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The effects of adjuvant therapies for sepsis on hepatic and renal function: a retrospective analysis of 108 ICU patients

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Aim: As liver and kidney failure have a direct effect on mortality, morbidity, and intensive care unit (ICU) length of stay in sepsis patients, maintaining their functions or minimizing the degree of failure should be one of the most important goals of therapy. In this retrospective study we investigated the effects of recently introduced adjuvant therapies on hepatorenal functions in septic ICU patients.

Materials and methods: We conducted comparative and retrospective data analysis of 108 patients with sepsis that were followed-up during a 2-year period in the ICU. We recorded AST, ALT, ALP, albumin, bilirubin, and INR in order to evaluate variations in hepatic functions, and we recorded creatinine, BUN, and mean hourly urinary output in order to evaluate variations in renal functions in patients that received standard antibiotherapy only (ST group), in those that received polyvalent IgM-enriched immunoglobulin therapy added to standard antibiotherapy (IVIg group), and in those that received recombinant human-activated protein C therapy added to standard antibiotherapy (APC group). Variables at the beginning of the treatments and 96 h post-treatment were assessed.

Results: In total, 108 patients were analyzed (IVIg group: n = 20 in; APC: group n = 22; ST group: n = 66). The groups were homogeneous in terms of initial hepatic and renal functions, according to AST, ALT, albumin, INR, bilirubin, BUN, creatinine, and mean hourly urinary output. In the APC group the AST level at 96 h was significantly lower than that at baseline (0 h), and in the ST group 96-h bilirubin was lower than that at baseline (0 h) (P = 0.035 and P = 0.015, respectively).

Conclusion: We retrospectively observed that the adjuvant therapies did not improve hepatorenal functions in our ICU septic patients.

Key words: Sepsis, hepatic functions, renal functions, activated protein C, intravenous immunoglobulin

Sepsiste uygulanan destek tedavilerin karaciğer ve böbrek fonksiyonlarına etkisinin değerlendirilmesi: yoğun bakımda 108 hastanın retrospektif analizi

Amaç: Böbrek ve karaciğer yetmezliği sepsiste mortalite, morbidite ve yoğun bakım ünitesi (YBÜ) kalış süreleri üzerinde direkt etkili olduğundan organ fonksiyonlarını korumak ya da yetmezliğin derecesini minimuma indirmek tedavinin en önemli hedeflerinden biri olmalıdır. Bu retrospektif çalışmada yakın zamanda kullanıma giren adjuvan tedavilerin YBÜ sepsis hastalarında karaciğer ve böbrek fonksiyonları üzerindeki etkilerini araştırdık.

Yöntem ve gereç: Bu çalışma YBÜ' de 2 yıllık periyotta sepsis tanısı ile takip edilen 108 hastanın kayıtlarının karşılaştırmalı ve retrospektif bir analizidir. Standart antibiyoterapi uygulanan (Grup ST) hastalarda, standart antibiyoterapiye ek olarak Polivalan IgM ile zenginleştirilmiş immunoglobulin tedavisi uygulananlarda (Grup IVIG) ve standart antibiyoterapiye ek olarak Rekombinant insane aktive protein C tedavisi uygulananlarda (Grup APC) karaciğer fonksiyonlarındaki değişiklikleri değerlendirmek için AST, ALT, ALP, albümin, bilirübin ve INR değerlerini, böbrek

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fonksiyonlarını değerlendirmek için kreatinin, BUN ve saatlik ortalama idrar çıkışını kayıt ettik. Tedavilerin başlangıcında ve tedavi başlangıcından 96 saat sonraki değişkenler değerlendirmeye alındı.

Bulgular: APACHE II skoru 25 ve üzerinde olan toplam 108 hasta (Grup IVIg n = 20, Grup APC n = 22 ve Grup ST n = 66) analiz edildi. Gruplar AST, ALT, albümin, INR, bilirübin, BUN, kreatinin ve saatlik ortalama idrar çıkışı ile değerlendirilen karaciğer ve böbrek fonksiyonlarının başlangıç değerleri açısından benzerdi. Grup APC de 96. saat AST değeri bazal (sıfırıncı saat) değerlerine gore, Grup ST de ise 96. saat bilirübin değerleri bazal (sıfırıncı saat) değerlere göre anlamlı düşük bulundu (sırasıyla P = 0,035 ve 0,015).

