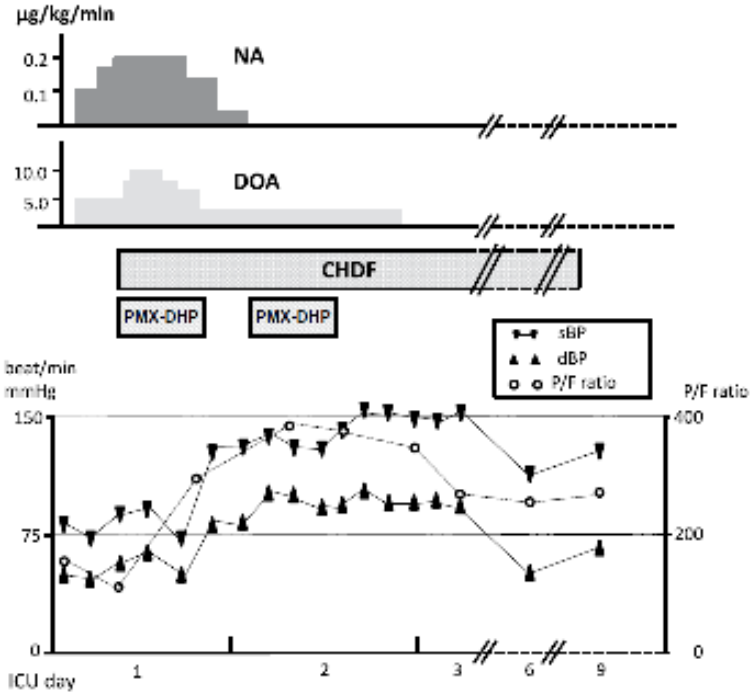

Fig 2. Clinical course after initiation of PMX-DHP. Catecholamines (noradrenaline and dopamine) were tapered off, and blood pressure and the PaO2/FiO2 ratio gradually improved.

2. Points

This paper reports a case of severe *Legionella* pneumonia complicated with acute kidney injury. *Legionella pneumophila* is a gram negative bacterium causative of legionellosis or Legionnaires' disease, a potentially fatal, acute infectious respiratory dysfunction. In this paper, the patient's hemodynamics and respiratory function were markedly improved by two sessions of Toraymyxin treatment together with CRRT treatment. This article is free-downloadable from the following site; http://www.apicareonline.com/wordpress/wp-content/uploads/2013/05/21-Successful-treatment-of-severe-Legionella.pdf) (By N. Ida)

Articles

Rev Esp Quimioter (2013) 26: 151-158

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

Javier Maynar[1], Fernando Martínez-Sagasti[2], Manuel Herrera-Gutiérrez[3], Francisco Martí[4],
Francisco Javier Candel[5], Javier Belda4, Sergio Castaño[1] and José Ángel Sanchez-Izquierdo[6]

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1. 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/m2. CI significantly increased in patients with initial CI<2.5 L/min/m2 (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 (213.9x103 ± 138.5x103 platelets/mm3 vs 91.0x103 ± 53.5x103 platelets/mm3, 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.

	PMX group	Control group
Norepinephrine (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	0.16 ± 0.24

Table 1. Mean norepinephrine doses administered during the study

2. Points

This paper reports the results of multi-center study of Toraymyxin, evaluating the hemodynamic change of severe septic patients due to intestinal perforation by two sessions of Toraymyxin treatment. Norepinephrine dose could be significantly reduced in Toraymyxin-treated patients compared to historical controls. Practical Toraymyxin treatment conditions such as anticoagulant dose and catheter size in each patient are also described. (By N. Ida)

Articles

Crit Care Med (2013) 41: DOI: 10.1097/CCM.0b013e31828cf4128

Blood Purification and Mortality in Sepsis: A Meta-analysis of Randomized Trials

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1. Abstract

Objectives: Although blood purification improves outcomes in animal studies of sepsis, results of clinical trials have been mixed. We conducted a systematic review and meta-analysis of randomized trials to determine the association between various blood purification techniques and all-cause mortality in humans with sepsis.

