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α -Melanocyte Stimulating Hormone in Critically Injured Trauma Patients

S. Rob Todd, MD,

Department of Surgery, Weill Medical College of Cornell University

Lillian S. Kao, MD, MS,

Department of Surgery The University of Texas Medical School at Houston, Houston, Texas

Anna Catania, MD,

Department of Surgery and Center for Preclinical Research Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e, Regina Elena, Italy.

David W. Mercer, MD,

Department of Surgery The University of Texas Medical School at Houston, Houston, Texas

Sasha D. Adams, MD,

Department of Surgery The University of Texas Medical School at Houston, Houston, Texas

Frederick A. Moore, MD

Department of Surgery, Weill Medical College of Cornell University

Abstract

Background: α -Melanocyte stimulating hormone (α -MSH) is a neuropeptide which modulates inflammation. Prior studies have documented decreased α -MSH concentrations in patients with acute traumatic brain injury and subarachnoid hemorrhage. We hypothesized that α -MSH levels would be decreased in critically injured patients and that this would correlate with poor outcome.

Methods: We performed a retrospective review of prospectively collected data more than 12 months ending December 2005. α -MSH concentrations were measured in major torso trauma patients (excluding severe head injuries) who underwent standardized shock resuscitation. α -MSH concentrations were measured every 4 hours for the first 24 hours of intensive care unit admission and daily thereafter for hospital days 2 to 5. Controls were similarly aged, healthy volunteers. Outcomes measured included lengths of stay, infectious morbidity, and the incidence of multiple organ failure (MOF) and mortality.

Results: Fifty-one trauma patients were studied with a median age of 33 (22–54) years. Seventy-five percent were male and 82% sustained blunt trauma. The median Injury Severity Score was 25 (16–34). Eighteen percent of the patients developed MOF, 18% died, and 24% developed MOF and died. The mean initial (first value on the first day) α -MSH concentration was significantly lower than in controls ($15.9 \text{ pg/mL} \pm 7.6 \text{ pg/mL}$ vs. $26.1 \text{ pg/mL} \pm 7.4 \text{ pg/mL}$, $p = 0.0008$) and did

not change significantly during the 5-day study period. On univariate and adjusted multivariate analyses, initial α -MSH concentrations did not predict either MOF or mortality.

Conclusions: The current study is the first to document significantly decreased α -MSH concentrations in critically injured trauma patients as compared with controls. Furthermore, α -MSH concentrations remained so throughout the study period.

Keywords

Alpha-melanocyte stimulating hormone; α -MSH; Critically injured trauma patients

Traumatic injury accompanied by hemorrhage and subsequent resuscitation activates increased concentrations of proinflammatory mediators including cytokines, chemokines, arachidonic acid derivatives, neutrophil degranulation products, and nitric oxide.^{1,2} In parallel, anti-inflammatory mediators are produced to modulate this inflammation.^{1,3} One such molecule is the 13-amino acid peptide α -melanocyte stimulating hormone (α -MSH), a potent immunomodulator derived from proopiomelanocortin, which is released by the pituitary gland. It is an imbalance between these dual immune responses that appears to be responsible for the increased susceptibility to infection and multiple organ failure (MOF) in critically ill patients.^{1,4-9}

Several studies have evaluated α -MSH levels during infectious and inflammatory states in humans.¹⁰⁻¹⁶ The majority of these revealed increased α -MSH concentrations as a compensatory immune response. More recently, α -MSH concentrations were measured in patients with acute traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH). In this population, α -MSH levels were significantly lower than in controls ($p < 0.0001$).¹⁷

Based on this and other studies, it appears that α -MSH may not be released in sufficient quantities to modulate infection and inflammation in certain disease processes.^{17,18} The primary objective of this study was to establish the early temporal pattern of α -MSH in critically injured trauma patients. Furthermore, we sought to determine whether there was a correlation between α -MSH concentrations and the development of MOF and mortality. We hypothesized that α -MSH levels would decrease initially after the traumatic insult. We further hypothesized that persistently decreased α -MSH levels would correlate with the development of MOF and mortality.