Sonuç: Adjuvan tedavilerin sepsis hastalarımızda karaciğer ve böbrek fonksiyonlarını iyileştirmediğini gözledik.

Anahtar sözcükler: Sepsis, karaciğer fonksiyonları, böbrek fonksiyonları, aktive protein C, intravenöz immunglobulin

Introduction

Sepsis is a clinical syndrome that complicates severe infection, and is characterized by systemic inflammation and widespread tissue injury (1). The syndrome is a process rather than an event; there is a spectrum of multiple organ dysfunction, with incremental degrees of physiological derangement in individual organs. Alteration in organ function can vary widely, from a mild degree of organ dysfunction to complete organ failure. Pulmonary failure, and liver and kidney failure have a direct effect on mortality, morbidity, and intensive care unit (ICU) length of stay (2). Sepsis is the most common cause of the progression of multiple organ dysfunction syndrome (MODS), and the kidneys and liver are the most important organs affected. Acute renal injury is a frequent and serious complication of sepsis in ICU patients, and is associated with a very high mortality rate (3). Moreover, experimental studies have indicated that hepatic oxidative and synthetic metabolism may decrease, and that hepatocellular dysfunction occurs soon after sepsis (4,5).

Therefore, preventing organ failure or minimizing the degree of failure should be one of the most important goals of any therapy for sepsis. Despite the evolution of supportive therapy, and the use of new and potent antibiotics, there has been little impact on lowering the mortality rate due to sepsis. Consequently, attempts have been made to lower the mortality rate with new adjuvant therapies that have a modulating role on the inflammatory response to sepsis. In this regard, immunoglobulins were reported to be very effective (6-9). Immunoglobulins, administered intravenously (a novel therapeutic approach to modulating immune response), have been shown to exhibit anti-inflammatory properties in sepsis (10).

Another adjuvant therapy, namely recombinant human activated protein C (rhAPC), is currently the only medicine for the treatment of severe sepsis approved by the US Food and Drug Administration (FDA), and only for high-risk patients (11). The recently introduced drug remarkably improved the outcome of septic patients (12). To the best of our knowledge there have not been any retrospective or prospective trials related to the specific role of this agent on hepatic and renal dysfunction in septic patients.

The aim of the present retrospective study was to determine the effects of standard antibiotherapy alone and with the addition of adjuvant therapies (IgM-enriched immunoglobulin and rhAPC) on hepatorenal functions in septic patients followed-up in our ICU from January 2004 to January 2006.

Materials and methods

Study population and treatment regimens

This retrospective observational study was conducted at Süleyman Demirel University Hospital, Isparta, Turkey, which is a tertiary care facility with 19 ICU beds. Informed consent was waived and data were obtained in an anonymous manner. Data collected on all patients that were admitted to our medical-surgical ICU between January 2004 and January 2006 were reviewed to identify all patients diagnosed with sepsis at any point during their ICU stay. In all, 108 patients aged between 18 and 90 years with severe sepsis were retrospectively identified. Patient acuity was determined using the Acute Physiology and Chronic Health Evaluation (APACHE) II survival probability score. The inclusion criteria were fulfilling the previously validated high-

risk criterion of an APACHE II (13) score ≥25 and severe sepsis (temperature >38 °C or <36 °C, heart rate >90 beat/min, respiratory rate >20 breath/min or $PaCO_2$ <32 mmHg, white blood cell count >12,000/mm^3 or <4000/mm^3, documented infection and at least 1 positive blood culture following therapy with at least 2 antibiotics in combination, and dysfunction of an organ or hypotension). Data were collected from the patients' records.

The patients included in the study were determined to have sepsis according to standard definitions. Then the patients diagnosed with sepsis were divided into 3 groups according to the therapy they received beginning the day sepsis was diagnosed. Patients treated with polyvalent IgM-enriched Ig (pentaglobulin, Biotest AG, Dreieich, Germany) 5 mL/kg daily on 3 consecutive days constituted the IVIg group. Patients treated with a 96-h course of rhAPC (Xigris®, Eli Lilly and Co., Indianapolis, IN, USA) 24 μg/kg/h beginning the day severe sepsis was diagnosed constituted the APC group. Standard antibiotherapy only (according to the hospital practice guidelines) was administered to the ST group.