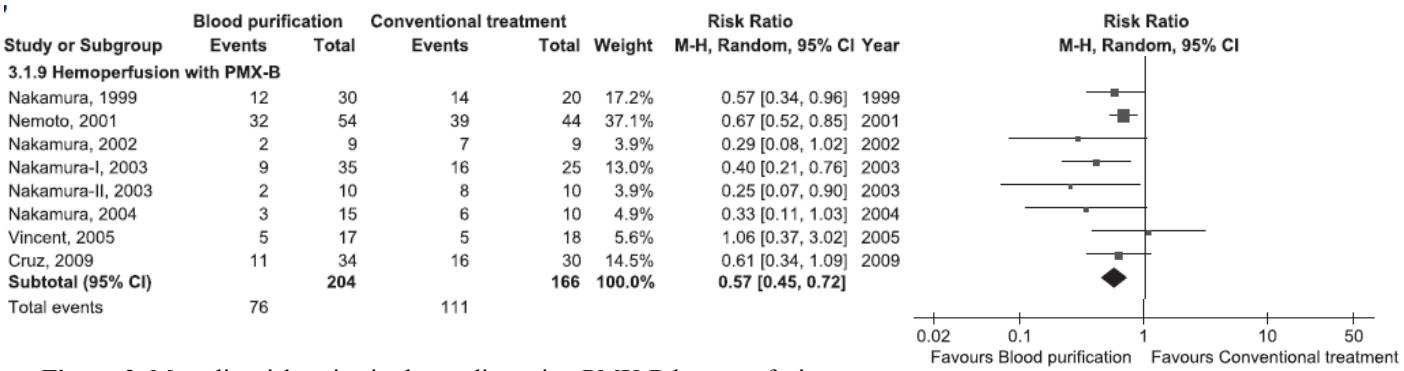
Data Sources: We searched for relevant studies in MEDLINE, EMBASE, and the Cochrane Library database from January 1966 to May 2012.

Study Selection: Inclusion required a diagnosis of sepsis and comparison of blood purification techniques including hemofiltration, hemoperfusion, plasma exchange, or hemodialysis with no blood purification (control group).

Data Extraction: Two authors independently selected studies and extracted data. Summary statistics, risk ratios, and CIs were calculated using random-effects modeling. Study quality was assessed using Jadad score, and publication bias was assessed using funnel plots and Egger's statistic.

Data Synthesis: Overall, blood purification decreased mortality compared with no blood purification (35.7% vs 50.1%; risk ratio, 0.69 [95% CI, 0.56–0.84]; $p < 0.001$; 16 trials, $n = 827$). However, these results were driven mainly by hemoperfusion (risk ratio, 0.63 [95% CI, 0.50–0.80]; $p < 0.001$; 10 trials, $n = 557$) and plasma exchange (risk ratio, 0.63 [95% CI, 0.42–0.96]; $p = 0.03$; two trials, $n = 128$). Pooling of all trials of blood purification for treatment of sepsis was no longer associated with lower mortality (risk ratio, 0.89 [95% CI, 0.71–1.13]; $p = 0.36$; eight trials, $n = 457$) after excluding trials using polymyxin B hemoperfusion.

Conclusions: Blood purification techniques including hemoperfusion, plasma exchange, and hemofiltration with hemoperfusion were associated with lower mortality in patients with sepsis. These results were mainly influenced by studies using polymyxin B hemoperfusion from Japan.



Study or Subgroup	Blood purification Events	Total	Conventional treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.1.9 Hemoperfusion with PMX-B							
Nakamura, 1999	12	30	14	20	17.2%	0.57 [0.34, 0.96]	1999
Nemoto, 2001	32	54	39	44	37.1%	0.67 [0.52, 0.85]	2001
Nakamura, 2002	2	9	7	9	3.9%	0.29 [0.08, 1.02]	2002
Nakamura-I, 2003	9	35	16	25	13.0%	0.40 [0.21, 0.76]	2003
Nakamura-II, 2003	2	10	8	10	3.9%	0.25 [0.07, 0.90]	2003
Nakamura, 2004	3	15	6	10	4.9%	0.33 [0.11, 1.03]	2004
Vincent, 2005	5	17	5	18	5.6%	1.06 [0.37, 3.02]	2005
Cruz, 2009	11	34	16	30	14.5%	0.61 [0.34, 1.09]	2009
Subtotal (95% CI)		**204**		**166**	**100.0%**	**0.57 [0.45, 0.72]**	
Total events	76		111				

Figure 2. Mortality risk ratios in the studies using PMX-B hemoperfusion

2. Points

A systematic review was published about clinical studies using blood purification therapies in sepsis was published. Among 16 papers selected, 8 were about Toraymyxin, including EUPHAS study with the highest quality using Jaded score. The authors concluded that blood purification techniques were associated with lower mortality in sepsis and these results were mainly influenced by Toraymyxin studies from Japan, while acknowledging the need for further research since overall quality of the reviewed studies were modest due to small numbers of enrolled patients in each study. (By N. Ida)

Articles

Crit Care Med (2013) 41: 2070-2079

A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

Vincent JL, Ramesh MK, Ernest D, Larosa SP, Pachl J, Aikawa N, Hoste E, Levy H, Hirman J, Levi M, Daga M, Kutsogiannis DJ, Crowther M, Bernard GR, Devriendt J, Puigserver JV, Blanzaco DU, Esmon CT, Parrillo JE, Guzzi L, Henderson SJ, Pothirat C, Mehta P, Fareed J, Talwar D, Tsuruta K, Gorelick KJ, Osawa Y, Kaul I.

