Early Administration of Hydrocortisone Replacement After the Advent of Septic Shock: Impact on Survival and Immune Response*

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Objectives: To investigate the impact of early initiation of hydrocortisone therapy on the clinical course of septic shock and on cytokine release.

Design: Prospective study in patients with septic shock treated with low doses of hydrocortisone.

Setting: ICUs and general wards.

Patients: Over a 2-year period, 170 patients with septic shock treated with low doses of hydrocortisone were enrolled. Blood was sampled from 34 patients for isolation of peripheral blood mononuclear cells and cytokine stimulation before and 24 hours after the start of hydrocortisone.

Interventions: None.

Measurements and Main Results: After quartile analysis, patients were divided into those with early initiation of hydrocortisone (< 9 hr after vasopressors, $n = 46$) and those with late initiation of hydrocortisone (> 9 hr after vasopressors, $n = 124$). After adjusting for disease severity and type of infection, a protective effect of early hydrocortisone administration against unfavorable outcome was found (hazard ratio, 0.20; $p = 0.012$). Time of discontinuation of vasopressors was earlier among patients with initiation of hydrocortisone within 9 hours. Production of tumor necrosis factor-α was lower among patients who had had hydrocortisone early.

Conclusions: In patients receiving hydrocortisone for septic shock, early initiation of treatment was associated with improved survival. This treatment was also associated with attenuated stimulation of tumor necrosis factor-α. (*Crit Care Med* 2014; 42:1651–1657)

Key Words: critical illness; critical illness–related corticosteroid insufficiency; hydrocortisone; outcome; relative adrenal insufficiency; sepsis; septic shock; steroid replacement; tumor necrosis factor-α

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Clinical and experimental data indicate that during critical illness, especially in severe sepsis and septic shock, a form of corticosteroid insufficiency develops, which is referred to as "critical illness–related corticosteroid insufficiency" (CIRCI). Inadequate secretion of cortisol, altered cortisol metabolism, tissue resistance to its actions, and adrenal endothelial dysfunction are some of the proposed mechanisms for CIRCI development. The result of the inadequate intracellular glucocorticoid activity is an exaggerated

proinflammatory response or imbalance between pro- and anti-inflammatory mediators (1–5). The most common manifestation of CIRCI is hypotension refractory to the IV administration of fluids and vasopressors. As a result, the diagnosis of CIRCI should be considered in every ICU patient requiring vasopressor support (2).

The introduction of CIRCI as a clinical entity led to the hypothesis that the administration of low doses of hydrocortisone as a supplement to treat the potential alteration in production, metabolism, or cellular response to cortisol may benefit the patients. Replacement with low doses of hydrocortisone for 5–7 days in a randomized clinical trial conducted in a French sepsis population reversed shock rapidly and improved outcome (6). The Corticosteroid Therapy of Septic Shock (CORTICUS) study attempted to repeat the results of the French trial. Although replacement with low doses of hydrocortisone in the CORTICUS trial did not decrease mortality, earlier resolution of cardiovascular failure occurred in the hydrocortisone treatment arm compared to the placebo-treated patients (7). Other studies conducted since then provided contradictory results (8–10). The Surviving Sepsis Campaign Guidelines recommend the administration of 200 mg hydrocortisone per day when fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability in septic shock patients (11).

In all previously conducted studies, administration of hydrocortisone was the sine qua non considered to target CIRCI without taking into consideration that hydrocortisone is a drug with major anti-inflammatory activities. None of these studies provided any evidence for an effect of hydrocortisone on the inflammatory cascade. Furthermore, a critical component that was not taken into consideration in the analysis of all these trials was the time elapsing between development of septic shock and start of hydrocortisone therapy.

The present study was designed to investigate 1) the importance of the time frame between development of septic shock and start of hydrocortisone for the final outcome and 2) the effect of hydrocortisone on cytokine release by circulating monocytes.

PATIENTS AND METHODS

Study Design

The present study is a nonrandomized prospective longitudinal study that was conducted in patients with septic shock in seven ICUs and four departments of Internal Medicine that participate in the Hellenic Sepsis Study Group (http://www.sepsis.gr) from January 2009 until January 2011 and from December 2012 until February 2013. The study protocol was approved by the ethics committees of all participating hospitals. Written informed consent was obtained from patients or their relatives to allow blood sampling and review of medical records.