Supportive treatment consisted of fluid resuscitation (fluids administered until central venous pressure measurement reached 10-15 mmHg), vasoactive drugs (when fluid administration failed to restore an adequate arterial pressure: mean arterial pressure above 60 mm Hg), and respiratory support (protective mechanical ventilation in sepsis-related patients in whom ALI/ARDS improved).

Measurements

Data for blood samples collected at 3 time intervals were evaluated in all 3 study groups. Demographic data included age, gender, total ICU length of stay, the mortality rate in each group and the total mortality rate, day of exitus, and admission category. Additionally, data on the origin of each patient (from where the patients were transported), prognostic factors and comorbidity, APACHE II score at the time therapy was initiated (APACHE II 0 h) and 96 h later (APACHE II 96 h), bacterial gram species isolated (+/-), CVP and MAP values at the beginning of therapy, and 6 and 96 h later, volume of fluid infused daily, serum glucose level, and diuretic and vasopressor (VP) therapy were obtained from the patients' records.

In order to assess renal and hepatic functions data were recorded in all of the groups, as follows:

At the time a positive blood culture specimen was obtained, which was when therapy began in each patient.

96 h after a positive blood culture specimen was obtained and therapy was initiated.

To evaluate hepatic functions in the septic patients alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, INR, and total bilirubin levels were recorded. For the evaluation of renal functions in the septic patients data for creatinine, blood urea nitrogen (BUN), and mean hourly urinary output were recorded.

Statistical Analysis

The Kruskal-Wallis test was used to analyze age, total ICU length of stay, and day of exitus, and gender, admission category, and mortality rates were analyzed using the chi-square test. The significance of difference in the volume of fluid infused daily, CVP, and MAP between the 3 groups was calculated using the Kruskal-Wallis test. Serum glucose levels at the start of therapy and at 96 h were analyzed using the Kruskal-Wallis test, the existence of vasopressor (VP) and diuretic therapy was analyzed using the chi-square test. Comparison of initial AST, ALT, ALP, albumin, bilirubin, INR, BUN, creatinine, and mean hourly urinary output was performed using the Kruskal-Wallis test, and variations between the 2 therapy time points (the beginning and 96 h of therapy) were determined using the Wilcoxon signed-rank test.

Results

Patient characteristics

Based on digital archive data, 825 patients were admitted to the ICU between January 2004 and January 2006. From among these patients, data recorded for 108 patients diagnosed with sepsis were retrospectively evaluated. There were no significant differences in age, gender, total ICU length of stay, mortality rate, or day of exitus between the 3 groups.

Baseline demographic characteristics of the 108 patients included in the study are shown in Table 1. The mortality rate in each group and total mortality

Table 1. Demographic profile, ICU stay time, and mortality data of all patients. Age, Total ICU Stay, and Day of Exitus Values are expressed as Median (Minimum – Maximum), mortality rate was defined by ratio value.

	Age (Year)	Gender (M/F)	Total ICU Stay (Day)	Mortality rate (n/Ex) (%)	Day of Exitus (Day)
APC group (n = 22)	57.5 (17-87)	14/8	23.5 (4-70)	22/15 (68%)	21.5 (4-70)
IVIg group (n = 20)	64 (30-84)	15/5	17 (7-52)	20/14 (70%)	17 (7-52)
ST group (n = 66)	63 (15-85)	37/29	17 (5-99)	66/56 (84%)	16.5 (5-99)
P[†]	0.579	0.303	0.515	0.146	0.833
Total (n = 108)	63 (15-87)	66/42	18 (4-99)	108/85 (78%)	23.5 (4-99)

[†] The significance level of the parameters among the 3 groups.

rate (78%) is shown in Table 1. There were significant differences between the groups according to admission category of the patients, as shown in Table 2. There were no differences in terms of prognostic factors, comorbidity, or bacterial gram species (+/-) isolated between the 3 groups (Table 3). The mean volume of fluid infused daily was similar in all 3 groups. The 6-h CVP was lower in the ST group than in the other 2 groups (P = 0.004), and MAP at the start of therapy, and 6 and 96 h later was significantly lower

Table 2. Admission category of the patients. Data were expressed as the number of patient (n) in each group.