1. Abstract

OBJECTIVES:: To determine the safety and efficacy of recombinant thrombomodulin (ART-123) in patients with suspected sepsis-associated disseminated intravascular coagulation.

DESIGN:: Phase 2b, international, multicenter, double-blind, randomized, placebo-controlled, parallel group, screening trial.

SETTING:: Two hundred and thirty-three ICUs in 17 countries.

PATIENTS:: All adult patients admitted with sepsis and suspected disseminated intravascular coagulation as assessed using a modified International Society on Thrombosis and Hemostasis score.

INTERVENTIONS:: Patients were randomized to receive IV ART-123 (0.06 mg/kg/d) for 6 days or placebo, in addition to standard of care. The primary endpoint was reduction in mortality. Secondary endpoints included reversal of overt disseminated intravascular coagulation and reduction in disease severity.

MEASUREMENTS AND MAIN RESULTS:: A total of 750 patients were randomized, nine of whom did not receive the allocated treatment so that 371 patients received ART-123 and 370 received placebo. There were no meaningful differences between the two groups in any of the baseline variables. Twenty-eight-day mortality was 17.8% in the ART-123 group and 21.6% in the placebo group (Cochran-Mantel-Haenszel two-sided p value of 0.273 in favor of ART-123, which met the predefined statistical test for evidence suggestive of efficacy). There were no statistically significant differences in event-free and alive days between the two groups. d-dimer, prothrombin fragment F1.2 and TATc concentrations were lower in the ART-123 group than in the placebo group. There were no differences between the two groups in organ function, inflammatory markers, bleeding or thrombotic events or in the development of new infections. In post hoc analyses, greatest benefit from ART-123 was seen in patients with at least one organ system dysfunction and an international normalized ratio greater than 1.4 at baseline.

CONCLUSIONS:: ART-123 is a safe intervention in critically ill patients with sepsis and suspected disseminated intravascular coagulation. The study provided evidence suggestive of efficacy supporting further development of this drug in sepsis-associated coagulopathy including disseminated intravascular coagulation. Future study should focus on using ART-123 in the subgroup of patients most likely to respond to this agent.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00334828.

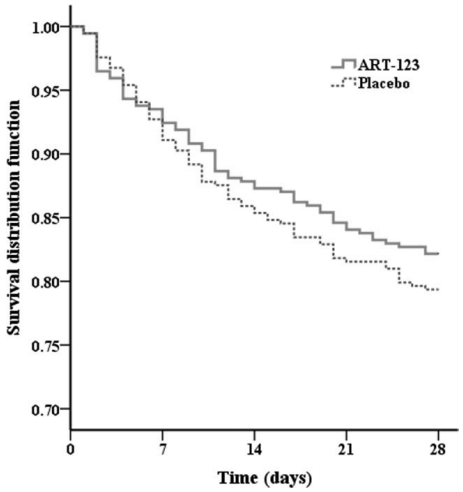


Figure. Kaplan–Meier plots of survival time for the two treatment arms: 28-d survival was 82.2% (95% CI, 77.9%, 85.7%) for the ART-123 group and 79.4% (95% CI, 74.9%, 83.2%) for the placebo group .

2. Points

ART-123, recombinant human thrombomodulin, is currently approved for the treatment of DIC only in Japan. The result of global phase 2b study of this drug was published in the latest issue of Crit Care Med. The target patient was sepsis with suspected DIC. The drug-treated arm showed better 28-d survival compared to the placebo arm, although the difference was not statistically significant (p=0.273). In the subgroup of patients with respiratory or cardiac dysfunction and coagulopathy characterized by international normalized ratio of prothrombin time greater than 1.4, survival benefit was more pronounced. Phase 3 study is now ongoing targeting this group of patients. (http://clinicaltrials.gov/ct2/show/NCT01598831) (By N. Ida)