Inclusion criteria were 1) age 18 years old or older and 2) presence of septic shock treated with norepinephrine at a dose greater than 0.5 μg/kg/min and low doses of hydrocortisone (daily administration of 50 mg q6h for 7 d according to clinical recommendations) (11, 12). The high dose of vasopressors was purposely selected in order to test the effect of the early start of hydrocortisone on outcome in a setting of severely shocked patients. Enrolled patients did not receive any other vasopressors. Septic shock was defined as severe sepsis aggravated by systolic arterial pressure less than 90 mm Hg, necessitating the administration of vasopressors despite adequate fluid resuscitation as defined by central venous pressure above 10 cm H_2O (11, 13). All enrolled patients had antimicrobials initiated for their current infection within the last 48 hours of hydrocortisone administration.

Exclusion criteria were the presence of any of the following: 1) HIV infection; 2) neutropenia defined as less than 1,000 neutrophils/mm^3; 3) chronic systemic treatment with corticosteroids, that is, more than 1 mg/kg of prednisone or equivalent for the last month; 4) any other cause of severe immunosuppression, that is, solid tumor malignancy, hematologic malignancy, and intake of any antineoplastic chemotherapy; and 5) any decision of therapy withdrawal or of only palliative treatment administration.

Patients' treatment including the time of start of hydrocortisone administration was at the discretion of the attending

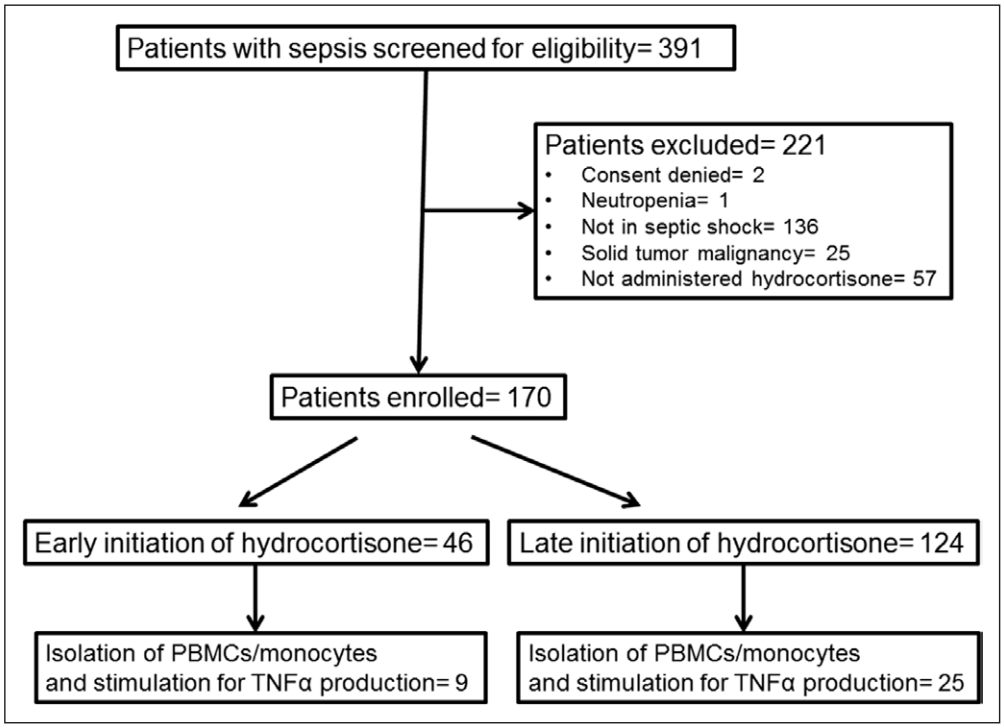

Figure 1. Study flowchart. Patient recruitment and classification in groups of early and late intiation of hydrocortisone. PBMCs = peripheral blood mononuclear cells, TNF-α = tumor necrosis factor-α.