Admission Category	IVIg group	APC group	ST group
Emergency Room	7	11	36
Ward	12	9	16
Other Hospital	1	0	1
Postoperative	0	2	13
P	0.011[†]	0.048[†]	<0.0001[‡]

[†] The level of significant distribution between the admission categories in IVIg group and APC group cases.
[‡] The level of very significant distribution between the admission categories in the ST group.

Table 3. The prognostic factors and comorbidity of patients and the identified bacterial gram species in each group. Data were expressed as positive cases/n, and the rate (%).

	IVIg group	APC group	ST group	P[‡]
Renal disease	2/20 (10%)	3/22 (13.63%)	2/66 (3.03%)	0.168
Malignancy	0/20 (0%)	1/22 (4.54%)	4/66 (6.06%)	0.528
Trauma	1/20 (5%)	4/22 (18.18%)	12/66 (18.18%)	0.344
Hypertension	2/20 (10%)	3/22 (13.63%)	8/66 (12.12%)	0.936
Diabetes Mellitus	3/20 (15%)	2/22 (9.09%)	7/66 (10.60%)	0.841
Identified Bacterial Gram Species (Positive/Negative)	10/10	16/6	41/25	0.317

[‡] The significance level of parameters among the 3 groups.

in the ST group than in the other groups (P = 0.008 and P < 0.0001, respectively) (Table 4). There were no significant differences in serum glucose levels or diuretic therapy between the groups; however, 6- and 96-h vasopressor therapy were significantly different in the ST group (P = 0.001 and P < 0.0001, respectively) (Table 5).

Renal and Hepatic Functions

All 3 groups were similar in terms of initial hepatorenal function, according to AST, ALT, albumin, INR, bilirubin, BUN, creatinine, and mean hourly urinary output (Table 6). In the APC group the AST level at 96 h was significantly lower than that at baseline (0 h) (P = 0.035). In the ST group 96-h bilirubin was lower than that at baseline (0 h) (P = 0.015). Hepatic functions in the 3 groups at 0 and 96 h are shown in Table 7. Renal functions (according to BUN, creatinine, mean daily urinary output) did not significantly differ between 0 and 96 h in the APC and IVIg groups (Table 8).

APACHE II scores

APACHE II scores in the 3 groups were similar at the start of therapy (P = 0.311), whereas the differences in 96-h APACHE II scores between the 3 groups were significant. In the ST group the 96-h APACHE II score was significantly higher than that in the other 2 groups (P < 0.0001), and the 96-h APACHE II score was significantly lower in the APC group than that in the IVIG group (P = 0.0018). The 96-h APACHE II score in the ST group was significantly lower than that at 0 h (P = 0.019). In the APC and IVIg groups the 96-h APACHE II score was significantly lower than that at 0 h (P < 0.0001) (Figure).

Discussion

The results of the present retrospective study show that rhAPC and IgM-enriched immunoglobulin therapy did not positively affect sepsis-related hepatorenal dysfunction. Although the 96-h AST level decreased significantly, with respect to 0 h, this finding may not be considered clinically relevant, as AST is not the only liver-specific enzyme. In the IVIg group no improvement in hepatorenal functions was observed.

In cases of severe sepsis and septic shock, the level of functioning of any vital organ may be reduced, regardless of the source of infection (14). In most fatal sepsis cases patients experience an insidious, progressive decline in vital organ function, i.e. MODS (15). The liver plays a major role in modulating systemic response in patients with severe sepsis, because it contains most of the body's macrophages (Kuppfer cells) and is able to clear the endotoxins and

Table 4. CVP and MAP values at the beginning of the therapies and in the following 6 and 96 h, daily infused fluid amount also at the beginning of the therapies and on the following 4th day. Data are expressed as medians (minimum-maximum). Daily infused fluid amount is expressed as mL/day. Central Venous Pressure (CVP) and Mean Arterial Pressure (MAP) are expressed as mmHg.

