The Effect of Stress Doses of Hydrocortisone During Septic Shock on Posttraumatic Stress Disorder in Survivors

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Background: *Exposure to intense physical and psychological stress during septic shock can result in posttraumatic stress disorder in survivors. Patients with chronic posttraumatic stress disorder often show sustained reductions in serum cortisol concentration. This investigation examines whether increasing serum cortisol levels with hydrocortisone treatment during septic shock reduces the incidence of posttraumatic stress disorder in survivors.*

Methods: *Patients (*n = *20) were recruited from a prospective, randomized double-blind study on the hemodynamic effects of hydrocortisone during septic shock. Eleven patients had received placebo and nine stress doses of hydrocortisone. Posttraumatic stress disorder was diagnosed 31 months (median) after intensive care unit discharge using SCID-IV (DSM-IV-criteria). Furthermore, the number of categories of traumatic memory from ICU treatment was determined in both groups at that time.*

Results: *Only one of nine patients from the hydrocortisone group developed posttraumatic stress disorder, compared with seven of 11 patients in the placebo group (*p = *.02). There was no significant difference with regard to the number of categories of traumatic memory between the hydrocortisone and placebo groups.*

Conclusions: *The administration of hydrocortisone during septic shock in a dosage similar to the endogenous maximal production rate was associated with a lower incidence of posttraumatic stress disorder in long-term survivors, which seems to be independent of the number of categories of traumatic memory.* Biol Psychiatry 2001; 50:978–985 © *2001 Society of Biological Psychiatry*

Key Words: Hydrocortisone, septic shock, posttraumatic stress disorder, PTSD, traumatic memories, intensive care unit

Introduction

Patients with septic shock face a 50% risk of death in the intensive care unit (ICU) (Matthay 2001) and are exposed to extensive physical and emotional stress, which is the combined result of severe systemic infection, multiple organ dysfunction, and the intensive care treatment itself. In addition, many survivors of septic shock or acute pulmonary failure report emotionally traumatic episodes such as anxiety, pain, respiratory distress, or nightmares from their stay in the ICU (Eddleston et al 2000; Hayden 1994; Schelling et al 1998). Due to this combined exposure to maximal physical and psychological stress, patients may develop long-term emotional sequelae such as posttraumatic stress disorder (PTSD) after ICU treatment (Jones 2001; Schelling et al 1998).

In addition to a characteristic pattern of emotional symptoms, neuroendocrine system alterations such as lower plasma (Yehuda et al 1991) or urinary cortisol levels (Mason et al 1986) and high noradrenergic activity (Mason et al 1988; Mellman et al 1995) are often found in patients with chronic PTSD. In a recent case-control study, we reported that patients who received hydrocortisone during septic shock and had increased serum cortisol levels in the ICU had a significantly lower risk of developing PTSD (Schelling et al 1999). Hydrocortisone was given to these patients because two prospective randomized studies have demonstrated a reduction in dosage and duration of norepinephrine requirements, which resulted in a significant shortening of the shock phase (Bollaert et al 1998; Briegel et al 1999). This effect of stress doses of hydrocortisone may be due, at least in part, to a down regulation of the severe systemic inflammatory response typically found during sepsis.

In addition, the aforementioned case-control study (Schelling et al 1999) suggested a possible role for lower cortisol levels during severe stress exposure as a co-factor for the development of PTSD. The design of this study was retrospective, however, because we had selected patients with septic shock from our database and matched

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patients with hydrocortisone with those with standard therapy (Schelling et al 1999). Hydrocortisone administration was not randomized in this study and, theoretically, patients in the hydrocortisone group could have been sicker and could have received more intensive sedation, thus resulting in a lower incidence of PTSD. Furthermore, sedation was not standardized in the matched case study, different drugs were used during different phases of the investigations, and no data were available regarding the duration of the shock phase, exposure to norepinephrine, the duration of hydrocortisone administration, or serum cortisol levels. Because of an increased understanding of how these variables might influence the development of PTSD, we decided to evaluate a subgroup of critically ill patients in whom data on stress hormone dosages, degree of sedation, or duration of the shock phase were prospectively recorded, and came up with patients from a prospective randomized study on hydrocortisone during septic shock that has been performed at our institution. Some data of 14 patients from this study had already been included in the previous report (mainly hydrocortisone yes/no, PTSD scores, and data on disease severity) (Schelling et al 1999), but the reevaluation of these data (together with data from six other patients from the original septic shock study) now evaluates two groups which are truly comparable with regard to other variables such as traumatic memories, level of sedation, or norepinephrine dosage, which are known to have possible additional effects on PTSD.