TABLE 1. Clinical Characteristics of Patients Enrolled in the Study

Variables	Early Initiation (*n* = 46)	Late Initiation (*n* = 124)	*p*
Male/female, *n* (%)	26 (56.5)/20 (43.5)	84 (67.7)/40 (32.2)	0.207
Age (yr, mean ± SD)	65.2 ± 19.7	62.8 ± 16.9	0.432
WBCs (×1,000/mm^3, mean ± SD)	18.4 ± 10.6	15.5 ± 8.6	0.072
Acute Physiology and Chronic Health Evaluation II score (mean ± SD)	26.3 ± 9.9	23.9 ± 11.5	0.229
Sequential Organ Failure Assessment score (mean ± SD)	11.5 ± 3.8	10.7 ± 3.6	0.307
Patients with comorbidities, *n* (%)	24 (52.2)	60 (48.4)	0.731
Type of comorbidities, *n* (%)			
Diabetes mellitus type 2	14 (30.4)	26 (18.1)	
Chronic obstructive pulmonary disease	10 (21.7)	16 (11.1)	
Chronic heart failure	10 (21.7)	26 (18.1)	
Chronic renal disease	3 (6.5)	9 (6.2)	
Infection, *n* (%)			0.144
Ventilator-associated pneumonia	14 (30.4)	63 (50.8)	
Primary bacteremia	13 (28.3)	33 (26.6)	
Intrabdominal infections	5 (10.9)	11 (8.9)	
Community-acquired pneumonia	4 (8.7)	8 (6.5)	
Urosepsis	6 (13.0)	5 (4.0)	
Others	4 (8.7)	4 (3.2)	
Microbiological identification, *n* (%)	29 (63.0)	85 (68.5)	0.582
Type of isolated pathogen, *n* (%)			
Klebsiella pneumoniae	11 (23.9)	25 (20.2)	0.673
Acinetobacter baumannii	4 (8.7)	32 (25.8)	0.019
Pseudomonas aeruginosa	5 (10.91)	15 (12.1)	0.532
Others	9 (19.6)	13 (10.5)	0.128
Appropriateness of antimicrobials, *n* (%)	27 (93.1)	68 (80.0)	0.149
Required intervention, *n* (%)			
Cholecystectomy	1 (2.2)	2 (1.6)	0.309
Abscess drainage	0 (0)	6 (4.8)	

physician. The following information was collected and analyzed for every enrolled patient: demographics, time elapsing from the start of vasopressors until the start of hydrocortisone administration, appropriateness of prescribed antibiotic treatment, infection source, and daily doses of vasopressors. Severity of illness was assessed with Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores from data collected during the 24 hours after shock. Time elapsing from the start of vasopressors until the start of hydrocortisone replacement was identified in the drug administration records of the nursing charts. Appropriateness of antimicrobials was defined as the administration of at least one antimicrobial active against the isolated pathogen according to the antibiogram showing the susceptibility pattern of the pathogen.

Laboratory Investigation

For 34 patients enrolled by two ICUs located at the same hospital as the study laboratory, 10 mL of heparinized whole blood was collected under aseptic conditions after venipuncture from a forearm vein. Sampling was performed before hydrocortisone administration and was repeated 24 hours after start of hydrocortisone treatment. Peripheral blood mononuclear cells (PBMCs) were isolated after gradient centrifugation of heparinized whole blood over Ficoll (Biochrom GmbH, Berlin, Germany). Following three washings in ice-cold PBS (phosphate-buffered saline) (pH, 7.2) (Biochrom), the viability of cells was more than 99% as assessed by trypan blue (AlterChem, Athens, Greece) exclusion of dead cells. PBMCs were then diluted in RPMI (Rosewell Park Medium) 1640

