

Initial free cortisol dynamics following blunt multiple trauma and traumatic brain injury: A clinical study

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Abstract

Objective: To determine free and total cortisol serum concentrations in the first 24 h after trauma and to evaluate the influence of traumatic brain injury (TBI) on their dynamics.

Methods: This prospective cohort study enrolled patients who had experienced multiple trauma and were admitted to a level I trauma centre. The patients were divided in two groups based on the presence of TBI according to clinical and radiological findings. Blood was collected initially as well as at 12 h and 24 h after the traumatic injury. Total cortisol, corticosteroid binding globulin (CBG) and free cortisol levels were determined.

Results: The study analysed data from 49 patients (36 males and 13 females) with a mean \pm SD age of 45.0 ± 16.0 years. Of these, 36 presented with TBI and 13 had multiple injuries without TBI. Patients with TBI showed significantly lower concentrations of total cortisol and free cortisol compared with patients without TBI. Repeated measures analysis revealed different concentration dynamics in patients with TBI, with no increase in cortisol after trauma.

Conclusion: Multiple trauma patients with TBI are at risk of acute impaired cortisol secretion and show an attenuated stress response as early as 12 h after injury.

Keywords

Cortisol, adrenal insufficiency, traumatic brain injury, multiple trauma

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Introduction

Traumatic brain injury (TBI) is one of the leading causes of early death.¹ Population studies show that with an incidence of up to 618 per 100 000, TBI is the major injury that triggers mortality in young trauma patients.¹ Excellent therapeutic regimens have been established to treat acute haemorrhage and increased intracranial pressure.^{2,3} Secondary damage caused by, for example, impaired blood flow, an affected blood–brain barrier, a deregulated immune system or impaired cellular function, are the focus of ongoing discussions.^{2,3} An issue possibly caused by these mechanisms that has attracted increasing attention in the last decade is secondary corticoid insufficiency caused by TBI. As seen in a histological series of fatal cases, pathological changes to the pituitary gland after TBI are present in up to one-third of patients, whereas the pathophysiology for pituitary insufficiency has not been fully identified.⁴ For acute care, corticotropin-releasing hormone–adrenocorticotrophic hormone (ACTH)–cortisol is the most important hormone axis because deficiencies might lead to electrolyte disorders and hypoglycaemia exacerbating hypotension and shock.⁵ Consequently, acute corticosteroid deficiency can lead to imminent adverse outcomes within the first few days, but may also affect the clinical course within the first few weeks as a result of the response to systemic inflammation and secondary infection. Some patients could possibly benefit from initial hormone substitution in physiological doses, but selection criteria for such a treatment have not been established. Furthermore, patients at risk for chronic pituitary insufficiency should be identified by hormone measurements as early as possible after the injury.

The foundation for scientific efforts concerning a possible treatment is the continuous evaluation of hormone concentrations

in patients experiencing TBI. Previous studies evaluated post-traumatic pituitary insufficiency and cortisol metabolism during intensive care unit (ICU) treatment as well as during the chronic stage after hospital discharge.^{4,5} This current study was designed to fill the gap in the published literature regarding the initial hours before ICU admission. Although hormone deficiency following TBI is well documented in the later periods,⁵ there are a lack of data representing the initial stress response to multiple trauma in the very early clinical stage. Post-TBI hormonal impairments must be investigated in comparison with severe trauma without TBI to disclose the effects of pituitary injury particularly for these patients with high mortality and morbidity. This current study hypothesized that trauma patients with TBI compared with trauma patients without TBI are at an increased risk for pituitary damage and blunted ACTH-cortisol levels. The aim of this current study was to compare the total and free cortisol levels in patients with severe multiple trauma with and without TBI in the early acute treatment phase.

Patients and methods

Study population

This prospective cohort study enrolled consecutive patients at a level 1 trauma centre at Ludwig Maximilians University Hospital, Munich, Germany between November 2008 and April 2012. The hospital is located in the centre of Munich and patients are admitted directly by emergency medical services or by airborne services from the surrounding regions. All patients triaged for immediate diagnostics and initial treatment by the resuscitation team were screened for the selection criteria.