Methods and Materials

The study was performed at a 20-bed multidisciplinary ICU of the tertiary care university hospital of the Ludwig-Maximilians University of Munich. The study was approved by the Institutional Review Board of our institution and data protection met the standard set by German law.

Forty patients with hyperdynamic septic shock were included in the original study (Briegel et al 1999). For enrollment, patients had to fulfill the criteria for hyperdynamic septic shock as proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) (Bone et al 1992). Patients were prospectively and randomly assigned to receive either placebo (saline, control group) or hydrocortisone (hydrocortisone group) with a loading dose of 100 mg given intravenously over 30 min, followed by a continuous infusion of .18 mg/kg/hour. This dose was kept constant for 6 days. When septic shock was reversed, the dose of hydrocortisone was reduced to .08 mg/kg/hour for an additional 6 days and then tapered in steps of 24 mg per day when the underlying infection was properly controlled. Infection was regarded as controlled when fever was absent and leukocyte count and plasma C-reactive protein concentration were normalized. Hydrocortisone doses were tapered slowly over many days because a faster withdrawal of hydrocortisone can result in rebound inflammation. For the purpose of this study, the duration of the shock phase (time to shock reversal) was defined as the duration of required vasopressor support to achieve a mean arterial pressure of 70 mmHg. All patients received protocol-driven supportive care for septic shock, which included antibiotic therapy, fluid resuscitation, mechanical ventilation, and norepinephrine as a vasopressor.

In a subgroup of randomly selected patients ($n = 12$), serum cortisol levels (including baseline values before administration of hydrocortisone) were measured daily (at 7:00 AM) over a period of 14 days. Blood for cortisol measurements was taken from a cannula permanently placed into the radial or femoral artery (without a painful venipuncture) together with other blood samples for routine blood chemistry and immediately sent to the laboratory. During the study, the attending physicians, the investigators, and the nursing staff were blinded with regard to the results of these measurements.

All patients were deeply sedated during septic shock using continuous infusions of the benzodiazepine midazolam and the opioid fentanyl. Sedation was assessed by calculating Glasgow Coma Scale (GCS) points daily at 7:00 AM. During the shock phase, midazolam and fentanyl were titrated to achieve a GCS value of 3 (indicating an unconscious patient with no response to verbal command or painful stimuli). After hemodynamic stabilization, control of septic shock and during the weaning phase from mechanical ventilation, the patients were gradually allowed to wake up and to cooperate in the weaning process according to clinical standards.

Follow-Up Investigation

Primary endpoints of the follow-up study were the incidence and intensity of PTSD and the number of predefined categories of traumatic memory the patients could recall from their period of critical illness. Eligible patients were identified using the database of the first part of the study, which, in addition, provided the following data: group assignment (hydrocortisone or placebo), the principal reason for development of septic shock (trauma, peritonitis, pneumonia, or other/unknown) at admission to the ICU, disease severity at 24 hours after admission to the ICU (Acute Physiology and Chronic Health Evaluation [APACHE] II scores) (Knaus and Draper 1985) and survival/nonsurvival during ICU stay and follow up.

For the follow-up study, we excluded patients with preexisting neurologic or psychiatric diseases (including alcohol and drug abuse) or those who could not complete a questionnaire in German language. This led to the exclusion of four patients from the hydrocortisone group (three for preexisting psychiatric disease; one for language difficulties) and one in the control group (language problems). Another four patients had died in the hydrocortisone group and six in the control group. One more patient from the hydrocortisone group had died after discharge from the ICU and four patients (two from each group) were lost to follow-up. This resulted in a total study population of 20 patients, nine given hydrocortisone and 11 given placebo. The time interval between discharge from the ICU and evaluation for PTSD was 31 months (median value, range 21–49 months) in both groups. Baseline and treatment characteristics of the hydrocortisone and placebo groups are compared in Table 1.