enriched with 2 mM of L-glutamine, 100 U/mL of penicillin G, and 100 μg/mL of gentamicin and suspended in wells of a 96-well plate. The final volume per well was 200 μL with a density of 2×10^6 cells/mL. PBMCs were stimulated for 24 hours at 37°C and 5% Co_2 with the following stimuli: 1) 10 ng/mL of lipopolysaccharide (LPS) of *Escherichia coli* O55:B5 (Sigma, St. Louis, MO), which was purified by chromatography; 2) 5 μg/mL of Pam3Cys-SKKK (EMC Microcollections, Tübingen, Germany); 3) 5 μg/mL of phytohemagglutin (PHA) of *Phaseolus vulgaris* (PHA-L, Roche Diagnostics GMBH, Mannheim, Germany); and 4) 5×10^5 colony-forming units/mL of heat-killed isolates of *Candida albicans*, *Pseudomonas aeruginosa*, and methicillin-resistant *Staphylococcus aureus*. At the end of the incubation, plates were centrifuged. The supernatants were collected and stored at –70°C until assayed for tumor necrosis factor (TNF)-α. TNF-α was measured in duplicate by an enzyme immunoassay (R&D, Minneapolis, MN). The lower detection limit was 20 pg/mL.

The monocyte fraction was also isolated. Isolated PBMCs were incubated with RPMI 1640 enriched with glutamine in the presence of penicillin G and streptomycin in flasks of 25 cm^3. After 1 hour of incubation at 37°C in 5% Co_2, nonadherent cells were removed; adherent monocytes were thoroughly washed with Hanks' solution (Biochrom). Monocytes were then harvested with a 0.25% trypsin/0.02% EDTA solution (Biochrom) and counted in a Neubauer plate. They were then incubated into wells of a 96-well plate at a final volume of 0.2 mL with RPMI 1640 supplemented with 2 mM of glutamine for 24 hours at 37°C in 5% Co_2 in the absence/presence of 10 ng/mL of purified endotoxin (LPS) derived from *E. coli* O55:He5. After plate centrifugation, cell supernatants were collected and kept refrigerated at –70°C until assayed for TNF-α as described above. Concentrations of TNF-α were expressed as pg/10^4 cells.

Study Endpoints

The primary study endpoint was the effect of time delay of initiation of hydrocortisone after start of vasopressors on final outcome. The secondary study endpoint was the effect of hydrocortisone on cytokine stimulation of circulating monocytes in relation to the time delay of initiation of therapy.

Statistical Analysis

Quartiles of the time delay between start of hydrocortisone and start of vasopressors were calculated. The first quartile was considered early initiation of treatment and the other three quartiles late initiation of treatment. To confirm that this type of selection of patients as early and late initiation was correct, receiver operator characteristics (ROC) curve analysis was performed. Comparisons of baseline characteristics between early and late initiation were done by Student *t* test for continuous variables and by the chi-square test for nominal variables. Odds ratio (OR) and 95% CIs were calculated by Mantel-Haenzel's statistics. Survival and time on vasopressors of the two groups were assessed by Kaplan-Meier analysis and compared by the log-rank test. Univariate analysis was done for the effect of nominal variables on final outcome. Significant variables were entered with APACHE II score as a marker of disease severity in forward stepwise Cox and logistic regression analyses; hazard ratio and 95% CI were calculated. Comparisons between TNF-α produced by PBMCs and monocytes of patients of different quartiles were done by analysis of variance. Any value of *p* less than 0.05 was considered significant.

RESULTS

From a total of 391 patients screened for eligibility, 170 patients were enrolled (**Fig. 1**). Regarding the exclusion of patients under chronic corticosteroid intake, it should be underscored that none of the enrolled patients was in any chronic intake of corticosteroids. Taking into consideration the time frame between start of vasopressors and start of hydrocortisone, four quartiles were defined: 1–9 hours with 46 patients; 10–24 hours with 46 patients; 25–72 hours with 39 patients; and more than 72 hours with 39 patients. The first quartile with 46 patients was considered the early initiation group; the other three quartiles with 124 patients in total were considered the late initiation group. There were no patients in whom the time delay for start of hydrocortisone was between 9 and 10 hours. Comparisons of demographic and clinical characteristics of the two groups are shown in **Table 1**.