Articles

Science (2013) 341: 1246-1249

Noncanonical inflammasome activation by intracellular LPS independent of TLR4

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Abstract

Gram-negative bacteria including Escherichia coli, Citrobacter rodentium, Salmonella typhimurium, and Shigella flexneri are sensed in an ill-defined manner by an intracellular inflammasome complex that activates caspase-11. We show that macrophages loaded with synthetic lipid A, E. coli lipopolysaccharide (LPS), or S. typhimurium LPS activate caspase-11 independently of the LPS receptor Toll-like receptor 4 (TLR4). Consistent with lipid A triggering the noncanonical inflammasome, LPS containing a divergent lipid A structure antagonized caspase-11 activation in response to E. coli LPS or Gram-negative bacteria. Moreover, LPS-mutant E. coli failed to activate caspase-11. Tlr4(-/-) mice primed with TLR3 agonist polyinosinic:polycytidylic acid [poly(I:C)] to induce pro-caspase-11 expression were as susceptible as wild-type mice were to sepsis induced by E. coli LPS. These data unveil a TLR4-independent mechanism for innate immune recognition of LPS.

Science (2013) 341: 1250-1253

Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock

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Abstract

Inflammatory caspases, such as caspase-1 and -11, mediate innate immune detection of pathogens. Caspase-11 induces pyroptosis, a form of programmed cell death, and specifically defends against bacterial pathogens that invade the cytosol. During endotoxemia, however, excessive caspase-11 activation causes shock. We report that contamination of the cytoplasm by lipopolysaccharide (LPS) is the signal that triggers caspase-11 activation in mice. Specifically, caspase-11 responds to penta- and hexa-acylated lipid A, whereas tetra-acylated lipid A is not detected, providing a mechanism of evasion for cytosol-invasive Francisella. Priming the caspase-11 pathway in vivo resulted in extreme sensitivity to subsequent LPS challenge in both wild-type and Tlr4-deficient mice, whereas Casp11-deficient mice were relatively resistant. Together, our data reveal a new pathway for detecting cytoplasmic LPS.

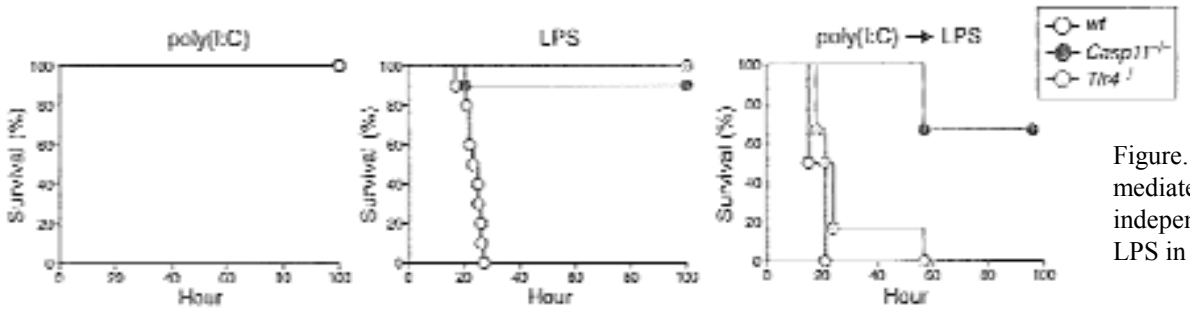

Figure. Lethal sepsis mediated by TLR4-independent sensing of LPS in mouse model.

Points

Two papers reporting a new mechanism of endotoxin-induced inflammation were published in September 13 issue of Science. Both research groups found that intracellular endotoxin causes inflammation, through toll like receptor 4-independent, inflammasome and caspase 11-mediated, pathway. At least in the mouse model of endotoxin shock, this pathway was shown to be a major route leading to death, since caspase 11-knockout mice, but not TLR4-knockout mice, were protected from lethal endotoxin challenge. This new finding may highlight the importance of endotoxin in sepsis pathogenesis from a new viewpoint.
Commentary on these papers was also published in the same issue (Science (2013) 341:1184-1185). (By N. Ida)

Articles

J Hepatobiliary Pancreat Sci (2013) PMID: 23798326

Severity and prognostic assessment of the endotoxin activity assay in biliary tract infection

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Abstract

Background Acute cholangitis and cholecystitis (AC) often progress to severe septic conditions.We evaluated the endotoxin activity assay (EAA) for assessment and prediction of the severity of AC.

Methods We retrospectively reviewed 98 patients diagnosed with AC. We divided them into low (<0.4) and high (≥0.4) groups based on EAA values.