Table 1. Comparison of Baseline and Treatment Characteristics between the Hydrocortisone and the Placebo Groups

Parameter	Control Group (n = 11)	Hydrocortisone Group (n = 9)	p
Gender (m/f)	5/6	3/6	.465
Age (y)[a,b]	55 (25–75)	48 (23–76)	.766
APACHE II score[a,d]	22 (14–35)	24 (14–29)	.370
Duration of ICU treatment (d)[a]	32 (11–99)	23 (17–72)	.503
Time interval[a,c] (months)	31 (21–49)	31 (23–49)	.941
Causes of sepsis			
Peritonitis (no/y)	4/7	1/8	.221
Pneumonia (no/y)	10/1	9/0	.550
Trauma (no/y)	9/2	9/0	.289
Other (no/y)	10/1	8/1	.159

ICU, intensive care unit.
[a]Values are given as medians (minimal-maximal value).
[b]Indicates patient age when in the ICU.
[c]Indicates the time interval between discharge from the ICU and data collection.
[d]APACHE II is a severity of disease classification system for ICU patients. APACHE II uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. An increasing score (range 0–71) is closely correlated with the subsequent risk of hospital death (Knaus and Draper 1985).

Eligible patients were initially contacted by phone and received a detailed explanation of the purpose of the study. The patients were informed that we were interested in their present state of physical and mental health without any direct referral to PTSD. A standard text was used for this initial approach, and after informed oral consent the patients were invited to our institution for PTSD evaluation.

Incidence and Severity of Posttraumatic Stress Disorder

Incidence of Posttraumatic Stress Disorder

The patients from the study cohort received a thorough psychiatric assessment by two experienced psychiatrists (HJK and HBR) in the setting of the university hospital using the Structured Clinical Interview for DSM-IV (SCID-IV) technique. The Structured Clinical Interview aimed to objectify a psychiatric diagnosis according to the DSM-IV diagnostic criteria for PTSD. In addition, the patients were asked to describe possible traumatic memories from the ICU and how they had experienced the situations and events that resulted in traumatic memory formation. During the psychiatric interview, the patients were asked to describe other episodes of exposure to severe stress or physical/emotional trauma (either before or after their stay in the ICU).

For the interviews, the psychiatrists were blinded with regard to treatment characteristics (group assignment, principal diagnosis, traumatic experiences, duration of treatment, etc.). They were informed only that the patients were long-term survivors of intensive care. The patients were blinded regarding the facts that their interviewers were psychiatrists and that the aim of the interviews was the diagnosis of PTSD. They were told that their interviewers were doctors with special training in interviewing techniques and that the object of the interviews was their memories from intensive care treatment and their current emotional well being.

Severity of Posttraumatic Stress Disorder

The severity of posttraumatic stress symptoms was measured using a modified German version of the Post-Traumatic Stress Syndrome 10-Questions Inventory (Weisaeth 1989), which has been validated in patients after ICU therapy (Stoll et al 1999). This instrument records the presence and intensity of 10 posttraumatic stress symptoms: sleep disturbance, nightmares, depression, hyperalertness, withdrawal (emotional numbing and inability to care for others), generalized irritability, frequent changes in mood, guilt, avoidance reactions with regard to the ICU, and increased muscle tensions. Patients rate their symptoms using a scale from 1 (never) to 7 (always). A sum score of more than 35 is associated with a high probability of patients fulfilling the diagnostic criteria for PTSD (Stoll et al 1999).

This questionnaire was validated by our group in a sample of long-term survivors of intensive care after acute pulmonary failure (Stoll et al 1999). In this study, the reliability and validity of the questionnaire was estimated and its specificity, sensitivity, and optimal decision threshold determined using receiver operating characteristic curve (ROC) analysis. The criterion to which the questionnaire's sensitivity and specificity was assessed was the diagnosis of PTSD by two experienced psychiatrists according to DSM-IV criteria using a double blind interview technique (Stoll et al 1999). Criterion validity of the questionnaire was demonstrated by ROC curve analysis with a sensitivity of 77.0% and a specificity of 97.5% at an optimal cut-off value of 35 points for the diagnosis of PTSD. The instrument showed a high internal consistency (Cronbach's $\alpha = .93$) and a high test-retest reliability (intraclass correlation coefficient $\alpha = .89$). There was evidence of construct validity by a linear relationship between scores and the number of traumatic memories from the ICU the patients described (Spearman's $\rho = .48$). The reliability coefficient (Cronbach's α) of the PTSD questionnaire in a different study population after ICU therapy was .86 (Schelling et al 1998).