ROC analysis confirmed the discriminating ability of early administration of hydrocortisone on overall survival (area under the curve = 0.613; $p = 0.014$). Furthermore, the clinically intuitive first quartile cutoff value of less than 9 hours for the early initiation of hydrocortisone concurs with the value that ROC analysis yields as the best trade-off between sensitivity and specificity. The proportion of survivors was significantly greater in the early in comparison to the late initiation group

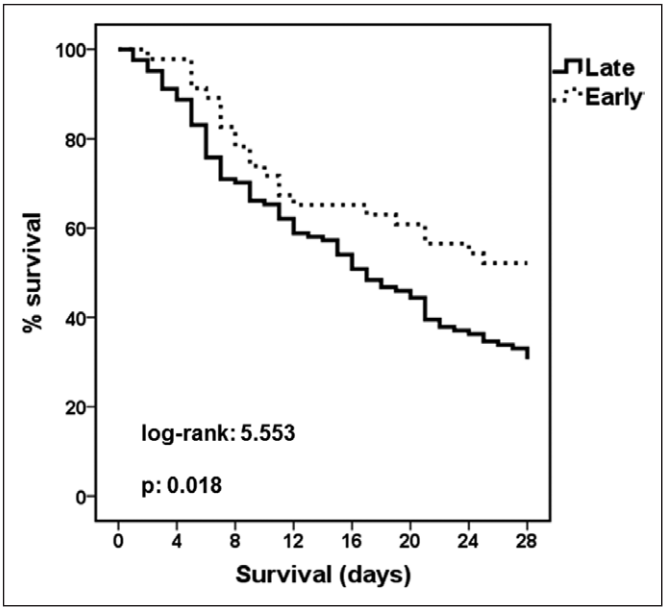

Figure 2. Impact of early initiation of hydrocortisone on final outcome. Using quartile analysis, two groups of patients were defined: those with early initiation of hydrocortisone treatment (i.e., < 9 hr from start of vasopressors, $n = 46$) and those with late initiation of hydrocortisone treatment (i.e., > 9 hr from start of vasopressors, $n = 124$). Statistical comparisons between early- and late-initiation groups are shown.

TABLE 2. Stepwise Forward Cox Regression and Logistic Regression Analysis of Factors Influencing Final Outcome

	Cox Regression Model			Logistic Regression Model		
Tested Variables	*p*	Hazard Ratio	95% CI	*p*	OR	95% CI
High Acute Physiology and Chronic Health Evaluation II score (≥ 19)	< 0.001	2.84	1.74–4.63	< 0.001	5.36	2.57–11.18
Early initiation of hydrocortisone (< 9 hr)	0.016	0.56	0.35–0.90	0.004	0.32	0.15–0.69

OR = odds ratio.

(52.2% vs 30.6%; Fisher exact test; $p = 0.012$), and the OR for favorable outcome for patients of the early initiation group was 0.40 (95% CI, 0.20–0.81). Furthermore, as Kaplan-Meier survival analysis showed (**Fig. 2**), survival was significantly prolonged among patients in the early initiation group compared to the late initiation group ($p = 0.018$).

To elaborate if early initiation of hydrocortisone was an independent risk factor associated with final outcome, univariate analysis was done to identify potential factors linked with unfavorable outcome. It was found that among all tested variables, only the APACHE II and SOFA scores and the delay until start of hydrocortisone were linked with unfavorable outcome (data not shown). ROC analysis confirmed the discriminating ability of APACHE II score (area under the curve = 0.653; $p = 0.002$) and SOFA score (area under the curve = 0.621; $p = 0.016$) on overall survival. However, the two scores are very highly correlated ($r = 0.625$); therefore, the inclusion of only the APACHE II score, as proven by stepwise logistic regression (data not shown) should suffice. The best trade-off providing sensitivity greater than 80% was an APACHE II score greater than or equal to 19. **Table 2** shows the results of the stepwise forward Cox regression and logistic regression analysis of high APACHE II score (≥ 19) and early initiation start of hydrocortisone on the final outcome.

As shown in Table 2, the effects of low or high APACHE II score and early or late hydrocortisone initiation are additive. In patients with high APACHE score (≥ 19), the early initiation of hydrocortisone increased the survival rate from 19.8% to 41.2% ($p = 0.021$). Likewise, in patients with low APACHE score (< 19), the early initiation of hydrocortisone increased the survival rate from 55.0% to 83.3%.