The local institutional ethics committee of Ludwig Maximilians University Hospital approved the protocol of this study

(no. 012/00). Whenever written informed consent could not be obtained directly, it was retrospectively obtained from the patient or, if deceased, from their next of kin.

Selection criteria

Blunt trauma patients aged ≥ 18 years were screened in the trauma centre. Patients were considered when initial computed tomography (CT) diagnostics revealed injuries resulting in a preliminary injury severity score (ISS) ≥ 16 .⁶ The preliminary ISS calculation used for assessment of eligibility was always based on the results of a whole-body trauma CT scan (defined trauma protocol) and calculated by a senior physician (trauma team leader) with a senior radiologist standing by. As the mean ISS in severely injured trauma patients is quite high at 36, the current study did not enrol any 'borderline' patients and did not have to exclude any after re-evaluation. Re-evaluation of the ISS calculation was performed after all radiological findings had been recorded in the final radiological report (after two senior radiologists had approved the report according to the four-eyes principle).

In order to obtain information about the initial changes of the hormone status, only patients that reached hospital within 90 min after the trauma were included in the study. Exclusion criteria were as follows: (i) prior treatment with corticosteroids or etomidate; (ii) initial critical or life-threatening conditions that prevented blood to be drawn for scientific purposes, including if not all three blood samples could be obtained; (iii) pregnancy; (iv) criminal prosecution; (v) withdrawal of consent in case of initial intoxication.

TBI definition for patient classification

In order to gain information about the trauma mechanism including involvement

of the head, initial clinical findings, CT reports, operations and clinical course documented in the patient medical records were screened retrospectively. As the distinction between TBI and minor head trauma appeared to be difficult in the presence of other severe injuries, impaired consciousness due to haemorrhagic shock or sedation, primary prophylactic intubation or psychological shock, a stepwise classification procedure was used. Distinct findings for the presence of TBI were intracranial haemorrhage, primary unconsciousness persistent on hospital admission and specific neurological clinical findings such as impaired cranial nerve function. If the trauma mechanism possibly caused strong forces to the skull (e.g. high-velocity motor vehicle accident, fall from height >2 m, specific injury mechanisms in sports such as horse riding or football) and if clinical or radiological findings such as major lesions to the scalp, skull fractures or higher-grade fractures of the facial bones (e.g. Le Fort fractures, complex orbital injuries) suggesting a major force to the head, patients were also classified as TBI-positive. Finally, if there was no other reason such as shock, sedation or intoxication for impaired consciousness in patients with a Glasgow coma scale (GCS) score ≤ 13 concurrent with an adequate trauma mechanism, TBI was also suspected. In summary, the selection criteria for TBI were as follows: (i) major head laceration/bruise with unconsciousness; (ii) skull or facial fracture with unconsciousness; (iii) impaired consciousness in the absence of shock, sedation or intoxication persistent on hospital admission; (iv) injury mechanism with severe force to the head; (v) detected intracranial haemorrhage.

Data collected in addition to the TBI status, intracranial bleeding and GCS score, included sex, age, survival and ISS. Furthermore, the number of packed red blood cell units given within 24 h was

recorded in order to estimate their influence on immune system stimulation.

Blood collection

Whole peripheral blood samples were drawn by study personnel within 90 min of admission to the trauma centre as well as at 12 h and 24 h after the trauma in order to obtain a very early measurement and to detect hormone dynamics within the first few hours after the trauma. Samples were collected using 9-ml serum tubes (S-Monovette with clotting activator; Sarstedt AG, Nuernbrecht, Germany), centrifuged at 2000 *g* for 10 min at 20 °C (Megafuge 8; Heraeus GmbH, Hanau, Germany), aliquoted and stored at -80 °C.