MATERIALS AND METHODS

This retrospective review of prospectively collected data were performed more than 12 months ending December 2005 at Memorial Hermann Hospital in Houston, TX, which is the lead regional Level I trauma center for Trauma Service Area Q, which includes nine counties in the upper Gulf Coast of Texas with a population of 5.5 million. All patients admitted to the Shock Trauma Intensive Care Unit (STICU) who underwent a computer-directed standardized shock resuscitation protocol were included in the study. The protocol facilitated the initial resuscitation (first 24 hours of admission) of all study patients (major torso trauma patients who were at high risk of developing MOF). Patients included (1) major torso trauma, defined as injury of more than or equal to two abdominal organs, multiple long bone

fractures, complex pelvic fracture, flail chest, or major vascular injury; (2) base deficit ≥ 6 mEq/L within 12 hours of hospital admission; and (3) anticipated packed red blood cell transfusion requirement of ≥ 6 units within 12 hours of hospital admission, or age ≥ 65 years with any two of the three previous criteria. Patients with concurrent severe TBI, defined as a Glasgow Coma Scale score ≤ 8 and an abnormal brain computed tomography scan were excluded unless the attending neurosurgeon deemed the patient's brain injury to be at low risk for worsening cerebral edema with crystalloid volume loading. This protocol has previously been described.^{19–21} In brief, it involved a series of escalating interventions in patients who fail to meet or maintain an oxygen delivery index ≥ 500 mL/min m².

Patients <14 years of age were excluded from the study because they were admitted to the Pediatric Intensive Care Unit and managed by pediatric intensivists. Controls were eight normal subjects from the university staff, with similar distribution for age and gender. Controls underwent a single blood sampling.

Study patients were monitored with serial blood samplings every 4 hours for the first 24 hours of STICU admission and daily (approximately 2 AM) thereafter for hospital days 2 to 5. Prior studies have demonstrated no fluctuation in α -MSH concentrations when measured over time (every 15 minutes for a 180-minute period).¹⁰ Blood samples (collected in tubes containing ethylene diamine tetra-acetic acid) for α -MSH determination were immediately centrifuged at 4°C and plasma aliquots stored at -80°C until the assays were performed. These assays were performed using a double antibody radioimmunoassay method (Eurodiagnostica, Malmo, Sweden).

Data were obtained from the Memorial Hermann Hospital electronic medical record, paper medical record, and trauma registry. The variables obtained included patient demographics (age, race, gender, comorbidities, and medications on presentation) and injury characteristics (mechanism of injury and Injury Severity Score [ISS]). The ISS for study patients was calculated after the identification of all injuries and verified upon discharge. In addition, resuscitation parameters and details surrounding the first 24 hours of admission were reviewed. The primary outcome measure was mortality. Secondary outcomes included lengths of stay (STICU and hospital), infectious morbidity (bronchoalveolar lavage documented pneumonias [positive quantitative cultures of bronchoalveolar lavage fluid, significant threshold $\geq 10^4$ colony forming units/mL] and surgical site infections), and the development of MOF. MOF was defined based on criteria derived from the modified Denver postinjury MOF score (Table 1).²³ All of these aforementioned data parameters were collected prospectively in a separate research database.

In comparing the two study groups, the Student's t test was utilized for continuous data. If the assumptions of this test were not met, the Mann-Whitney U test was utilized. A χ^2 analysis was used for categorical data. When appropriate, this was substituted with the Fisher's exact test. Repeated measures of analysis of variance were utilized to compare α -MSH levels at multiple time points among study patients (excluding controls). For the first day, both the mean and initial α -MSH levels were tested in separate analyses. Univariate and multivariate (linear and logistic regression) analyses were performed to determine associations between initial α -MSH concentrations and the outcome variables. Numeric data

are presented as mean $\pm$ SD and median (inter-quartile range) where appropriate. A p value of <0.05 was considered significant. Number Cruncher Statistical Systems (Kaysville, UT), 2004 was utilized for all statistical analyses.

The collection and review of the specimens and data were approved by The University of Texas Health Sciences Center at Houston Committee for the Protection of Human Subjects.

RESULTS

During the study period there were 2,679 Trauma Center admissions. Of 439 consecutive patients admitted to the STICU, 51 (12%) met study inclusion criteria. The median age was 33 years.(22–54) Thirty-eight (75%) were male and 42 (82%) sustained a blunt mechanism of injury. These were severely injured patients with a median ISS of 25.(16–34)

There were no patients with concurrent severe TBI in the study cohort. Nine (18%) of the patients developed MOF; (6 of 9) 67% of those patients died. Of the remaining 42 (82%) patients without MOF, three died, all within 1 day of being admitted to the ICU.