The time until withdrawal of vasopressors was earlier in the early-initiation group than in the late-initiation group (**Fig. 3**). More precisely, median time until discontinuation of vasopressors was 4 days for patients of the early-initiation group; it was prolonged to 15 days for patients of the late-initiation group ($p < 0.0001$).

The demographic characteristics of patients of the early- and late-initiation groups identified a considerable lower rate of infection with *Acinetobacter baumannii* in the early-initiation group than in the late-initiation group. This may lead to erroneous results because the appropriateness of antimicrobial therapy was 66.7% among the total of *A. baumannii*–infected patients compared with 90.3% among patients infected by other type of pathogens ($p = 0.006$). Survival analysis was repeated after excluding patients treated with inappropriate antimicrobials for *A. baumannii*. Mortality was 33.3% in the early-initiation group and 53.3% in the late-initiation group (log-rank, 4.760; $p = 0.029$). Cytokine stimulation by PBMCs and monocytes of patients in relation with the quartile of delay from start of hydrocortisone showed that the production of TNF-α was lower from cells coming from patients who were initiated early hydrocortisone (mainly from the first two quartiles). The differences were pronounced when cells were stimulated with LPS, Pam3Cys, PHA, and heat-killed *P. aeruginosa* (**Fig. 4**).

DISCUSSION

Stress replacement with low doses of hydrocortisone is part of the suggested adjunctive therapies for patients with protracted or refractory septic shock (7, 11, 12). This treatment strategy has been a subject of great criticism due to the inconsistent findings of conducted clinical trials. The difference in the time

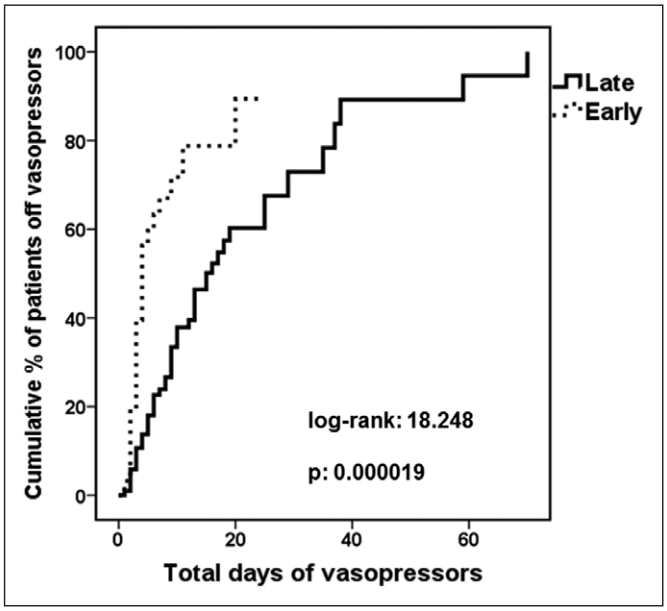

Figure 3. Impact of early initiation of hydrocortisone on the total time on vasopressors. Using quartile analysis, two groups of patients were defined: those with early initiation of hydrocortisone treatment (i.e., < 9 hr from start of vasopressors, $n = 46$) and those with late initiation of hydrocortisone treatment (i.e., > 9 hr from start of vasopressors, $n = 124$). Statistical comparisons between early- and late-initiation groups are shown.