Table 2. Item definitions and specific questions used in the evaluation of different categories of traumatic memory in survivors of septic shock

Categories of traumatic memory	Question ("When I think back to the time I spent in the ICU, I remember one or more episodes of . . .")	Hydrocortisone group (n = 9) Yes/No (% yes)	Placebo group (n = 11) Yes/No (% yes)
Nightmares	Distressing dreams or nightmares	3/6 (33.3)	6/5 (54.5)
Pain	Severe pain	4/5 (44.5)	2/9 (18.2)
Anxiety/panic	Extreme anxiety or panic	4/5 (44.5)	5/6 (45.5)
Respiratory distress	Trouble breathing or feelings of suffocation	4/5 (44.5)	5/6 (45.5)
Feelings of imminent death	Feelings of being about to die	2/7 (22.2)	2/9 (18.2)

A total of 20 patients were investigated. The right two columns compare the frequency of different categories of traumatic memories between the hydrocortisone and the control groups.

ICU, intensive care unit.

Evaluation of Traumatic Memories from the Intensive Care Unit

In addition to the standardized inventory evaluating PTSD symptoms, all patients completed a structured questionnaire asking them to report different categories of traumatic memory from ICU treatment. For the purpose of this and other studies from our group (Schelling et al 1998; Schelling et al 1999; Stoll et al 1999), a category of traumatic memory as measured by the inventory was defined as the patient's subjective recollection of respiratory distress/dyspnea or feelings of anxiety/panic or fear of imminent death, pain, or nightmares at any time during ICU treatment. The exact questions used in evaluating these items are given in Table 2. The patients were asked to answer each of the five items with a yes or no response, independent of the number of occasions the adverse experience occurred (only frequencies were scored). The frequency with which each of these five items is answered with a yes response by a subject is termed the number of categories of traumatic memory. This variable was used because PTSD incidence and intensity and this number were highly correlated in previous studies in patients after intensive care (Schelling et al 1998; Stoll et al 2000). The intensity of traumatic memories was not specifically evaluated.

Statistical Analysis

We calculated the average daily serum levels of cortisol by dividing the total sum of each individual measurement (not including the baseline value) by the number of observation days (14). The average daily score on the Glasgow Coma Scale (as a measure of the average degree of sedation) were calculated in a similar way. Continuous variables between the hydrocortisone and the placebo group were compared using the nonparametric Mann–Whitney U score and discrete variables were compared with the χ^2 or Fisher's Exact Test, when appropriate. All statistical calculations were performed using the SPSS 9.0 statistical package (SPSS Inc., Chicago, IL, USA). Spearman's correlation coefficient was calculated as a nonparametric measure of correlation between ordinal variables. Because of the non-normal distribution of most variables, results are expressed as medians and ranges. A probability level of less than .05 was regarded as statistically significant.

Results

There was no significant difference with regard to cause of sepsis, duration of ICU treatment, or other baseline or treatment data between patients from the hydrocortisone group and the placebo group (Table 1). Serum cortisol levels were available from five patients from the hydrocortisone and seven patients from the placebo group. Hydrocortisone was administered for a median of 18 days (range 14–35 days) after the onset of septic shock. Patients receiving hydrocortisone showed a strong trend toward a faster shock reversal. Norepinephrine was required for 52 hours in the hydrocortisone group whereas patients from the placebo group required vasopressor support for a total of 120 hours (median values, $p = .07$). Higher total doses of norepinephrine were needed by patients from the control group (31.30 μg/kg body weight, range 9.80–610.40 μg/kg) than by patients receiving hydrocortisone (25.60 μg/kg body weight, range 4.20–110.50 μg/kg), but this difference did not reach statistical significance ($p = .41$). Patients from the hydrocortisone and the control group had similar GCS scores during their stay in the ICU (8.92 vs. 8.35 points for the average value over 14 days of treatment, $p = .66$).