	IVIg group	APC group	ST group	P
Daily infused fluid amount of beginning of therapy day	5000 (4300-5300)	5000 (3500-5400)	5000 (3500-5400)	0.966
Daily infused fluid amount on day 4	3700 (3400-4350)	3600 (2750-4300)	3700 (2750-4350)	0.804
CVP of beginning of therapy	2.5 (0-9)	4 (0-9)	3 (0-9)	0.483
CVP at 6 h	8 (4-12)	9 (6-13)	6 (3-16)	0.004†
CVP at 96 h	8.5 (4-13)	9 (6-12)	9 (2-15)	0.275
MAP at beginning of therapy	70 (60-83)	65.5 (59-85)	64 (60-80)	0.008†
MAP at 6 h	74 (66-86)	74 (62-86)	63.5 (50-80)	<0.0001‡
MAP at 96 h	78 (70-92)	79.5 (70-89)	62.5 (47-92)	<0.0001‡

† Level of significant differences among IVIg group, APC group, and ST group
‡ Level of very high significant differences among IVIg group, APC group, and ST group

Table 5. Serum glucose levels, existence of diuretic therapy at the beginning of the therapies and on the following 4th day, presence of vasopressor therapy (VP) at the beginning of the therapies and in the following 6 h and 4th day. Glucose data were expressed as median (minimum-maximum). Diuretic and vasopressor data were expressed as positive case/n.

	IVIg group	APC group	ST group	P
Glucose Levels beginning of therapy	131 (84-220)	134.5 (72-230)	132 (78-319)	0.980
Glucose Levels at 96 h	120.5 (93-162)	123.5 (83-142)	137.5 (89-141)	0.882
Diuretic use beginning of therapy	2/20 (10%)	3/22 (13.63%)	6/66 (9.09%)	0.830
Diuretic use at 96 h	2/20 (10%)	4/22 (18.18%)	5/66 (7.57%)	0.362
VP of beginning therapy	15/20 (75%)	18/22 (81.81%)	61/66 (92.42%)	0.091
VP at 6 h	12/20 (60%)	13/22 (59.09%)	60/66 (90.9%)	0.001†
VP at 96 h	2/20 (10%)	2/22 (9.09%)	9/66 (86.36%)	<0.0001‡

† Significant differences among IVIg group, APC group and ST group
‡ Very high significant differences among IVIg group, APC group and ST group

Table 6. Renal and hepatic functions data at the beginning of the therapies. Data are expressed as median (minimum-maximum), AST and ALT (U/L), albumin, bilirubin, BUN, and creatinine (mg/dL), Hourly urinary output (mL/h), and INR (ratio).

	IVIg group	APC group	ST group	P†
ALT	29 (4-135)	35.5 (13-291)	25 (2-755)	0.175
AST	30.5 (8-109)	45 (16-163)	37 (7-289)	0.172
ALP	363 (359-571)	323 (135-364)	331 (208-503)	0.211
Albumin	3 (2.2-4.8)	3.1 (2.5-3.6)	3.2 (1.7-4.8)	0.843
Bilirubin	1 (0.16-5.7)	0.9 (0.01-11.9)	0.8 (0.05-3.7)	0.836
INR	1.13 (0.9-1.6)	1.14 (0.89-1.39)	1.2 (0.8-2.3)	0.262
BUN	30.35 (8-76)	27.5 (8-125)	27.5 (7-180)	0.859
Creatinine	0.84 (0.4-2.3)	1.05 (0.4-6.1)	0.9 (0.3-4.48)	0.496
Hourly Urinary Output	101 (48-230)	94.5 (39-203)	88 (5-222)	0.648

† Significance level of differences among IVIg group, APC group, and ST group

bacteria that can stimulate systemic inflammatory response. Hepatic injury has been investigated primarily in critically ill patients, and few studies have included only septic patients (4,15,16). Criteria used to define hepatic injury include jaundice, hyperbilirubinemia, elevated plasma concentrations of transaminases, alkaline phosphatase, or lactate dehydrogenase, and a decrease in the serum albumin concentration. In cases of septic shock aminotransferase (AST, ALT) levels are usually mildly elevated and are disproportionately lower than bilirubin levels (17). Unfortunately, conventional hepatic function markers are either relatively non-specific or have a long half-life, which make them poor predictors of acute injury (18).