The mean initial concentration (first value on the first day) of α -MSH in the study group was significantly lower than in controls (15.9 pg/mL $\pm$ 7.6 pg/mL vs. 26.1 pg/mL $\pm$ 7.4 pg/mL, $p = 0.0008$). There was no significant difference over time in individual patients' α -MSH levels during the first 5 days, either using the initial α -MSH or mean α -MSH levels for the initial time point. Mean daily α -MSH concentrations for the study population did not change significantly during the 5-day study period (Fig. 1). Similarly, there was no significant difference in α -MSH concentrations for the study population during the first 24 hours of the study period (Fig. 2). Neither age nor ISS were correlated with the initial α -MSH concentrations ($r = -0.04$, 95% confidence interval [CI] -0.14 to 0.11 for age and $r = 0.06$, 95% CI -0.16 to 0.24 for ISS) in the study patients. There was also no significant difference in initial α -MSH concentrations between genders in the study group; the median concentration was 15.5 pg/mL(10.4–20.7 pg/mL) for men and 17.3 pg/mL (8.9–23.0 pg/mL) for women ($p = 0.60$).

On univariate analysis, initial α -MSH concentrations did not predict either MOF or mortality (Tables 2 and 3). Similarly, age, gender, ISS, and mechanism of injury were not statistically significant predictors of outcome in the study cohort. The development of MOF, however, was a predictor of mortality. Study patients with MOF had a ninefold increase in relative risk of dying (relative risk 9.3, 95% CI 2.5 to 33.4). On multivariate analysis, when adjusting for age, ISS, and mechanism of injury, initial α -MSH concentrations likewise did not predict either MOF or mortality (Tables 4 and 5).

DISCUSSION

Traumatic injury activates increased concentrations of proinflammatory mediators. If left unregulated by anti-inflammatory mechanisms, this systemic inflammatory response syndrome (SIRS) will progress to MOF.^{1,4–9} Endogenous anti-inflammatory molecules are produced to modulate this inflammation.^{1,3} One such molecule is the neuropeptide α -MSH. α -MSH modulates inflammation by three mechanisms: direct action on peripheral

inflammatory cells; actions on brain inflammatory cells to modulate local reactions; and indirect activation of descending neural anti-inflammatory pathways that control peripheral tissue inflammation.^{22,24} All of these anti-inflammatory functions are accomplished in some fashion via inhibition of the nuclear transcription factor NF- κ B.²⁴

In 1998, Catania et al. studied the plasma concentration of α -MSH in 234 normal blood donors. The mean age was 39.9 ± 11.16 years, and 151 (65%) were male.¹⁰ The mean α -MSH concentration (Eurodiagnostica radioimmunoassay kit) was $21.30 \text{ pg/mL} \pm 0.63 \text{ pg/mL}$ (mean $\pm$ standard error of the mean) with no significant difference between men and women. There were no significant variations appreciated over time, even in samples obtained after a prolonged interval. Although α -MSH levels were stable over time in normal subjects, there were age-related changes. In 125 normal elderly controls (79.63 ± 5.8 years; range, 66–95), the mean plasma concentration of α -MSH was significantly decreased in comparison with the younger population ($15.87 \text{ pg/mL} \pm 0.38 \text{ pg/mL}$, $p < 0.001$). This age-associated discrepancy is consistent with previous mammalian studies.²⁵ There was no correlation between α -MSH levels and age in trauma patients in our study, but the sample size was small.

Several studies have further evaluated α -MSH concentrations during infectious and inflammatory conditions in humans to assess changes in peptide levels in naturally occurring disease states.^{10–16} Most of these revealed increased α -MSH plasma concentrations. In patients infected with human immunodeficiency virus (Centers for Disease Control groups III and IV), plasma α -MSH levels were elevated.^{10–12} Furthermore, in patients with acquired immunodeficiency syndrome, there was a positive correlation between α -MSH level and 6-month survival.¹¹ Increases in α -MSH plasma concentrations were also found in patients with arthritis, myocardial infarction receiving thrombolytic therapy, multiple sclerosis with high disability scores, and on chronic hemodialysis with plasma endotoxin detectable.^{13–16} These studies imply that in the presence of infection or more importantly inflammation, α -MSH plasma concentrations are increased as a compensatory reaction.

Despite these findings, and the fact that in healthy subjects injected with endotoxin α -MSH levels increase, α -MSH concentrations decrease during the early stages of sepsis.¹⁸ More importantly, the concentration of α -MSH in plasma returns to normal in those septic patients who survive and the same remains decreased in those who die.

In a 2003 study, Magnoni et al. evaluated α -MSH concentrations in patients with acute TBI and SAH.¹⁷ Twenty-three patients (18 had TBI and 5 SAH) were evaluated during the first 4 days after injury. α -MSH levels were significantly lower than in 33 normal controls ($p < 0.0001$). This reduction in α -MSH was consistent during the 4-day study period. These findings are consistent with those in our current study. The mean initial concentration of α -MSH in our study population was significantly lower than in controls ($15.9 \text{ pg/mL} \pm 7.6 \text{ pg/mL}$ vs. $26.1 \text{ pg/mL} \pm 7.4 \text{ pg/mL}$, $p = 0.0008$). Similarly, in our study the mean α -MSH concentrations in patients did not change significantly during the 5-day study period. As previously mentioned, there were no correlations between α -MSH concentrations and outcome variables in our current study.