Results Endotoxin levels showed no correlation with EAA values. Serum C-reactive protein (8.57 vs. 5.23 mg/dl, $P = 0.02$), procalcitonin (2.45 vs. 0.48 ng/ml, $P = 0.004$), and the positive culture rate of blood (50% vs. 15%, $P < 0.001$) were significantly higher in the high group than in the low group. Platelet counts were significantly lower in the high group than in the low group (23.9 vs. 13.5 104/ml, $P = 0.004$). The ratio of patients with a Japanese Association for Acute Medicine disseminated intravascular coagulation score ≥4 (32% vs. 14%, $P = 0.032$) was significantly higher in the high group than in the low group. There was a significantly higher percentage of patients with a severe grade of AC in the high group than patients

Conclusions Endotoxin activity assay is useful for assessment and early prediction of septic conditions due to AC.

Table. Characterstics of patients of high EAA (≧0.4) group and low EAA (<0.4) group

Variables	EAA level		*P*-value
	Low: 0 0.39	High: ≥ 0.4	
	(*n* 64)	(*n* 34)	
Age (range)	70 (52 85)	69 (54 81)	0.352
Gender (Male : Female)	43:21	24:10	0.457
Inflammatory response			
WBC (/μl)	9350 + 3918	8900 + 6231	0.499
CRP (mg/dl)	5.23 + 6.58	8.57 + 6.67	0.060
Procalcitonin (ng/ml)	0.48 ⊥ 9.07	2.45 ⊥ 13.5	0.004
Positive rate of blood cultures	15% (10/64)	50% (17/34)	<0.001
Coaglation factor			
Platelet (104/ml)	23.9 + 7.70	13.5 + 6.60	0.001
PT-INR	1.16 + 0.24	1.24 + 0.41	0.088
FDP-E (μg/ml)	9.90 ⊥ 24.9	15.0 ⊥ 26.7	0.063
JAAM DIC score	1 ⊥ 1.79	2 ⊥ 2.23	0.030
≧4	14% (9/64)	32% (9/34)	0.032
SOFA score	2 ⊥ 1.93	2 ⊥ 2.00	0.071
≧5	6% (4/64)	21% (7/34)	0.038
Disease severity			
(Mild and Moderate: Severe)	54:10	23:11	0.050
Hospitalization (Days)	10 + 11.1	15 + 23.9	0.008

CRP C-reactive protein, *EAA* endotoxin activity assay, *FDP-E* fibrin degradation product E, *JAAM DIC* Japanese Association for Acute Medicine disseminated intravascular coagulation, *PT-INR* prothrombin time international normalized ratio, *SOFA* sequential organ failure assessment, *WBC* white blood cell count

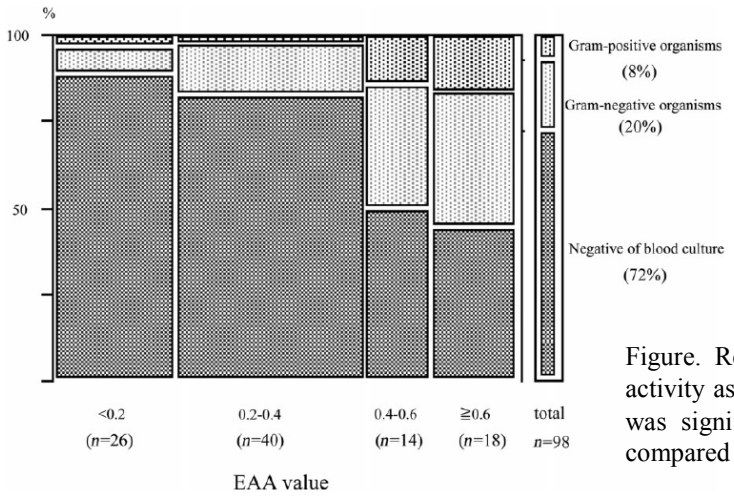

Figure. Results of blood culture according to the endotoxin activity assay (EAA) values. The positive culture rate of blood was significantly high in the patients with EA level ≧0.4 compared to those of <0.4. (50% vs. 15%, P < 0.001)

Points

In this paper from Japan, blood endotoxin levels in acute cholangitis and cholecystitis patients were measured using EAA. The authors found that EAA level significantly correlate with positive rate of blood culture. Furthermore, EAA levels were strongly correlated with DIC related markers such as platelet count and the Japanese Association for Acute Medicine (JAAM) DIC score as well as length of hospitalization.

EAA could be a good marker for the early prediction of sepsis and DIC conditions caused by biliary tract infection. (By N. Ida)