In our ICU patients ALT and AST are routinely used to measure hepatic functions. ALT is primarily a hepatic enzyme. The spillover of this enzyme into blood is routinely used as a marker of hepatic-cell damage. This helps to identify hepatic disease caused by cell damage. The enzyme AST has a similar role,

Table 7. ALT, AST, ALP, albumin, bilirubin, and INR value variations of groups during 2 time periods (zero as the beginning of the therapies and +96 as 96 h of the therapies. Data were expressed as median (minimum-maximum), AST and ALT (U/L), albumin, bilirubin (mg/dL), Hourly urinary output (ml/h), and INR (ratio).

	Periods	ALT	AST	ALP	Albumin	Bilirubin	INR
IVIg group (n = 20)	Zero	43 (15-81)	46 (10-110)	363 (147-612)	2.95 (2.1-4.4)	1 (0.16-5.7)	1.09 (0.9-1.49)
	+96	34.5 (13-83)	36 (18-72)	245 (172-529)	2.8 (2.46-3.7)	0.7 (0.03-5.01)	1.2 (0.9-1.79)
	P†	*0.480*	*0.374*	*0.655*	*0.824*	*0.180*	*0.126*
APC group (n = 22)	Zero	68 (23-191)	66 (21-115)	335 (135-472)	2.85 (2.3-3.5)	0.94 (0.01-8.3)	1.27 (1-2.01)
	+96	51.5 (14-158)	48 (30-102)	213 (143-384)	2.9 (2.3-3.6)	0.9 (0.2-3)	1.11 (0.89-2.93)
	P†	*0.082*	*0.035*	*0.180*	*0.320*	*0.754*	*0.500*
ST group (n = 66)	Zero	25.5 (2-527)	41 (8-147)	366.5 (105-806)	2.85 (2-4.6)	1.36 (0.4-3.11)	1.2 (0.9-1.9)
	+96	34 (5-269)	49 (14-143)	413 (163-542)	2.9 (2-4.4)	1 (0.4-3)	1.21 (0.9-2.3)
	P†	*0.424*	*0.481*	*0.180*	*0.417*	*0.015*	*0.450*

†Significance level between zero and +96 time periods. The statistically significant results appeared as decrease in AST levels in APC group and in bilirubin levels in ST group.

Table 8. BUN, creatinine, and hourly average urinary output variations of groups during 2 time periods (zero as the beginning of the therapies and +96 as 96 h of the therapies). Data were expressed as median (minimum-maximum), BUN and creatinine data mg/L, hourly average urinary output mL/h.

	Periods	BUN	Creatinine	Hourly average urine output
IVIg group (n = 20)	Zero	30.35 (8-76)	0.84 (0.4-2.3)	101 (48-230)
	+96	45.5 (12-98.1)	0.86 (0.2-4.5)	124.5 (25-193)
	P†	*0.061*	*0.349*	*0.877*
APC group (n = 22)	Zero	27 (8-125)	1 (0.4-6.1)	96 (39-203)
	+96	30.35 (15-107)	0.85 (0.5-3.4)	90 (0-351)
	P†	*0.198*	*0.234*	*0.717*
ST group (n = 66)	Zero	27.5 (7-180)	0.9 (0.3-4.48)	88 (5-222)
	+96	35.5 (8-93)	0.9 (0.4-5.5)	109 (5-232)
	P†	*0.096*	*0.641*	*0.850*

†Significance level of differences in groups between zero and +96 time periods

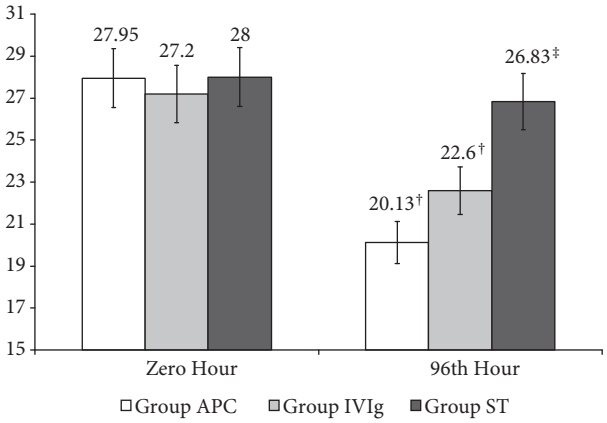

Figure. APACHE II score variations 0 and 96 h after the beginning of the therapies in 3 groups.