Blood sample analysis

All frozen serum samples were simultaneously transferred to a specialized laboratory of the Department of Internal Medicine IV: Endocrinology, Ludwig Maximilians University Munich and defrosted for the determination of total cortisol and corticosteroid binding globulin (CBG) concentrations. Quantitative cortisol measurements were carried out with a competitive immunoassay using solid phase antigen-linked technology (LIAISON[®] Cortisol; DiaSorin, Saluggia, Italy). For determination of CBG, a radioimmunoassay technique (CBG RIA; ZenTech, Liège, Belgium) was used. Free cortisol was calculated by Coolens equation.⁷

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, NY, USA). Sample size calculations that anticipated a mean difference of at least 9 µg/dl in total cortisol with a required power of 80% and $\alpha=0.05$ showed a minimum size of 12 patients per group. To prevent statistical errors of multiple testing, the SPSS repeated

measures general linear model was used for all statistical tests. *P*-values for the time course and for interactions between time and independent variables were calculated using Wilks' Lambda distribution for multivariate hypothesis testing. Group comparisons for all repeated measures were performed using analysis of variance in the SPSS general linear model. A *P*-value <0.05 was considered statistically significant.

Results

This prospective cohort study screened a total of 74 patients: of these, 25 patients were excluded for either etomidate treatment (21 patients) and/or cortisol therapy (eight patients). As a result, the study analysed data from 49 patients (36 males and 13 females) with a mean \pm SD age of 45.0 \pm 16.0 years. Patient characteristics are presented in Table 1.

The first blood sample was drawn after a mean \pm SD of 56.0 \pm 12.7 min after the traumatic injury and the subsequent timed samples at exactly the intended intervals. Injury severity was high with a mean ISS of 34 for the overall study population. Secondary diagnostics led to a higher final ISS in four cases with an increase between 4 and 9 points. It was not necessary to adjust the ISS scores negatively, so two-stage ISS scoring did not affect patient eligibility. Blood transfusions were administered in 38 of 49 patients (77.6%) within the first 24 h and the mean number of packed red blood cell units was 13. Mass transfusion was received by 19 of 49 patients (38.8%) with each receiving more than 10 units of packed red blood cells. TBI was present in 36 of 49 patients (73.5%). Fifteen patients presented with TBI symptoms but were negative on CT imaging. In 21 patients, TBI led to intracranial bleeding. A total of 33 of 49 patients (67.3%) initially presented with impaired consciousness with a GCS

Table 1. Demographic and clinical characteristics of all patients and in those stratified according to the presence of multiple trauma with or without traumatic brain injury (TBI).

Characteristic	All patients <i>n</i> = 49	Multiple trauma with TBI <i>n</i> = 36	Multiple trauma without TBI <i>n</i> = 13
Age, years	45.0 ± 16.0	43.9 ± 15.5	49.6 ± 17.7
Females	13 (26.5%)	10 (27.8%)	3 (23.1%)
Injury severity score	34.4 ± 13.3	39.1 ± 12.2	22.5 ± 8.6
Packed red blood cells, units	12.6 ± 12.8	13.0 ± 13.4	11.2 ± 11.0
Glasgow coma scale score	9.8 ± 4.8	8.8 ± 4.6	13.6 ± 3.7
Intracranial bleeding	21 (42.9%)	21 (58.3%)	0 (0.0%)
Early operation	32 (65.3%)	26 (72.2%)	6 (46.2%)
Survival rate	39 (79.6%)	26 (72.2%)	13 (100.0%)

Data presented as mean ± SD or *n* of patients (%).

Table 2. Total cortisol, free cortisol and corticosteroid binding globulin (CBG) dynamics of the overall study population (*n* = 49) of patients with multiple trauma.

	Time since the traumatic injury, h			Statistical significance ^a
	0	12	24	
Total cortisol, µg/dl	15.8 ± 11.2	16.8 ± 11.3	13.1 ± 9.4	<i>P</i> = 0.015
CBG, µg/ml	26.1 ± 9.4	33.0 ± 8.7	33.4 ± 8.0	<i>P</i> < 0.001
Free cortisol, µg/dl	2.3 ± 2.7	2.1 ± 2.4	1.3 ± 1.9	<i>P</i> = 0.014

Data presented as mean ± SD.