Posttraumatic Stress Disorder

As assessed by the psychiatric interview, patients in the hydrocortisone group ($n = 9$) had a significantly lower incidence of PTSD (only one of nine patients from the hydrocortisone group, as compared with seven out of 11 patients in the control group who had PTSD, $p = .02$, χ^2 test). All patients with PTSD ($n = 8$) had scores on the PTSD questionnaire that were well over 35 points (22.0 vs. 38.5, median values, $p < .001$) and the diagnosis of PTSD according to the questionnaire and by psychiatric interview was concordant in all cases. Patients from the placebo group had higher PTSD scores than patients who had received hydrocortisone, this difference was not sta-

tistically significant (36 vs. 27 points, median values, $p = .30$), but significantly more patients from the placebo group had scores above the PTSD threshold of the questionnaire (seven out of 11 patients in the placebo group vs. one of nine patients from the hydrocortisone group, $p = .02$, chi^2 test, Figure 1). All patients with more than three categories of traumatic memory ($n = 3$) had PTSD. None of them had received hydrocortisone. There was no statistically significant difference with regard to age (55 vs. 52 years, median values, $p = .85$) or gender ($p = .61$), cause of sepsis ($p > .15$), or average GCS scores (12.9 vs. 12.5 points, $p = .79$) between patients with and without PTSD. A linear correlation (Spearman's) did not show any relationship between PTSD scores and duration of the shock phase ($r = -.114$, $p = .63$), duration of ICU treatment ($r = .218$, $p = .36$) or total norepinephrine requirements ($r = -.098$, $p = .68$).

Among the 12 patients with measured serum cortisol levels, patients with PTSD ($n = 5$) had significantly lower average serum cortisol levels during ICU therapy than patients who did not develop the syndrome ($n = 7$) (15.7 vs. 55.4 μg/dL, $p = .02$).

Traumatic Memories

All patients specifically denied exposure to any other highly stressful situations and none of the patients reported other traumatic experiences either before or after their stay in the ICU. The most common categories of traumatic memory from the ICU in the total study sample were nightmares, respiratory distress and anxiety/panic followed by "fear of imminent death" (Table 2). When asked during the psychiatric interview, the majority of patients described the experience of respiratory distress, anxiety/panic and nightmares in the ICU as being accompanied by intense emotions of helplessness and sometimes horror. There was no significant difference with regard to the number of categories of traumatic memory between patients from the hydrocortisone group and patients who received placebo (2 vs. 1, median values, $p = .88$, Figure 2). Pain, anxiety/panic and respiratory distress were associated with significantly higher cortisol values measured before randomization ($p \leq .02$).

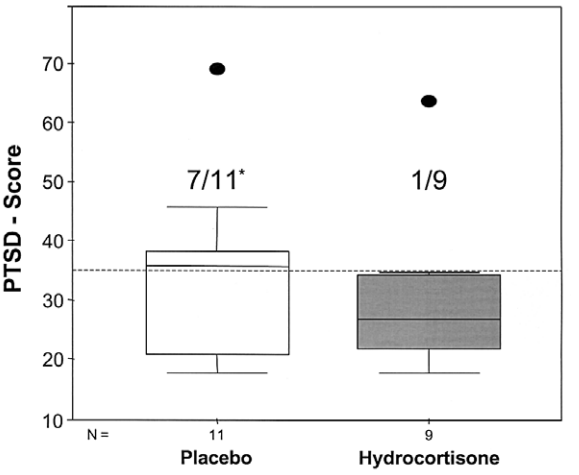

Figure 1. Boxplots comparison of PTSD scores between patients from the hydrocortisone and the placebo group. The broken line shows the 35 point cut off value of the PTSD questionnaire for diagnosis of PTSD (Stoll et al 1999). The numbers above the individual plots indicate the number of patients in both groups with PTSD scores above the threshold value of the questionnaire for diagnosis of PTSD (*$p = .02$). PTSD was confirmed by psychiatric interview in all patients. The "whiskers" at the top and bottom of each box indicate the minimal and maximal values of the distribution, respectively; the top and bottom of each box the 75th and 25th percentiles; the line through the box the median (the 50th percentile) and "●" indicates outliers (defined as a data value between 1.5 and 3 box lengths from the upper or lower edge of the box, the box length is the interquartile range).