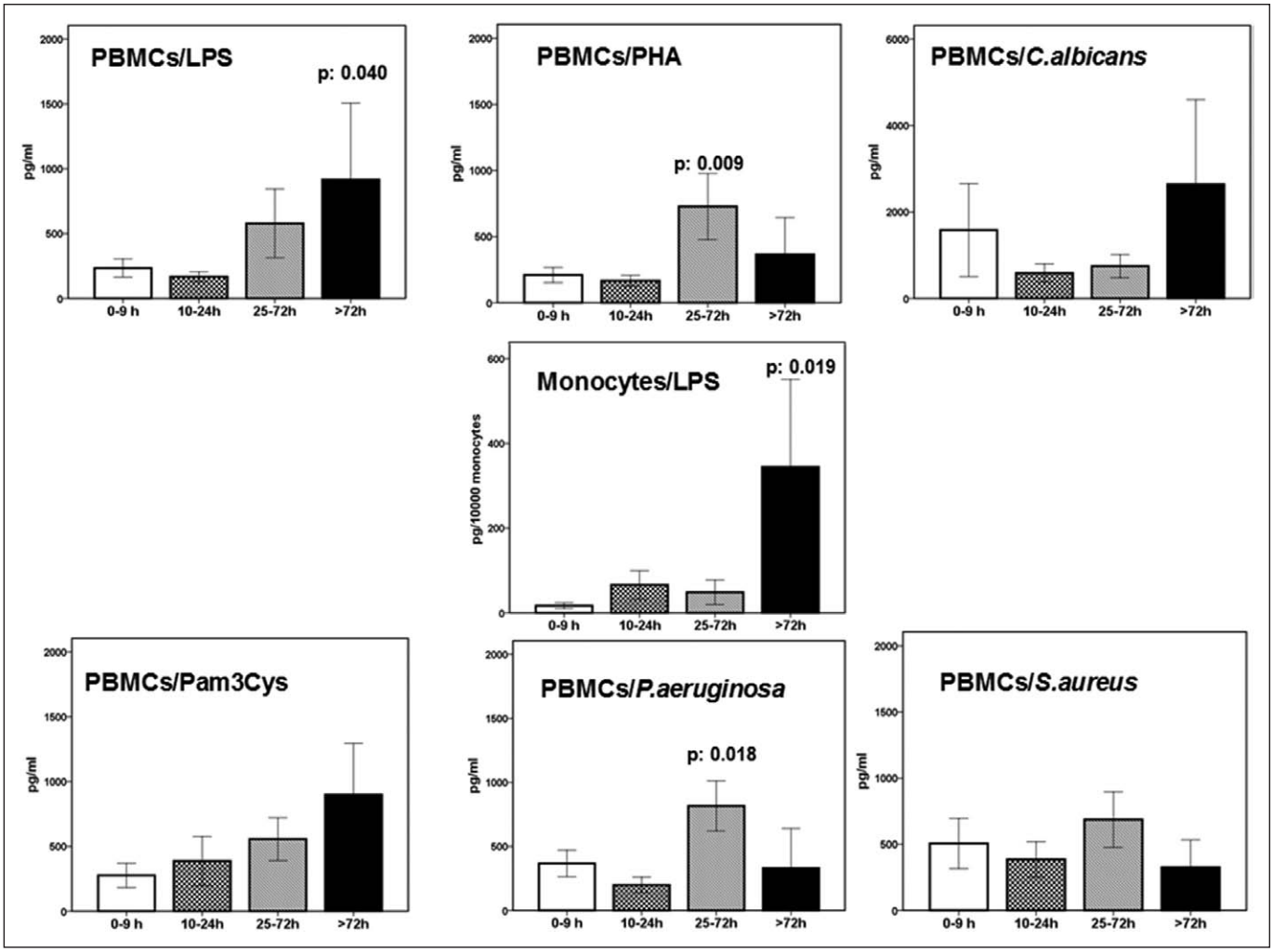

Figure 4. Impact of hydrocortisone on the release of tumor necrosis factor (TNF)-α. Production of TNF-α from peripheral blood mononuclear cells (PBMCs) or monocytes isolated 24 hr after initiation of therapy is shown in relation with the quartiles of delay of start of hydrocortisone from start of vasopressors. The numbers of patients in each quartile are as follows: 0–9 hr, nine patients; 10–24 hr, 10 patients; 24–72 hr, seven patients; and > 72 hr, eight patients. Release from unstimulated cells was below the lower limit of detection. The type of stimulus is shown and the types of cells tested are shown. *p* values indicate statistically significant comparisons with the 0–9 hr quartile. LPS = lipopolysaccharide, PHA = phytohemagglutin.

elapsed between development of septic shock and initiation of hydrocortisone therapy could explain this inconsistency. In the study by Annane et al (6), this time frame was initially 3 hours and then it was increased to 8 hours. In the CORTICUS study, the initial time frame of 24 hours increased to 72 hours (7). In our nonrandomized prospective study, we provide evidence that survival benefit is correlated with the time delay of initiation of hydrocortisone from start of vasopressor therapy. Initiation of hydrocortisone within 9 hours from vasopressor initiation was associated with improved survival compared to delayed initiation.