^aWilks' Lambda distribution for multivariate hypothesis testing.

score <14; and 22 of 49 patients (44.9%) were unconscious with a GCS score ≤8.

When the dynamics of total and free cortisol serum concentrations were investigated in multiple trauma patients with and without TBI, there was no significant increase in total serum cortisol serum concentrations seen within 24 h after the traumatic injury. Serum concentrations of total and free cortisol remained relatively stable within the first 12 h, whereas between 12 h and 24 h after the traumatic injury, multivariate testing showed a significant decrease of total and free cortisol serum concentrations (*P* < 0.05 for both comparisons) (Table 2). CBG levels were significantly higher at 12 h and 24 h after the traumatic injury (*P* < 0.001).

In order to determine the impact of TBI on the dynamics of total and free cortisol serum concentrations, patients were stratified according to whether or not they had TBI. Patients with TBI had lower total and free cortisol serum concentrations compared with patients without TBI (Table 3). Trauma patients without TBI demonstrated an increase in total and free cortisol serum concentrations at 12 h after the traumatic injury. In patients with TBI, the mean serum concentrations of total and free cortisol did not increase after the traumatic injury. There was a significant difference between the groups with and without TBI (*P* = 0.02). Total cortisol showed significantly different dynamic changes (*P* = 0.032) in patients with TBI, with there being no increase after the trauma.

Table 3. Total and free cortisol dynamics in patients with multiple trauma with or without traumatic brain injury (TBI).

	Time since the traumatic injury, h					
	0		12		24	
	With TBI	Without TBI	With TBI	Without TBI	With TBI	Without TBI
Total cortisol, $\mu\text{g/dl}$	15.1 \pm 12.0	18.3 \pm 7.8	14.4 \pm 10.0	25.9 \pm 12.0	12.2 \pm 7.7	16.6 \pm 14.0
Free cortisol, $\mu\text{g/dl}$	2.2 \pm 2.9	2.6 \pm 1.7	1.6 \pm 2.0	4.0 \pm 3.1	1.1 \pm 1.0	2.4 \pm 3.7

Data presented as mean \pm SD.

Analysis of the initial GCS score and serum total cortisol concentration revealed decreasing hormone concentrations with an impaired consciousness as demonstrated by a GCS < 14 ($P = 0.049$). There was no distinct correlation between the whole GCS spectrum and serum total cortisol concentration as some of the most severely injured patients presented with a GCS score of 3 due to non-cranial reasons such as severe shock.

With regard to identifying risk factors, a strong correlation was found between serum cortisol concentrations and age. The mean value calculated from the three blood samples were approximately 6 $\mu\text{g/dl}$ higher in patients older than the median age of 44 years ($n = 24$; 18 with TBI and six without TBI). A subgroup analysis of these older patients revealed a tendency to have a more inadequate post-traumatic cortisol level response (Figure 1). Repeated measures testing confirmed a strong effect of TBI on total and free cortisol levels in the older patients (data not shown for total cortisol; $P = 0.01$). A similar correlation existed with the transfusion of packed red blood cells. Mass transfusion, usually defined as the administration of ≥ 10 units per day, was significantly accompanied by higher serum cortisol concentrations after 12 h and 24 h ($P = 0.015$).

Patients with total cortisol serum concentrations lower than the threshold of 5 $\mu\text{g/dl}$ did not demonstrate distinct risk

factors for an absolute impairment of corticosteroid hormones such as age, injury severity or reduced GCS score. Although absolute concentrations were decreased after TBI, there was no difference in the number of patients below the threshold between the two groups of patients with or without TBI.

Discussion

The current study is the first to evaluate total and free cortisol serum concentrations in the early clinical stage within 24 h following multiple blunt trauma with and without TBI. Hormone concentration dynamics were not only measured after initial operative treatment and admission to the ICU, but also as soon as possible after admission and within defined intervals related to the traumatic event.