There were no significant predictors of initial or mean α -MSH levels in our study, but conclusions cannot be drawn because of the small sample size and large number of potential variables. The heterogeneity of the population and interventions such as blood transfusions also limit the conclusions that can be drawn from this pilot study.

The primary limitation to this current study involved our sample size, which was determined by the time period funded. No definitive conclusions can be made about differences over time. Because this was a pilot study, serial measurements were not made in controls—funding and resources were limited; previous data have demonstrated that α -MSH levels do not vary over time in nonstressed individuals; and consent may have been difficult to obtain for 10 separately timed blood draws per individual. Thus, larger studies are required better to evaluate changes in α -MSH levels over time and to analyze whether these trends are correlated to outcomes in critically injured trauma patients.

CONCLUSION

The current study is the first to document significantly decreased α -MSH concentrations in critically injured trauma patients as compared with controls. Furthermore, α -MSH concentrations remained so throughout the study period.

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Fig. 1.
 α -MSH concentration during the 5-day study period. α -MSH, α -melanocyte stimulating hormone.

Fig. 2.
 α -MSH concentration during the first 24 hours. α -MSH, α -melanocyte stimulating hormone.

Table 1Modified Denver Postinjury Multiple Organ Failure Score²²

	Grade 0	Grade 1	Grade 2	Grade 3
Pulmonary score				
(PaO ₂ /FIO ₂)	>250	175–250	125–174	<124
Renal score				
Serum creatinine (mg/dL)	1.8	1.8	>2.5	>5.0
Hepatic score				
Serum total bilirubin (mg/dL)	2.0	>2.0	>4.0	>8.0
Cardiac score (cardiac index <3.0 L min ⁻¹ m ⁻² + infusion levels below)				
Dopamine (μg kg ⁻¹ min ⁻¹)	0	<5	5–15	>15
Dobutamine (μg kg ⁻¹ min ⁻¹)	0	<5	5–15	>15
Milrinone (μg kg ⁻¹ min ⁻¹)	0	<0.4	0.4–0.6	>0.6

Table 2

Univariate Analysis of Predictors of Multiple Organ Failure

Variable	MOF	No MOF	<i>p</i>
No. patients	9	42	—
Age	41 (28–59)	33 (23–152)	0.50
Male	78% (7/9)	74% (31/42)	1.00
Injury Severity Score	29 (22–134)	25 (13–134)	0.24
Penetrating mechanism	22% (2/9)	17% (7/42)	0.65
Initial * α -MSH level	16.8 (14.7–25.3)	15.6 (9.9–21.0)	0.23
ICU length of stay	21 (8–51)	11 (3–18)	0.04
Hospital length of stay	44 (8–54)	21 (12–31)	0.10
Infectious morbidity	22% (2/9)	19% (8/42)	1.00
Mortality	67% (6/9)	7% (3/42)	0.0003

* First value on the first day.

MOF, multiple organ failure; α -MSH, α -melanocyte stimulating hormone; ICU, intensive care unit.

Table 3

Univariate Analysis of Predictors of Mortality

Variable	Death	Survival	<i>P</i>
No. patients	9	42	—
Age	44 (22–65)	33 (23–52)	0.51
Male	78% (7/9)	74% (31/42)	1.00
Injury Severity Score	27 (17–32)	25 (13–34)	0.80
Penetrating mechanism	33% (3/9)	14% (6/42)	0.19
Initial * α -MSH	17.3 (14.7–24.3)	15.5 (9.9–21.0)	0.27

* First value on the first day.

α -MSH, α -melanocyte stimulating hormone.

Table 4**Multivariate Analysis of Predictors of Multiple Organ Failure**

Variable	Odds Ratio	95% CI
Age	0.97	0.93–1.01
Injury Severity Score	0.94	0.86–1.02
Penetrating mechanism	0.23	0.03–2.15
Initial * α -MSH level	0.94	0.86–1.04

*
First value on the first day.

CI, confidence interval; α -MSH, α -melanocyte stimulating hormone.

Table 5**Multivariate Analysis of Predictors of Mortality**

Variable	Odds Ratio	95% CI
Age	1.03	0.99–1.08
Injury Severity Score	1.04	0.96–1.13
Penetrating mechanism	7.09	0.88–57.34
InitialInitial * α -MSH	1.04	0.95–1.15

* First value on the first day.

CI, confidence interval; α -MSH, alpha-melanocyte stimulating hormone.