Discussion

This study in a small number of survivors of septic shock suggests a protective effect of increased serum cortisol levels during the acute phase of septic shock stress with regard to the later development of PTSD. Patients with chronic PTSD often show low serum cortisol values (Yehuda et al 1996). Furthermore, patients with low cortisol levels immediately after a car accident (McFarlane et al 1997) or a lower urinary cortisol excretion during the first 15 hours after a motor vehicle accident (Delahanty et al 2000) are known to be at a higher risk for developing PTSD. Women with a history of previous assault had a lower mean acute cortisol level after the severe stress exposure of a repeated rape, but a higher probability of subsequently developing PTSD (Resnick et al 1995). The cortisol level did not predict the diagnosis of PTSD in those patients at follow-up, however, and there are other reports which describe opposite findings, namely elevated levels of urinary cortisol in women with PTSD (Lemieux and Coe 1995) or in male patients with recent onset of PTSD (Hawk et al 2000). Such discrepancies may be due to the facts that patients with PTSD represent a very heterogeneous population and that in many patient cohorts endocrine measures are taken only after clinical manifestation of PTSD. It is therefore generally difficult or even impossible to determine whether these neuroendocrine variations are secondary effects or whether they play a pathogenetic role in the development of PTSD. In contrast, patients in the ICU are relatively homogenous and are monitored intensively from the start of the traumatic experience and therefore constitute an ideal model for examining putative stress hormone effects on PTSD de-

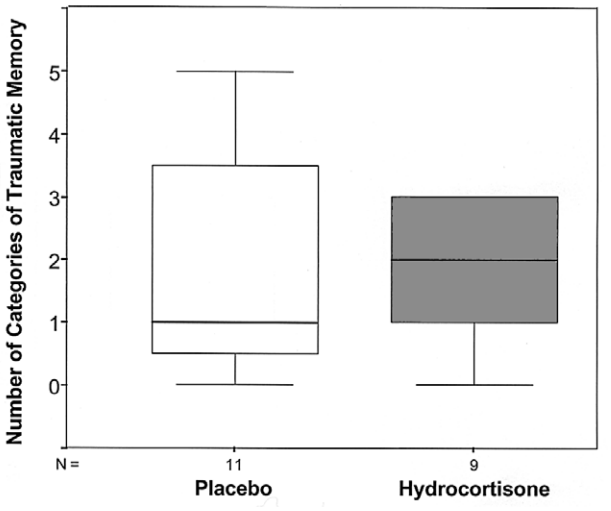

Figure 2. Boxplots comparison of the number of categories of traumatic memory between patients from the hydrocortisone and the placebo groups. The "whiskers" at the top and bottom of each box indicate the minimal and maximal values of the distribution, respectively; the top and bottom of each box the 75th and 25th percentiles; the line through the box the median (the 50th percentile). The difference between both groups was not statistically significant ($p = .88$).

velopment. Our study in such patients has demonstrated a reduced incidence of PTSD with increased levels of serum cortisol during the acute severe stress exposure of septic shock. We have shown previously that patients during sepsis have reduced adrenocortical responsiveness caused primarily by the effects of inflammatory mediators (Briegel et al 1996). All our patients were sedated and given the opioid fentanyl, however, which could have further reduced endogenous cortisol levels. Therefore, cortisol levels in the control group could have been inadequately low, resulting in a higher incidence of PTSD. Hydrocortisone treatment could have reversed these low serum cortisol levels and thereby lowered the incidence of PTSD.

The administration of hydrocortisone in our, as well as in an earlier completed second study (Bollaert et al 1998), resulted in a shortening of the shock phase and a reduced need for vasopressor support by norepinephrine. Although this difference did not reach significance in the present study, in our original study as well as in the work of Bollaert and colleagues this difference was significant. An alternative explanation for the increased incidence of PTSD in the placebo group could therefore be the higher dosage of norepinephrine required by these patients. It is interesting to note that patients with chronic PTSD often show a high urinary norepinephrine excretion (Kosten et al 1987; Southwick et al 1999; Yehuda et al 1992) and a high plasma (Yehuda et al 1996) or urinary norepinephrine/cortisol ratio (Mason et al 1988). Patients with higher heart rates following a traumatic event (indicative of increased catecholaminergic activity) are also known to be at a higher risk for developing PTSD (Shalev et al 1998). Furthermore, there is some evidence of a protective effect of the catecholaminergic antagonist propranolol with regard to the development of PTSD symptoms (Famularo et al 1988). These combined findings suggest that low serum cortisol levels together with high catecholaminergic stimulation are not simply a consequence of PTSD, but that the development of PTSD may be facilitated by such an atypical biological condition (e.g., excessive catecholaminergic stimulation and a minimal or absent cortisol response) during or in the immediate aftermath of a severe stress exposure, which in turn results in a maladaptive psychological state.