Concentration dynamics undertaken in the current study showed no significant increase of total and free cortisol serum concentrations due to the traumatic injury, however significant decreases were observed in the overall study population between 12 h and 24 h after the traumatic injury. This decrease was even more obvious in multiple trauma patients with TBI, who showed decreased total and free cortisol serum concentrations as soon as 12 h after the traumatic injury. In patients with TBI, the traumatic injury did not appear to result in an increase in total and free cortisol levels.

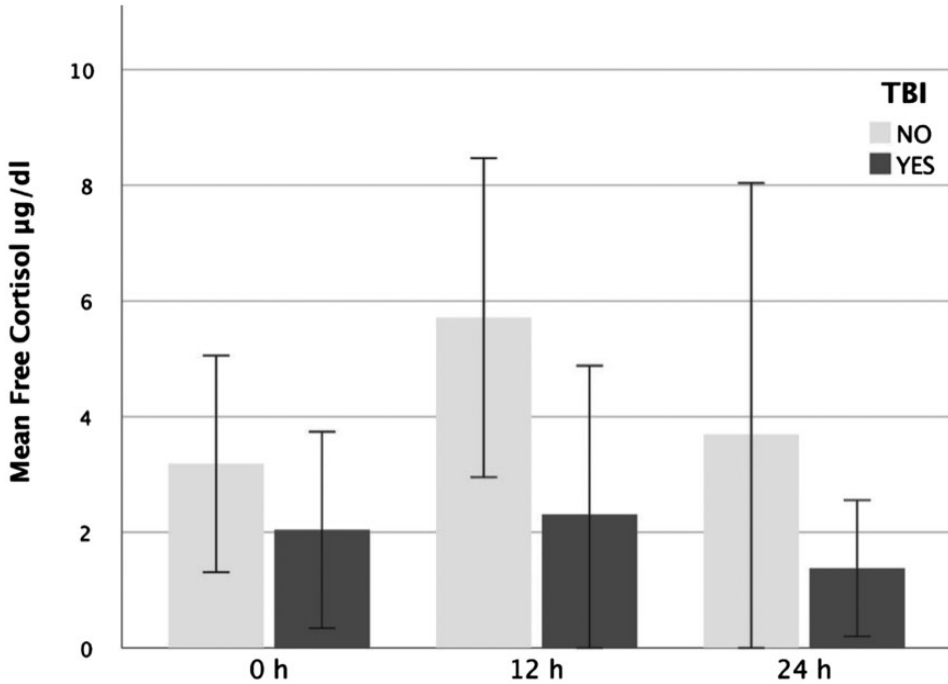


Figure 1. Free cortisol dynamics in patients with multiple trauma with or without traumatic brain injury (TBI) who were over the age of 44 years. Data presented as mean \pm SD.

Because of an overrepresentation of patients with TBI in this current cohort, these data should be regarded with caution. For patients with TBI, these current findings suggest an attenuation of the cortisol-mediated inflammatory response.

Secondary adrenal insufficiency has been studied extensively for decades. The first case reports that were published more than a century ago already indicated the possible fatal consequences.^{8,9} Numerous successive studies investigating corticosteroid changes following TBI have been undertaken.^{10–16} Each of these studies had a different focus, resulting in a variety of study protocols. Differing cortisol concentrations with and without TBI were found.¹² For example, a previous study compared TBI patients with those with multiple trauma, but the patients had lower ISS and only one timed blood

collection during the first 24 h, which was not adjusted to the time of the injury.⁵ Using this design, the authors found no absolute changes after TBI but diagnosed adrenal insufficiency using distinct thresholds.⁵ A recent investigation identified corticosteroid insufficiency in 10.3% of patients in the first week after trauma.¹⁷ Multiple measurements were not taken for the first 24 h and consequently no threshold values or data could be derived for the early clinical phase.¹⁷ Another approach in critical care patients used stimulation testing and found insufficiency in 24 patients.¹⁸ However, stimulation testing for critical care patients in the early phase seems unfeasible and therefore more knowledge of the correlation between hormone concentrations and clinical parameters is needed. Overall, the variation in study design, sampling and diagnostics result in different incidences of

adrenal insufficiency among the examined populations and makes drawing any conclusions very difficult.