† *The significance of decrease in 96 h values compared to 0 h with paired samples-t test in APC group and IVIg group; P < 0.0001*

‡ *The significance of decrease in 96 h values compared to 0 h with paired samples-t test in ST group; P = 0.019*

but this enzyme tends to be found in other tissues, such as the heart, and therefore is not specific to the liver (17). A recent study that included healthy volunteers in whom sepsis was induced reported that glutathione S-transferase A1-1 may be a useful marker of early hepatic injury in septic shock patients due to its relatively short half-life (1 h) and rapid release into the blood after hepatic damage (18).

AST has a circulatory half-life of approximately 12-24 h; therefore, levels rise in response to hepatic damage and clear quickly once damage ceases. ALT has a longer half-life (37-57 h) than AST; consequently, its elevation persists longer after hepatic damage has ceased. In the present study we measured AST and ALT levels at 96-h, a time interval that was sufficiently long for evaluating changes in the long half-life enzyme ALT in septic patients. However, 96-h changes in this enzyme were not significant in any of the groups, whereas AST decreased significantly in the APC group.

Sepsis and septic shock remain the most important triggers of acute renal failure (ARF) in ICU patients. Despite the advent of sophisticated renal replacement therapies that employ high-dose hemofiltration and high-flux membranes, mortality and morbidity from sepsis-induced acute kidney injury remain high (3). Patients with sepsis-related ARF have much higher mortality than patients with acute renal failure that do not have sepsis. A possible explanation for the high incidence and poor outcome of septic ARF relates to the lack of specific therapies (19), and a limited understanding of septic-related acute renal injury and its pathogenesis (20).

The question that remains is whether or not adjuvant therapies, such as immunoglobulin preparations and rhAPC, added to standard sepsis therapy can improve sepsis-induced renal injury. In the present retrospective study creatinine, BUN, and mean hourly urinary output levels were taken into consideration while evaluating the impact of adjuvant therapy strategies on renal damage in septic ICU patients. We did not observe any significant changes in renal functions based on the data obtained from all 3 study groups.

There is a limited quantity of data on the relationship between sepsis-related renal failure and rhAPC therapy in the current literature. Gupta et al. (21) recently reported that administration of rhAPC protects against renal dysfunction, but the underlying mechanism is unknown. An experimental study performed by the same researchers reported that serine protease protein C levels during systemic inflammatory response may be pathophysiologically related to renal dysfunction, and that the ability to improve renal function and pathology suggests the potential for the clinical use of rhAPC in the treatment of sepsis-induced ARF (22). Moreover, Mikaszewska-Sokolewicz et al. (23) reported there was improvement in renal excretory function after rhAPC infusion in 2 septic ICU patients. Such studies highlight the role of protein C and activated protein C. In the present retrospective study significant improvement in renal function in the patients administered activated protein C was not observed; however, we think because only 108 patients were evaluated the results obtained are limited, and that additional research including larger groups of septic patients is needed.

IgM-enriched immunoglobulin is a promising adjuvant therapy, both clinically and economically, for the treatment of adults with severe sepsis and septic shock (14). The efficacy of polyclonal immunoglobulins in therapy for sepsis and septic

shock was supported for the first time by various trials that were collected in a recent Cochrane Library meta-analysis (6). Clinical studies indicate there are potential differences in the efficacy of immunoglobulin preparations in patients with sepsis (24). Sepsis remains one of the important causes of vital organ dysfunction. In addition to standard treatment regimens, new adjuvant agents are in clinical use; however, the cost/benefit ratio raises questions about the feasibility of their use in sepsis patients. This fact also makes planning prospective trials difficult. We hope that future clinical trials that evaluate the benefits of these agents on multi-organ dysfunction will provide promising results.

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