How these stress hormones influence PTSD is still unknown, but emerging evidence suggests that interactions of these hormones with memory processes may play a pivotal role. Posttraumatic stress disorder is considered to be associated with traumatic memories resulting from an event that threatened a person's life or physical integrity and that invokes a response of fear, helplessness, or horror (American Psychiatric Association 1994). Extensive evidence from animal experiments (McGaugh 2000; McGaugh et al 1996; Quirarte et al 1997; Roozendaal et al 1996) and recent experiments in humans (Buchanan and Lovallo 2001) have shown that glucocorticoids and norepinephrine have profound dose-dependent–enhancing effects on long-term memory consolidation processes for emotionally arousing events. These hormones, circulating in the blood stream during memory formation, could theoretically promote the development of PTSD. Our observation that patients with a high number of traumatic memories all developed PTSD supports this hypothesis; however, our findings also indicate that hydrocortisone reduced PTSD scores without significantly influencing the number of categories of traumatic memory. It should be noted that the effects of administration of these hormones on the exact number of traumatic memory categories are difficult to predict because of time-dependent variables and complex interactions between hormonal systems. In the control group, memory formation might have been facilitated by higher levels of catecholamines required during the acute stress phase, whereas in the hydrocortisone group high serum cortisol levels might have enhanced memory consolidation. In addition, the total dosages of benzodiazepines and opioids administered to our patients were not available. They could have influenced the effectiveness of adrenal stress hormones in enhancing memory consolidation processes and this can be regarded as a limitation of our study. Nevertheless, the dissociation between hydrocortisone effects on PTSD scores and the number of categories of traumatic memory strongly suggests that it is unlikely that the effect of hydrocortisone on reducing PTSD scores is medi-

ated exclusively through effects on memory consolidation processes; however, as we measured only the number of categories of traumatic memory, it cannot be excluded that hydrocortisone influenced the intensity or emotionality of the memories.

Hydrocortisone treatment may have reduced PTSD scores through interference with other aspects of memory function. It has been shown in both rats and humans that exposure to stress levels of glucocorticoids may result in a temporary impairment in memory retrieval (de Quervain et al 1998; de Quervain et al 2000). These effects appear to be independent of glucocorticoid effects on memory formation and may even occur simultaneously. As it has been proposed that PTSD develops over time because of positive feedback mechanisms in which the traumatic memories are constantly retrieved and restored (Pitman et al 1993), disrupting retrieval mechanisms at the onset of septic shock may therefore act protectively against the development of PTSD. Conversely, low effective serum cortisol levels such as found in septic shock patients may lead to excessive retrieval, resulting in a high incidence of PTSD. Taken together, our findings support the hypothesis that stress doses of hydrocortisone in combination with norepinephrine can influence PTSD incidence and severity through complex and simultaneous interactions with memory formation and retrieval.

In contrast to other patient populations with PTSD, our patient cohort had received a combination of exogenously administered stress hormones during the actual stress exposure and this, together with the small number of subjects in our study, makes it difficult to extrapolate our findings to other patient populations exposed only to endogenous cortisol and catecholamines. Our data suggest, however, that the concurrent administration of stress doses of hydrocortisone along with exogenous catecholamines during septic shock has a beneficial role that exceeds the hemodynamic effects demonstrated in previous studies (Bollaert et al 1998; Briegel et al 1999). Our study also highlights the possibility that both arms of the stress response (the cortisol and the catecholaminergic part) are equally important in health and that iatrogenic skewing in one direction could result in persistent atypical stress reactions such as PTSD. This possibility should be taken into consideration in patients requiring high doses of exogenous catecholamines for circulatory shock and PTSD should be included as an end point in larger multicenter studies evaluating new immunologic or catecholaminergic therapies for septic shock.

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