The presented findings corroborate the recently published results of a retrospective analysis of 178 patients with septic shock, treated with low doses of hydrocortisone, by Park et al (14). The investigators found that as early as 6 hours start of therapy with hydrocortisone from the start of vasopressors resulted in significant survival benefit. However, in this study, the investigators defined septic shock as the decrease of systolic blood pressure despite adequate fluid resuscitation. These findings generated two questions: 1) Can these results be replicated in a completely independent cohort of patients with septic shock under the need of intense administration of vasopressors? and 2) What may be the mechanism of action of hydrocortisone and can this be related with some modulation of the innate immune response?

The present study has two major differences compared with the study by Park et al (14): 1) it is conducted in a septic shock population requiring high doses of norepinephrine and 2) it suggests a possible mechanism of action of hydrocortisone.

The mechanism behind survival benefit from early start of low doses of hydrocortisone is not clear. Part of the explanation may rely on the modulation of the metabolism of endogenous cortisol which is down-regulated in critically ill patients (3, 4) or prevention of the development of resistance of lymphocytes to the anti-inflammatory effect of glucocorticosteroids (5) or to increased sensitization of the vasculature to vasopressors caused by hydrocortisone or with the mineralocorticoid properties of hydrocortisone (15). However, our data imply that an

immunomodulating effect of low-dose hydrocortisone treatment may also play some role.

In a prior study, whole blood from 33 patients with sepsis was stimulated ex vivo by LPS for cytokine production in the absence and presence of dexamethasone. Results showed that addition of dexamethasone decreased the production of proinflammatory cytokines TNF-α, interleukin (IL)-6, and IL-8 in a dose-dependent manner (16). It is not possible to compare the results from the ex vivo addition of dexamethasone in blood cultures with the cytokine production from systemically treated patients with hydrocortisone. Although hydrocortisone possesses a 25-fold lower glucocorticoid activity than dexamethasone, results of systemically treated patients of the present study indicate attenuated proinflammatory responses.

The anti-inflammatory properties of hydrocortisone in septic shock have been proven in two prospective randomized clinical studies. The first study had a crossover design; 20 patients with septic shock were allocated to placebo and another 20 patients to the continuous infusion of 10 mg/hr of hydrocortisone for 3 days after an initial bolus loading dose of 100 mg. Then the two groups were reversed. Serum concentrations of the proinflammatory mediators IL-6 and IL-8 were decreased during hydrocortisone treatment. The effect was abolished upon crossover to placebo. Similar findings were observed for the anti-inflammatory cytokines IL-4 and IL-10 (17). In the second prospective study, patients with hyperdynamic shock were randomized to either placebo ($n = 23$) or low dose of hydrocortisone ($n = 18$). Circulating levels of IL-6 and IL-10 on the first 5 days were significantly decreased within hydrocortisone-treated patients (18). However, no study has ever described the effect of hydrocortisone on cytokine stimulation of circulating monocytes. This is described for the first time here and provided evidence that circulating monocytes are one of the sites of action of hydrocortisone. The finding that the TNF-α production was attenuated in patients belonging to the first two quartiles implies that the time window of hydrocortisone administration could even be expanded to 24 hours.

Two major limitations of the present study should be acknowledged: 1) it is nonrandomized and 2) the lack of a comparator untreated arm. Despite these limitations, the presented results underscore the importance of early administration of hydrocortisone in septic shock. When it is decided that hydrocortisone is going to be administered, this should be done as early as possible because patients who received early hydrocortisone had improved survival.

CONCLUSIONS

A survival benefit was observed in patients with septic shock treated with low doses of hydrocortisone, when hydrocortisone was administrated within 9 hours after shock development. In these patients, production of TNF-α by PBMCs and monocytes was reduced.

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