Within the last 20 years, studies on chronic post-traumatic changes, most of them in the setting of rehabilitation units, have demonstrated a prevalence of 27.5% for hormonal changes of the pituitary hormone axes.¹⁹ Consequently, scientific and clinical attention has focused on this problem and therapeutic supplemental were initiated. The CRASH trial caused a significant change in the approach to therapeutic hormone supplementation because high-dose corticosteroids did not show an improvement in outcomes, with the treatment group having a higher 2-week mortality rate.²⁰ The unanswered question to date has been whether lower or stress-equivalent doses may improve the outcome and clinical course after severe TBI.

Inconsistent results can be found throughout literature in terms of whether total cortisol levels should be used to estimate adrenal function in critically-ill patients or if free cortisol concentrations would be better. To date, the measurement of the unbound form of cortisol has not been established for routine clinical diagnostics. Consequently, most of the aforementioned studies did not calculate free cortisol or they only measured CBG levels at a single time-point.¹⁹ CBG levels may vary significantly in different clinical situations such as sepsis or systemic inflammation.²¹ The present study demonstrated a significant increase in CBG levels in the overall study population of patients with multiple trauma with and without TBI, which effectively results in less available free cortisol and supports the need for obligatory free cortisol measurements for scientific research. These findings also support the need to establish CBG measurements in routine clinical practice.

This current study had a number of limitations. First, the inhomogeneity of the

sample of patients with multiple trauma in terms of their different injuries, operative treatment, type of sedation used, haemoconcentration and resulting fluid supplementation. The latter factor might result in a dilution effect that alters the measured concentrations of total and free cortisol and CBG. However, the total and free cortisol concentrations in the group of patients without TBI increased initially, so the diluting effect of fluid therapy appears to be modest. Secondly, the types of TBI were varied in a general trauma setting. In particular, damage to the pituitary gland might be caused by diffuse tissue injury or ischaemic pathological mechanisms in mild TBI, whereas in severe cases the hypothalamic or pituitary injury might happen directly. Thirdly, although more novel scoring systems exist for injury severity, the historical inclusion threshold of ISS 16 was used for reasons of practicality and to ensure an adequate minimal trauma stimulus in all patients. A statistical limitation in the current study was the unequal patient distribution among the two trauma groups. The reason for this is that the most severely injured patients suffer from at least mild TBI, which makes equal sample sizes difficult to realize. Furthermore, by determining total and free cortisol concentrations, this study was limited to estimating adrenal function. It was not designed to evaluate the need for therapeutic intervention as it did not provide evidence for functional glucocorticoid deficiency. As there was a clear correlation with age in this study and the characteristics of the corticosteroid hormone axis differ extensively among patients, threshold values are not helpful. In our opinion, the decision for therapeutic intervention can only be made if concentrations are below very low thresholds such as 2.5 µg/dl for total cortisol or if a variety of clinical conditions such as refractory hypotension and/or electrolyte and glucose

metabolism disorders are also present along with relatively impaired hormone levels.

In conclusion, the results of this current study demonstrated lower total and free serum cortisol concentrations in severely injured patients with TBI. The impairment of the corticosteroid hormonal axis was aggravated by a stimulated production of CBG and consequently lower effectively available free cortisol. The physiological response in cortisol production to the traumatic trigger was shown to be severely attenuated. Consequently, in the first 24 h, multiple trauma patients with TBI might be at risk of experiencing an inadequate stress response. Clinically, it remains to be elucidated whether these patients might benefit from glucocorticoid replacement therapy. Therefore, further studies should be performed to investigate the very early post-traumatic period in addition to the ongoing clinical course and should screen for specific symptoms to elaborate the clinical relevance of these findings.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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